REVIEW ARTICLE

Diagnostic Values of CEUS, CECT and CEMRI for Renal Cystic Lesions on the Current Bosniak Criterion–A Meta-analysis

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Objective: CT-based Bosniak classification system has been routinely used to assess complex renal cystic lesions and also been applied to contrast-enhanced magnetic resonance imaging (CEMRI) and contrast-enhanced ultrasound (CEUS). Besides, the 2019 new version incorporated MRI into the Bosniak system. However, the role of US in the Bosniak system has not been clearly established. The aim of this study was to compare the diagnostic ability of CEUS, CECT and CEMRI for renal cystic lesions based on the current Bosniak classification.

Methods: Related studies were searched in PubMed, EMBASE, and the Cochrane Library databases from January 1, 2010 to December 14, 2020. QUADAS-2 was used to assess the study quality. Meta-analysis was performed by "midas modules" of Stata SE 15.0 software. The bivariate mixed-effect model was used. The pooled sensitivity and specificity of these three modalities were calculated and compared. Meta-regression and subgroup analyses were conducted to reveal the source of heterogeneity.

Results: CEUS showed highest pooled sensitivity and specificity, which were 98% (95% CI: 91%, 100%) and 80% (95% CI: 64%, 90%) respectively. Pooled estimates of CEMRI were slightly lower than those of CECT with the sensitivity 85% (95% CI: 77%, 91%) versus 88% (95% CI: 77%, 94%) and specificity 71% (95% CI: 52%, 85%) versus 79% (95% CI: 70%, 86%), respectively.

Conclusions: Based on the current Bosniak classification, CEUS seemed superior to CECT and CEMRI for the diagnosis of complex renal cystic masses, and could serve as a valuable alternative for CECT and CEMRI.

Key words: Renal cystic lesions; Contrast-enhanced ultrasonography (CEUS); Contrast-enhanced computed tomographic (CECT); Contrast-enhanced magnetic resonance imaging (CEMRI); Bosniak classification

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The incidence of renal cystic lesions has been increasing steadily, with a positive correlation with age [1]. It was reported that approximately 50% of the people over 50 years old developed renal cysts [2]. In spite of the progress on imaging techniques, the diagnosis of complex renal cystic lesions remains one of the most challenging problems for the clinicians. Simple renal cysts with homogeneous anechoic content, posterior acoustic enhancement, and sharply defined borders can be easily recognized by ultrasound, and do

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not need further management or surveillance; however, there are still some complex cystic lesions that are difficult to differentiate, requiring further imaging characterization. For example, the simple cysts may show complicated imaging appearances due to bleeding, infection or ischemia [3]. By contrast, some malignant lesions such as cystic clear cell renal cell carcinomas may present the cysts-like appearances on imaging [4]. As the "gold standard", biopsy has a risk of spillage of cyst contents, and only a small proportion of cells within a cyst may contain malignancy. Therefore, as non-invasive modality, imaging is still indispensable for the preoperative diagnosis of renal cystic lesions.

At present, there are three imaging techniques including contrast enhanced ultrasound (CEUS), contrast enhanced CT (CECT) and contrast enhanced MRI (CEMRI) for the diagnosis of renal cystic lesions. Bosniak classification was originally established in 1986 based on CT imaging features, and has been applied to other modalities [5]. There are 5 categories in the classification system. Category I, II correspond to benign cystic renal lesions that do not require additional imaging or follow-up. IIF lesions are considered probably benign, and requiring a period of surveillance. Category III are considered 50% risk of malignancy and recommended surgical treatment, while category IV lesions are considered malignant and require surgical removal. In 2019, Silverman et al proposed an updated version of the Bosniak classification in order to overcome several shortcomings of the current version, and MRI was formally incorporated into it. Notably, although the Bosniak classification has been used to ultrasound (US) from time to time, the role of US in it has not been fully established yet [6,7].

Because of the advantages and drawbacks of the three different imaging modalities, it is uncertain which one showed the highest overall accuracy with the current Bosniak classification. Although a few similar studies have been conducted in the past [8,9], there were still some problems as follows: firstly, only one or two imaging methods were compared previously; second, some original studies included in the previous meta-analysis lacked the applications of the Bosniak classification. Therefore, we retrieved and updated origin articles to compare three imaging methods, aiming to assess the diagnostic performance of CEUS, CECT and CEMRI in the evaluation of cystic renal lesions with the current Bosniak classification.

Materials and Methods

Search strategy

Two review authors independently performed a systematic search of the Cochrane Library, PubMed and Embase to identify relevant articles listed in the last 10 years (from 1 January 2010 to 14 December 2020). Disagreements were resolved by discussion with a third review author. Key terms for the literature search included "renal", "kidney", "cysts", "cystic lesions", "cystic masses", "contrast-enhanced", "ultrasound", "US", "sonography", "CEUS", "computed tomography", "CT", "CECT", "magnetic resonance imaging" and "MRI". The search strategy was adjusted according to the specific database.

Study selection

Two review authors independently examined titles and abstracts to select eligible studies. Disagreements were resolved by discussion with a third review author until consensus was reached. Study populations were patients with renal cystic masses who underwent at least one type of enhanced imaging examinations. The included studies were related to the diagnostic performance of CEUS, CECT or CEMRI based on the current version of Bosniak classification. Inclusion criteria were the following conditions: (a) pathological findings or follow-up observation (> 1 year) were used as the reference standard for the final diagnosis, (b) the number of cases in the study had to be no less than 30, (c) 2 × 2 contingency tables could be extracted directly from the article or by calculation and (d) eligible studies had to be published in English. The exclusion criteria were as follows: (a) only traditional imaging methods are studied, not enhanced imaging examinations, (b) studies that lacked the use of the Bosniak classification system to categorize the lesions, (c) conference papers or secondary literatures, such as experience exchanges, abstracts, lectures and reviews. At last, studies meeting the inclusion and exclusion criteria were reviewed in full text.

Data extraction

The following data were collected: author name; publication year; study type (retrospective or prospective); region; mean or median age of patients, number of lesions; mean diameter of lesions, contrast-enhanced materials; reference standard (pathology or follow-up, duration of follow-up); the categories of lesions in the original studies (Bosniak categories I, II, IIF, III or IV); the true positive (TP), true negative (TN), false positive (FP) and false negative (FN) were extracted or calculated according to the original data of the included studies.

Quality assessment

For the assessment of the risk of bias, each included study was evaluated according to the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 by two reviewers. QUADAS-2 consists of four domains: patient selection, index test, reference standard, and flow and timing. The risks of bias and the applicability were rated as low, high, or unclear. Disagreements were resolved by discussion with a third review author.

Statistical analysis

Statistical analyses were performed using Stata SE 15.0 and MetaDiSc 1.4 software.

The "Midas modules" of Stata SE 15.0 was used for the meta-analysis. The bivariate mixed-effect model was used. Forest plots and a summary receiver operating characteristic (SROC) curve were constructed to illustrate individual and pooled parameters. Pooled sensitivity, specificity, area under the SROC curve (AUC), and positive and negative likelihood ratios and their corresponding 95% CIs were calculated.

The threshold effect was evaluated by Spearman correlation coefficients using Meta-Disc version 1.4 software. Then, the chi-squared test and inconsistency index were used to determine interstudy heterogeneity using Stata SE 15.0. $P < 0.05$ and $I^2 \geqslant 50\%$ indicates significant heterogeneity. The meta-regression and subgroup analyses were performed to explore the sources of heterogeneity, according to the following factors: (a) study type (prospective or retrospective); (b) region (Europe or Asia); (c) gold standard ("pathology only" or "pathology or follow-up"), (d) size (the number of included lesions (<100 or ⩾100)). P-values of <0.05 means a significant result.

Sensitivity analysis was conducted to assess the impact of individual studies on the pooled statistics. To investigate the publication bias, the Deeks' funnel plot was performed.

Results

Study characteristics

At last, 16 eligible studies were selected (Fig. 1). Five of the 16 included studies were cohort studies, one study compared CEUS with CECT [10], one CEUS with CEMRI [11], and three CECT with CEMRI [12-14]. Among the 11 descriptive studies, 4 studies related to CEUS [15-18], 5 CECT [19-23] and 2 CEMRI [24,25]. The 16 studies enrolled a total of 1849 lesions. The region of 8 studies was European or American [10,12,14-16,20,21,24], while the remaining 9 studies were Asian [11,13,17,19,21-23,25]. Six studies only included lesions of Bosniak II and IIF or Bosniak IIF alone as benign lesions [10,13,14,17,20,23], others included lesions of all categories [11,12,15,16,18, 19,21,22,24,25]. The contrast material used in all CEUS studies was SonoVue. In the MRI studies, there were two kinds of contrast agents: Magnevist, and Gadovist. Studies on CECT had a variety of contrast agents: Omnipaque, Ultravist or Iopamiro. The detailed characteristics of the 16 included studies are shown in Table 1.

Quality assessment of the studies

Summaries of the QUADAS-2 evaluation are shown in Figure 2. The information bias mainly came from "patient selection" and "flow and timing". Patient recruitment was consecutive in six studies while the remain studies didn't mention. Studies without Bosniak I lesions or Bosniak I and II lesions were considered to have inappropriate exclusions. The reference standard in 9 studies were pathology or follow-up. The other 7 studies were referenced by pathology only.

Meta-analysis

There was no threshold effect, as the Spearman correlation coefficient (p-value) for CEUS, CECT and CEMRI were 0.31 (P = 0.544), 0.05 (P = 0.881) and 0.543 (P = 0.266) respectively. The homogeneity test of CEUS, CECT and CEMRI showed that I^2 was 75%, 88% and 83%, and the p-value was 0.010, 0.000 and 0.001, respectively. The heterogeneity was obvious. Therefore, a random effects model of "midas modules" in the Stata SE version 15.0 software was utilized.

The pooled sensitivity of CEUS, CECT and CEMRI was 98 % (95 %CI 91–100), 88 % (95 %CI 77–94) and 85 % (95 %CI 77–91), respectively. The pooled specificity of CEUS, CECT and CEMRI was 80% (95 %CI 64–90), 79% (95 %CI 70–86) and 71% (95 %CI 52–85), respectively (Fig. 3 and 4). The pooled positive likelihood ratio of CEUS, CECT and CEMRI was 4.9 (95% CI 2.6–9.3), 3.9 (95% CI 2.7–5.5) and 3.0 (95% CI 1.7–5.0), respectively. The pooled negative likelihood ratio of CEUS, CECT and CEMRI was 0.02 (95% CI 0.00–0.11), 0.14 (95% CI 0.07–0.27) and 0.21 (95% CI 0.15–0.29), respectively. The AUC-SROC of the CEUS, CECT and CEMRI were 0.97% (95% CI 0.95 - 0.98), 0.89% (95% CI 0.86 - 0.92) and 0.87% (95% CI 0.84 - 0.90), respectively (Fig. 4). The results of the meta-analysis are presented in Table 2.

Meta-regression and subgroup analysis

Meta-regression analyses of CECT revealed that the reference standard and the study design significantly affected heterogeneity, while the differences of the region and the reference standard were the main sources of the heterogeneity of CEUS (all $P < 0.05$). In contrast, no evidence suggested that the heterogeneity of CEMRI was associated with these factors (Fig. 5). Detailed subgroup results are provided in Table 3. No significant difference was found between the results of subgroups with the overall results.

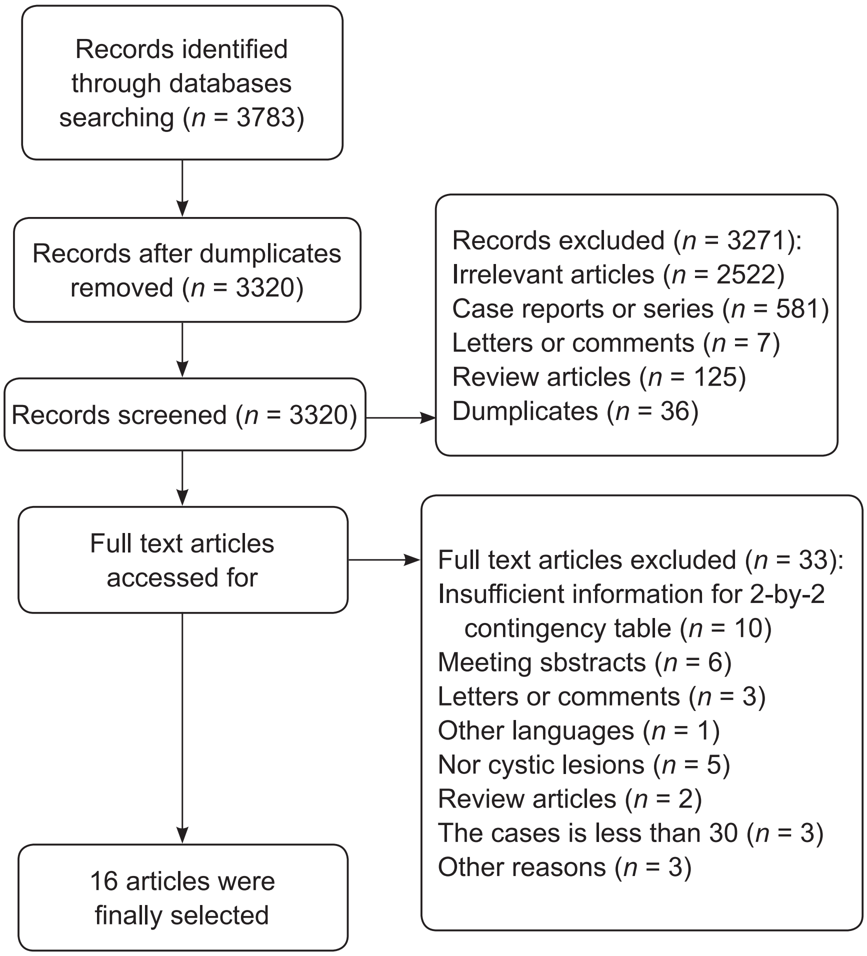

Figure 1 Flowchart summarizing study selection.

Table 1 Characteristics of the included studies

Study ID	Year	Country	Imaging technique	Study type	Patients select	Patients age (years)	No. of lesions	Reference standard
Sanz et al. [10]	2016	Spain1	CEUS vs CECT	PRO	NA	median 67.8	67	P+F
Edenberg et al. [15]	2016	Norway1	CEUS	REP	consecutive	mean 63.8 (33–86)	132	P+F
Chen et al. [11]	2015	China2	CEUS vs CEMRI	REP	NA	mean 49.6 (21–78)	71	P+F
Nicolau et al. [16]	2015	Spain1	CEUS	PRO	consecutive	mean 64.2 (34–85)	83	P+F
Xu et al. [17]	2014	China2	CEUS	REP	NA	mean 45.3 (23–75)	87	P
Defortescu et al. [14]	2017	France1	CECT vs CEMRI	PRO	consecutive	median 64.7 (37–76)	47	P+F
Oh et al. [19]	2016	Korea2	CECT	REP	NA	mean 59.88	324	P
Reese et al. [20]	2014	America1	CECT	REP	NA	median 57	113	P
Keseroglu et al. [21]	2019	Turkey1	CECT	REP	NA	mean 57	191	P
Ferreira et al. [12]	2016	Brazil1	CECT vs CEMRI	REP	NA	mean 51.4 (11–82)	42	P+F
Zhong et al. [13]	2017	China2	CECT vs CEMRI	REP	NA	mean 49 (22–69)	35	P+F
Kim MH et al. [23]	2014	Korea2	CECT	REP	NA	mean 56 (21–90)	164	P+F
Kim DY et al. [22]	2010	Korea2	CECT	REP	NA	mean 54 (22–75)	125	P
Qiu et al. [18]	2020	China2	CEUS	REP	consecutive	median 55.5 (21~86)	102	P+F
Tse et al. [24]	2020	America1	CEMRI	REP	consecutive	mean 55 (18~83)	59	P
Bai et al. [25]	2020	China2	CEMRI	REP	consecutive	mean 49 (16-75)	207	P

NA, not available; REP, retrospective; PRO, prospective; P, pathology; F, follow-up; Patients Age, the data in parentheses is the age range

Continued Table 1 Characteristics of the included studies

Study ID	Contrast material	Mean diameter (cm)	Time of following	Grades of lesions included	PC	FC
Sanz et al. [10]	CEUS: Sonovue CECT: NA	CEUS: 3.8 CECT: 3.9	NA	CEUS:II、IIF、III、IV CECT:II、IIF、III、IV	24	43
Edenberg et al. [15]	Sonovue	3	> 2 Y	I、II、IIF、III、IV	29	103
Chen et al. [11]	CEUS: Sonovue CEMRI: Magnevist	3.6	12~40 M	I、II、IIF、III、IV	43	28
Nicolau et al. [16]	Sonovue	2.1	23~41 M	I、II、IIF、III、IV	32	51
Xu et al. [17]	Sonovue	4.9	-	IIF、III、IV	87	0
Defortescu et al. [14]	CECT: Omnipaque CEMRI: Gadovist	3.8	17–48 M	CECT:IIF、III、IV CEMR:IIF、III、IV	19	28
Oh et al. [19]	NA	5.47	-	I、II、IIF、III、IV	324	0
Reese et al. [20]	NA	NA	-	II、IIF、III、IV	113	0
Keseroglu et al. [21]	NA	NA	-	I、II、IIF、III、IV	191	0
Ferreira et al. [12]	CECT: NA CEMR: Magnevist	CECT: 3.6 CEMR: 3.8	Mean 40.9 M	CECT:I、II、IIF、III、IV CEMR:I、II、IIF、III、IV	13	29
Zhong et al. [13]	CECT: Ultravist CEMRI: Magnevist	NA	36 ~ 41 M	CECT:II、IIF、III、IV CEMR:IIF、III、IV	28	7
Kim MH et al. [23]	Ultravist or Iopamiro	NA	>2 Y	II、IIF、III、IV	85	79
Kim DY et al. [22]	Ultravist or Iopamiro	NA	-	I、II、IIF、III、IV	125	0
Qiu et al. [18]	Sonovue	4.0	24~61 M	I、II、IIF、III、IV	56	46
Tse et al. [24]	Gadovist	4.1	-	I、II、IIF、III、IV	59	0
Bai et al. [25]	NA	NA	-	I、II、IIF、III、IV	207	0

NA, not available; M, months; Y, years; PC, pathological cases; FC, follow-up cases

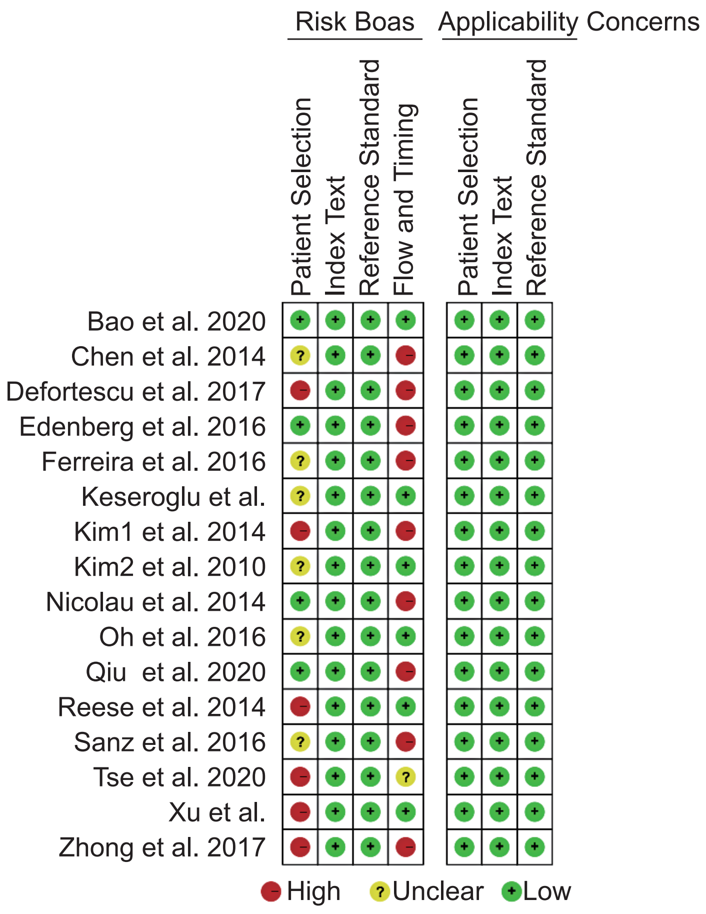

Figure 2 Results of QUADAS-2 assessment.

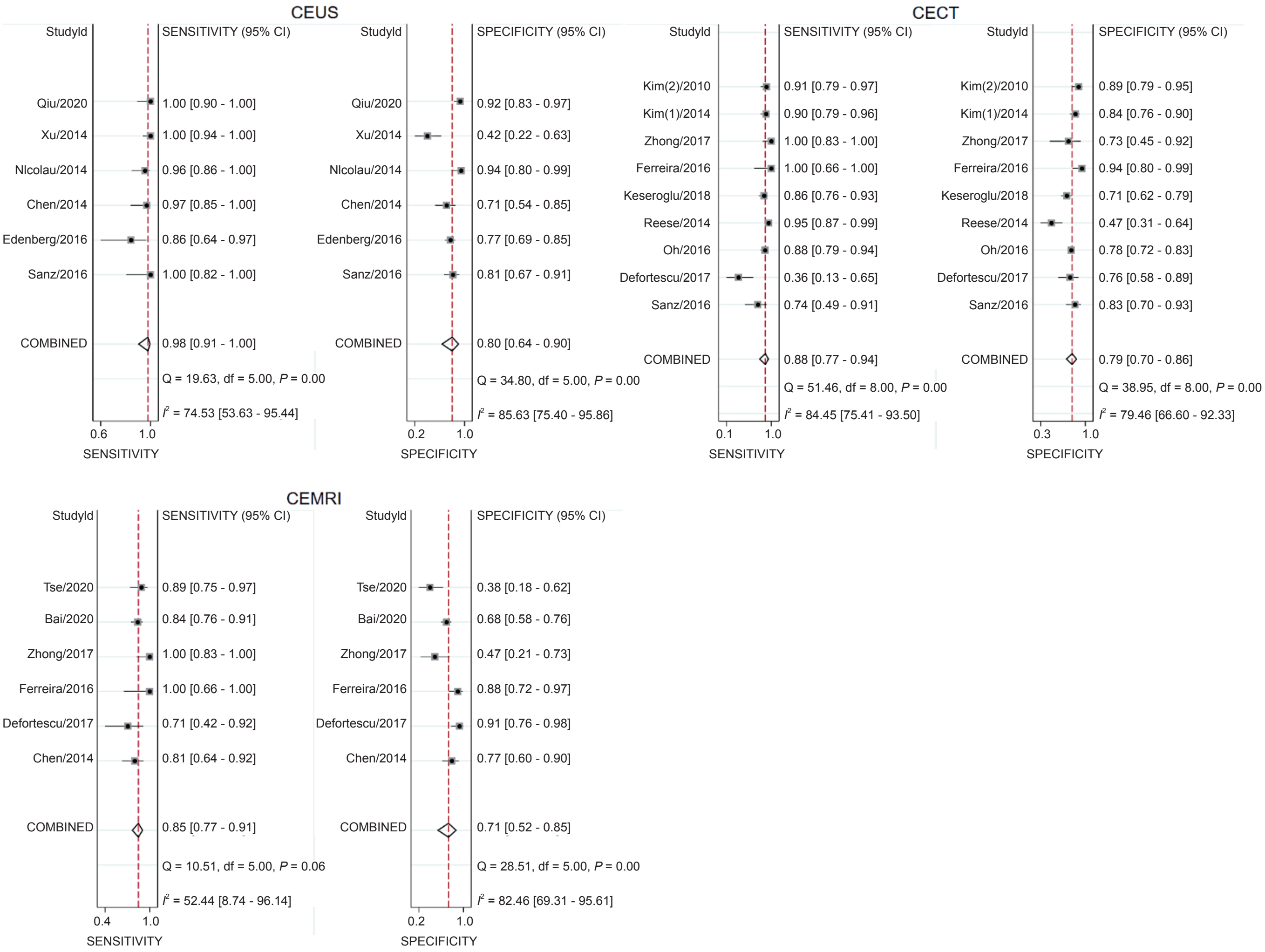

Figure 3 Forest plots for the pooled sensitivity and specificity of CEUS, CECT and CEMRI.

Table 2 The results of Meta-analysis

Imaging technique	No. of studies	Pooled sensitivity (%)	Pooled specificity (%)	Pooled AUC-value	Pooled positive likelihood ratio	Pooled negative likelihood ratio	I^2/P value
CEUS	6	0.98 (0.91, 1.0)	0.80 (0.64, 0.90)	0.97 (0.95 - 0.98)	4.9 (2.6, 9.3)	0.02 (0.00, 0.11)	75%/0.010
CECT	9	0.88 (0.77, 0.94)	0.79 (0.70, 0.86)	0.89 (0.86 - 0.92)	3.9 (2.7, 5.5)	0.14 (0.07, 0.27)	88%/0.000
CEMR	6	0.85 (0.77, 0.91)	0.71 (0.52, 0.85)	0.87 (0.84 - 0.90)	3.0 (1.7, 5.0)	0.21 (0.15, 0.29)	83%/0.001

Data in parentheses are 95% CIs

Table 3 The results of subgroup analysis

Imaging technique	Subgroups	No. of studies	Pooled sensitivity (%)	Pooled specificity (%)	Pooled AUC-value	I^2/P value
CECT	Study design	PRO (n = 2)	-	-	-	-
		REP (n = 7)	0.91 (0.88, 0.94)	0.76 (0.73, 0.79)	0.92 (0.90 – 0.94)	86%/0.000
	Reference standard	P (n = 4)	0.90 (0.86,0.93)	0.76 (0.63, 0.85)	0.91 (0.89 - 0.94)	79%/0.004
		P + F (n = 4)	0.93 (0.29,1.00)	0.84 (0.74, 0.91)	0.88 (0.85 - 0.91)	78%/0.005
CEUS	Region	European or American (n = 4)	0.97 (0.86, 0.99)	0.86 (0.78, 0.92)	0.96 (0.93 - 0.97)	0%/0.353
		Asian (n = 2)	-	-	-	
	Reference standard	P (n = 1)	-	-	-	
		P + F (n = 5)	0.96 (0.92, 0.99)	0.83 (0.78, 0.87)	0.96 (0.94 - 0.97)	0%/0.473

Data in parentheses are 95% CIs. Abbreviations were shown as Table 1

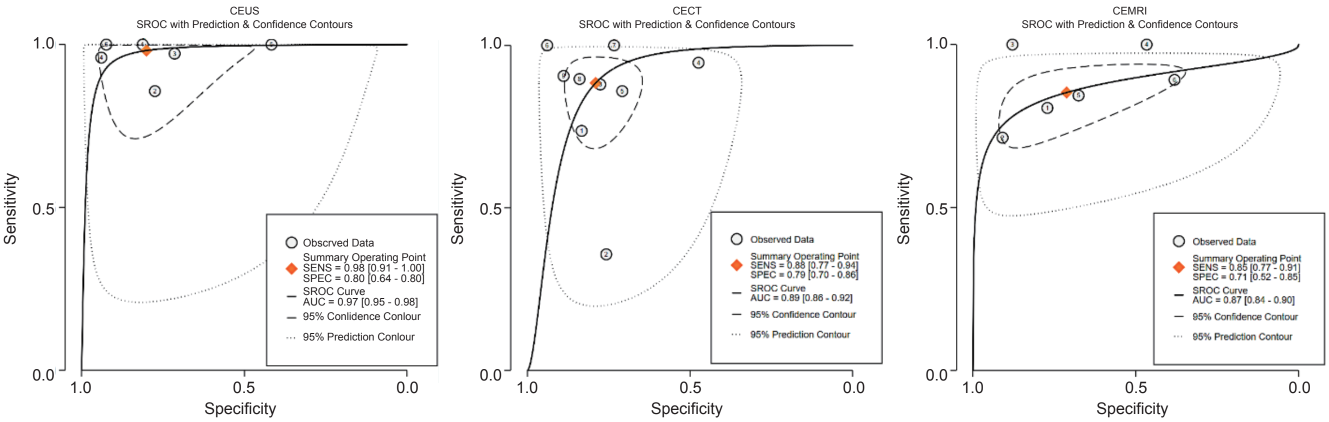

Figure 4 The SROC curves.

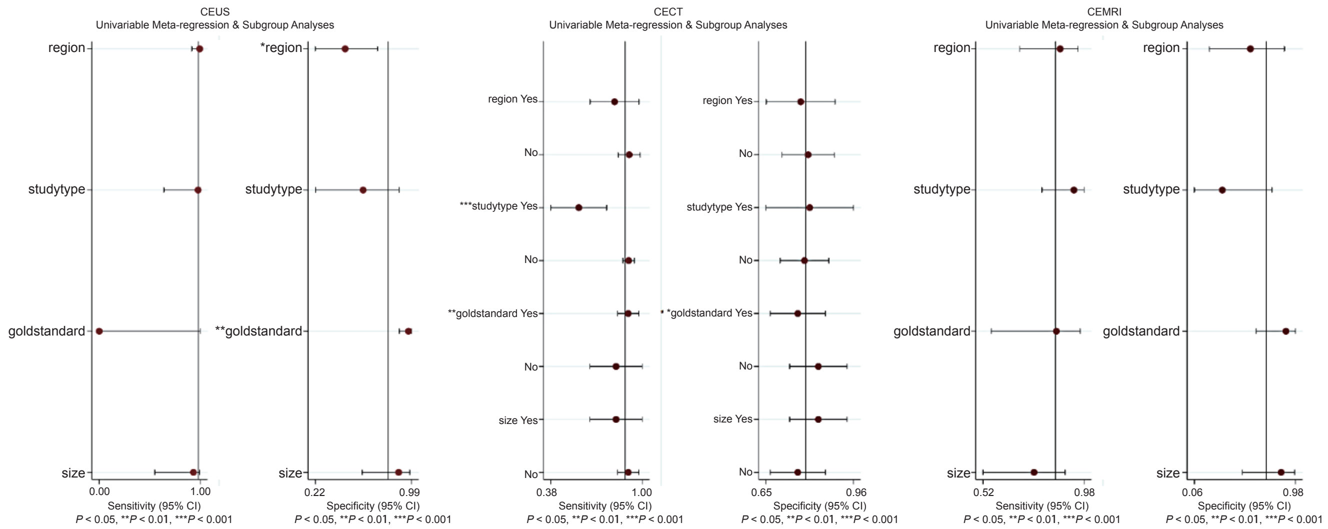

Figure 5 The results of the meta-regression analysis.

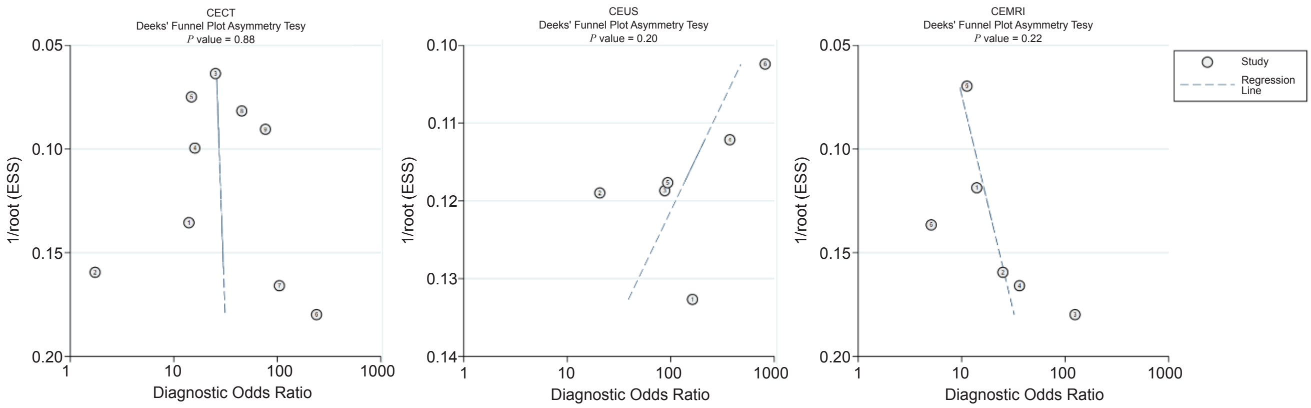

Figure 6 The Deek's funnel plot asymmetry test.

Sensitivity analysis and publication bias

Sensitivity analysis was performed by removing each study individually and then calculating the pooled statistics again. No significant change was found, indicating that our results were credible. The Deek's funnel plot asymmetry test indicated no publication bias existed (all $P > 0.05$) (Fig. 6).

Discussion

In this meta-analysis, CEUS showed highest sensitivity and specificity (sensitivity, 98%; 95% CI: 91%, 100%; specificity, 80%; 95% CI: 64%, 90%), compared with CEMRI or CECT. This result was in line with the original study by Defortescu et al [14]. With the wide application of the second-generation contrast agents such as "SonoVue", CEUS has developed as a promising modality for evaluating renal cystic masses. The high sensitivity to the harmonic signals produced by microbubbles makes CEUS even more effective than contrast-enhanced CT and MRI during the detection of contrast enhancement in tumors. In addition, CEUS improves the detection rate of low-speed small blood vessels. Thus some researchers demonstrated that CEUS could detect more intracystic septum than CT [26]. However, under some conditions, CEUS might be so sensitive to upgrade the Bosniak classifications [11,14,16]. In other words, CEUS might increase the incidence of false-positive diagnoses of complex renal lesions. For instance, Chen et al. reported the higher sensitivity and a higher rate of misdiagnoses of CEUS than MRI [11]. Indeed, it is wise to be cautious to avoid overclassifying when interpreting CEUS images of complex cystic renal masses. New studies are required to confirm whether the new Bosniak version could improve specificity of CEUS.

In contrast, sensitivity and specificity for CECT versus CEMRI were 88% and 79% versus 85%, and 71%. Although the Bosniak classification was initially established on CT findings, it was reported the diagnostic performance of CECT was inferior to that of CEUS [27], just in accordance with the present results. This might be related to "pseudoenhancement", "partial volume effect" or "lower soft tissue contrast" [12,28]. In addition, our results showed the pooled parameters of MRI was slightly lower than those of CT, which was different from the results of previous studies [12,28]. Moreover, the pooled sensitivity and specificity of MRI were significantly lower, compared with the previous meta-analysis by Zhou et al (92% and 91%, respectively) [8]. One reason was related to the poor spatial resolutions of MRI in spite of the superiority in soft tissue resolution. Besides, the updated original articles might account for the difference, because two latest retrospective studies in 2020 were included in this study. The purposes of them were both to compare the effects between the current and the 2019 new versions of Bosniak classification on the diagnostic efficiency of MRI [24,25].

As for the performance of MRI, Israel and his colleagues firstly reported that MRI might lead to an upgrade of Bosniak classification [6]. Studies included in this meta-analysis also suggested upgrades of the cystic lesions with MRI, due to the ability of MRI to provide more septa or thicker septa/walls [13], similar to what has been seen in CEUS. What's more, consistent with previous studies, we also found the low specificity of these imaging techniques with the current Bosniak classification. Besides, the current version was thought to cause the large interobserver variability and the high prevalence of benign findings among lesions classified into Bosniak Ⅲ. In order to reduce the subjectivity, Silverman et al. proposed the 2019 version and defined terms numerically, such as "thick" and "many" [7]. The categories of IIF and III were further refined and standardized with specific and quantitative definitions. Only complex cystic lesions with marked wall or septal thickening (⩾4 mm and ⩾3 mm, respectively) would belong to Bosniak category III in the 2019 version. These modifications contributed to a greater proportion of lesions being reclassified into category IIF, as confirmed by Tse et al.'s study [24]. It was remarkable that the 2019 version formally incorporated MRI into the Bosniak system. According to several recent MRI-related prospective studies, it remained kind of controversy about the improvement of the interobserver agreement or the reduction of the mean category with the 2019 version [24,25,29]. More studies are warranted to verify the diagnostic efficiency of the new version with different imaging techniques. In addition, as a first-line inspection tool, regardless of the current or 2019 version of Bosniak classification, ultrasound barely received attention.

On the other hand, disadvantages and contraindications with different techniques should be considered. CEUS can be influenced by shadowing from calcification, bowel gas interposition or deep location of lesions. The ionizing radiation in CT examination is inevitable, which needs to be considered especially when the patients are young. The drawbacks of MRI include high cost, long acquisition times, the requirement of good breath-holding abilities from patients. For both CECT and CEMRI, the adverse reactions of patients with intravenous contrast must be considered. In contrast, contrast agents of CEUS do not interfere with renal function. Considering these advantages such as avoidance of radiation, lower cost, rare adverse effects, continuous real-time multi-angle imaging, CEUS is therefore emerging as a valuable alternative to contrast-enhanced CT and MRI.

There are some limitations in our study. First, the number of available articles, especially those of MRI and CEUS were limited, and the majority were retrospective studies. Second, a large amount of heterogeneity regarding CECT and CEMRI remained unexplained, which probably was caused by interobserver variability, size of lesions, or age, sex ratio and other factors of the subjects. In addition, differences of the field strength and scanning slice thickness in studies of MRI could be another source of heterogeneity. Finally, the small number of studies in subgroups might lead to unreliable pooled diagnostic parameters.

Conclusion

As a widely used imaging modality, CEUS showed high sensitivity and specificity when evaluating complex renal cystic lesions based on the current Bosniak classification system, and could serve as a valuable alternative for CECT and CEMRI.

Conflict of Interest

The authors have no conflict of interest to declare.

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