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Contrast-enhanced ultrasound targeted versus conventional ultrasound guided systematic prostate biopsy for the accurate diagnosis of prostate cancer

A meta-analysis

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Abstract

Background: Conventional transrectal ultrasonography (TRUS) guided prostate biopsy is the standard method for accurate diagnosis of prostate cancer (PCa). However, the limitations of this technique in terms of missed diagnosis cannot be ignored. Based on previous studies, contrast-enhanced ultrasound (CEUS) may be able to more distinctly detect malignant lesions with increased microvessels. Therefore, to evaluate the diagnostic efficiency and clinical application prospects of CEUS-guided prostate biopsy for patients with suspected PCa, we performed a meta-analysis comparing CEUS-targeted with TRUS-guided systematic biopsy.

Methods: A systematic search of PubMed, Web of Science, Embase and CNKI was performed up to March, 2022 for the relevant published studies. After data extraction and quality assessment, meta-analysis was performed using the RevMan 5.3 software.

Results: The results showed that the overall sensitivity was higher for CEUS targeted biopsy than systematic biopsy ($P = .03$), so was the accuracy ($P = .03$). However, significant heterogeneity and inconsistent results from certain subgroup analyses challenged the validity of the results. Meanwhile, CEUS yielded a much higher sensitivity in patients with prostate specific antigen (PSA) level of 4 to 10 ng/mL ($P = .007$). On the other hand, the positive rate of each core ($P < .001$) and the detection rate of clinically significant PCa ($P = .006$) were significantly improved using CEUS.

Conclusion: CEUS showed the advantage of a higher detection rate of clinically significant PCa, which might provide more specific indications for subsequent treatment. More feasible, real-time data are required to confirm our findings.

Abbreviations: CEUS = contrast-enhanced ultrasound, mpMRI = multiparametric magnetic resonance imaging, MRI = magnetic resonance imaging, PCa = prostate cancer, PSA = prostate specific antigen, TRUS = transrectal ultrasonography.

Keywords: biopsy, contrast-enhanced ultrasound, diagnosis, meta-analysis, prostate cancer

1. Introduction

Prostate cancer (PCa) is the second most common malignant disease in men, with a steadily increasing incidence worldwide. Since population screening was valued and initiated, early detection has been proved to be associated with a decrease in cancer-related mortality.[1] For clinical diagnosis, systematic prostate biopsy with 8 to 12 cores under transrectal ultrasound (TRUS) has long been applied in primary hospitals. However, the strategy of TRUS-guided biopsy has been poorly developed since it was first introduced in 1981.[2,3] Because of these inherent limitations, systematic biopsy using TRUS may fail to discover almost 20% of clinically significant PCa.[4] Meanwhile, among the TRUS-positive cases, a relatively high percentage

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Ethical approval was not required for this study in accordance with national guidelines. Written informed consent from participants was not required in accordance with national guidelines.

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turned out to be clinically insignificant PCa, which requires no aggressive treatment.[4] Given the above concerns, the improvement of current diagnostic methods is imperative.

Contrast-enhanced ultrasound (CEUS) using microbubbles, which are ideal contrast agents for enhancing small vessels, can provide more distinct the visualization of lesions with microvessels.[5] In recent years, CEUS has been gradually used for the diagnosis of various tumors, such as breast cancer, hepatocellular carcinoma, renal cancer, thyroid cancer and so on.[6–9] Li et al performed a meta-analysis, indicating that CEUS is a promising tool for the detection of PCa, but could not replace the role of systematic biopsy.[10] Compared with normal prostate tissues, PCa generally shows increased microvessel density, which is associated with pathological parameters, including Gleason scores.[11] Theoretically, CEUS might be more sensitive in detecting PCa, especially in high-grade lesions. Some published studies have compared CEUS with baseline TRUS, illustrating the superiority of CEUS, in terms of higher diagnostic accuracy, fewer cores and increased sensitivity of clinically significant PCa.[12–24] However, there are also preliminary studies suggesting that the real advantages of CEUS in clinical practice remains controversial.[25,26] In view of these arguments, we performed this meta-analysis to determine whether CEUS-guided biopsy is superior to conventional systematic biopsy and evaluate the performance of CEUS in the diagnosis of PCa.

2. Methods

2.1. Search strategy

Following the recommendations of the Cochrane Collaboration and Quality of Reporting of Meta-analyses guidelines, this meta-analysis was performed.[27,28] To identify eligible studies, we searched the literature published from 2000 to 2022 in PubMed, Web of Science, Embase, and CNKI. The following MESH terms were used: "comparative studies," "contrast-enhanced ultrasound," "gray-scale ultrasound" or "transrectal ultrasound" or "conventional ultrasound," "prostate cancer," "targeted," "systematic" and "prostate biopsy." The "related articles" function was used to broaden the search, and all abstracts, studies, and citations were reviewed.

2.2. Inclusion criteria and exclusion criteria

The following inclusion criteria were used: clinical studies comparing CEUS with TRUS during prostate biopsy, targeted biopsy alone was performed for abnormal findings on CEUS, patients with suspected PCa who underwent prostate biopsy for the first time, and the final diagnosis of PCa was defined by pathological testing.

Studies were excluded if: patients had a history of PCa or repeated biopsy, without numerical outcomes or impossible to calculate, and biopsy was performed with other imaging assistance, for example, MRI-targeted biopsy.

2.3. Study outcomes

We compared the diagnostic efficiency of CEUS-targeted with that of TRUS-guided systematic biopsy. The sensitivity, specificity and accuracy of the patients were analyzed. We then evaluated the sensitivity according to PSA ladders (4–10 ng/mL, 10–20 ng/mL, and >20 ng/mL), to validate the association with different clinical characteristics. Moreover, we compared the detection rate of clinically significant PCa, namely, a Gleason score of >6. In the core analysis, the proportion of positive biopsy sites was also compared between the 2 techniques. All disagreements regarding eligibility were resolved by discussion until a consensus was reached. In all cases of missing or incomplete data, the corresponding authors were contacted; however, no additional information was provided.

2.4. Quality assessment

We used the levels of evidence to evaluate the methodological quality of the included studies, according to criteria from the Centre for Evidence-Based Medicine in Oxford UK (available at http://www.cebm.net/ocebm-levels-of-evidence/). All included studies were independently assessed by 2 investigators after a full-text review. Studies on levels 1a to 3b were considered feasible.

2.5. Statistical analysis

All pooled data were discontinuous variables, that were reported as odds ratios (OR). The Mantel-Haenszel method was used for the meta-analysis, and the data were synthesized using the Z test. Heterogeneity among studies was evaluated using the chi-square statistics and I-square (I^2) tests. We used a fixed-effects model when heterogeneity was not significant ($P > .1$ and $I^2 < 50\%$), otherwise, a random-effects model was applied. Funnel plots were used to evaluate publication bias. Sensitivity analysis was performed by omitting 1 certain study at a time. Statistical significance was set at $P < .05$. All calculations were conducted using the RevMan software (version 5.3; Cochrane Library Software, Oxford, UK).

3. Results

A total of 362 studies were retrieved using the initial search strategy. After 3 rounds of screening, 15 studies were selected, including 1 randomized controlled trial, 11 prospective studies and 3 retrospective studies. Based on the levels of evidences, all pooled studies were listed as feasible evidence. A flowchart illustrating the selection strategy for this meta-analysis is shown in Figure 1. The characteristics of the included studies are listed in Table 1.

Targeted and systematic biopsy procedures were paired in most included studies. Based on the analyses of pooled studies, CEUS seemed to be more sensitive than TRUS for the detection of PCa (OR: 1.77; 95% CI: 1.05–2.99; $P = .03$). However, remarkable heterogeneity was observed among the included studies (Fig. 2). To investigate the possible source of heterogeneity, we performed subgroup analyses according to time (before 2010 vs after 2010), institute (China vs other countries) and study design (retrospective vs prospective). It seemed that the results were influenced by all 3 parameters, indicating that the advantage of CEUS was not feasible. The results are presented in Table 2. In addition, the diagnostic sensitivity was compared between CEUS and TRUS biopsy according to PSA levels. In the PSA 4 to 10 ng/mL subgroup, the sensitivity was significantly greater for CEUS than for TRUS (OR: 2.66; 95% CI: 1.30–5.41; $P = .007$), and so was in the 10 to 20 ng/mL (OR: 1.75; 95% CI: 1.04–2.97; $P = .04$), while no significant difference was revealed in the > 20 ng/mL subgroup (OR: 0.82; 95% CI: 0.40–1.66; $P = .58$) (Fig. 3). In the biopsy core analysis, the positive rate of suspicious lesions on CEUS was significantly greater than that on TRUS (OR: 2.45; 95% CI: 1.57–3.81; $P < .001$) (Fig. 4).

In addition to diagnostic sensitivity, we also compared the specificity, which showed no significant difference between CEUS and TRUS (OR: 1.42; 95% CI: 0.43–4.73; $P = .56$) (Fig. 5). However, the overall accuracy was higher for CEUS (OR: 1.73; 95% CI: 1.05–2.85; $P = .03$) (Fig. 6). On the other hand, among the same patients whose biopsy was positive, there was an increased detection rate of clinically significant PCa with a Gleason score > 6 for CEUS compared to TRUS (OR: 2.55; 95% CI: 1.31–4.95; $P = .006$) (Fig. 7).

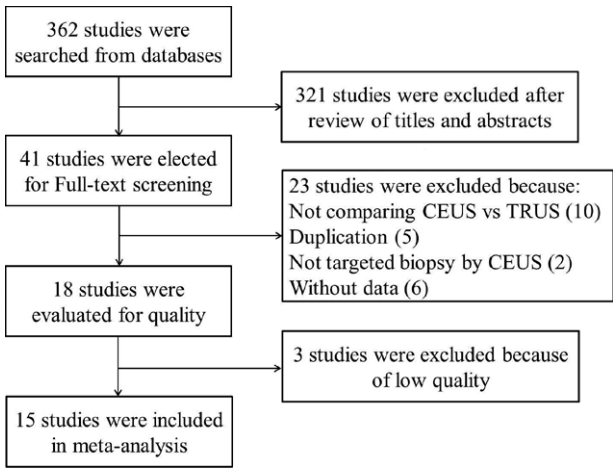

Figure 1. Flowchart showing the selection of studies for meta-analysis.

Sensitivity analysis was performed by removing 1 certain study each time. The results showed that, when particular studies were omitted,[14,15,23] the final results of diagnostic sensitivity changed to no statistical difference between CEUS and TRUS, challenging the solidity of this analysis. However, when we analyzed the subgroups mentioned above, no significance was influenced due to the absence of a single study. For specificity, clinically significant PCa detection rate, and positive rate of each core, sensitivity analyses indicated that the comparisons were relatively stable. Funnel plots were used to assess the publication bias of the included studies, and no palpable publication bias was noted.

4. Discussion

The application of multiparametric ultrasound including new sonographic modalities such as elastography, CEUS, improved B-mode, micro-ultrasound and micro-Doppler has provided preliminary superiority for the detection of suspicious prostate lesions compared with conventional TRUS.[29,30]

Table 1

The characteristics of included studies.

Author yr	Country	Study interval	PSA (ng/mL)	Age	Contrast agent	Study design	LOE
Chen 2019	China	2015.01–2018.07	4–10	Mean ± SD:67.3 ± 9.2	SonoVue®	Retrospective	2b
Frauscher 2002	Austria	2000.12–2001-07	>1.25	Ranging:41–77; Mean:56	Levovist	Prospective	1b
Halpern 2012	USA	2006.11–2011.06	Mean ± SD:6.5 ± 7	Ranging:36–83; Mean:62	DEFINITY®	Prospective	1b
Lai 2016	China	2014.05–2015.10	>4	Mean ± SD:67.5 ± 14.5	NR	Prospective	1b
Li 2015	China	2010.06–2011.11	Ranging:4.01–99; Mean:22.94	Mean ± SD:69.33 ± 8.31	SonoVue®	Retrospective	2b
Liu 2020	China	2015.01–2019.07	Ranging:4.2–25.3; Median:7.2	Ranging:50–87; Median:67.2	SonoVue®	Retrospective	2b
Lu 2018	China	2013.07–2016.07	Mean ± SD:32.62 ± 25.94	Mean ± SD: 72.4 ± 7.2	SonoVue®	Prospective	1b
Mitterberger 2007	Austria	NR	Ranging:1.4–35; Mean:4.6	Ranging:36–83; Mean:62	SonoVue®	Prospective	1b
Mitterberger 2009	Austria	NR	Ranging:2.8–32.2; Mean:8.5	Ranging:45–74; Mean:63.9	SonoVue®	Prospective	1b
Taverna 2011	Italy	NR	Ranging:2.5–9.9	Ranging:45–76; Median:65.9	SonoVue®	RCT	1b
Taymoorian 2007	Germany	2004.01–2006.02	Ranging:4–48; Median:10	Ranging:44–73; Median:66	SonoVue®	Prospective	1b
Wang 2017	China	2014.09–2016.01	Ranging:4.32–10	Mean ± SD:69.6 ± 8.85	SonoVue®	Prospective	1b
Xie 2011	China	2009.06–2010.09	Ranging:4.16–85.80; Median: 14.35	Ranging:45–86; Median:69	SonoVue®	Prospective	1b
Yi 2005	Korea	2003.08–2004.02	Ranging:4–10	Mean ± SD:62 ± 8	Levovist	Prospective	1b
Zhu 2018	China	2014.03–2017.06	Mean ± SD:11.2 ± 6.4	Mean ± SD:68.5 ± 8.3	SonoVue®	Prospective	1b

LOE = Level of evidence, NR = not reported, PSA = prostate specific antigen, RCT = randomized control studies, SD = standard deviation.

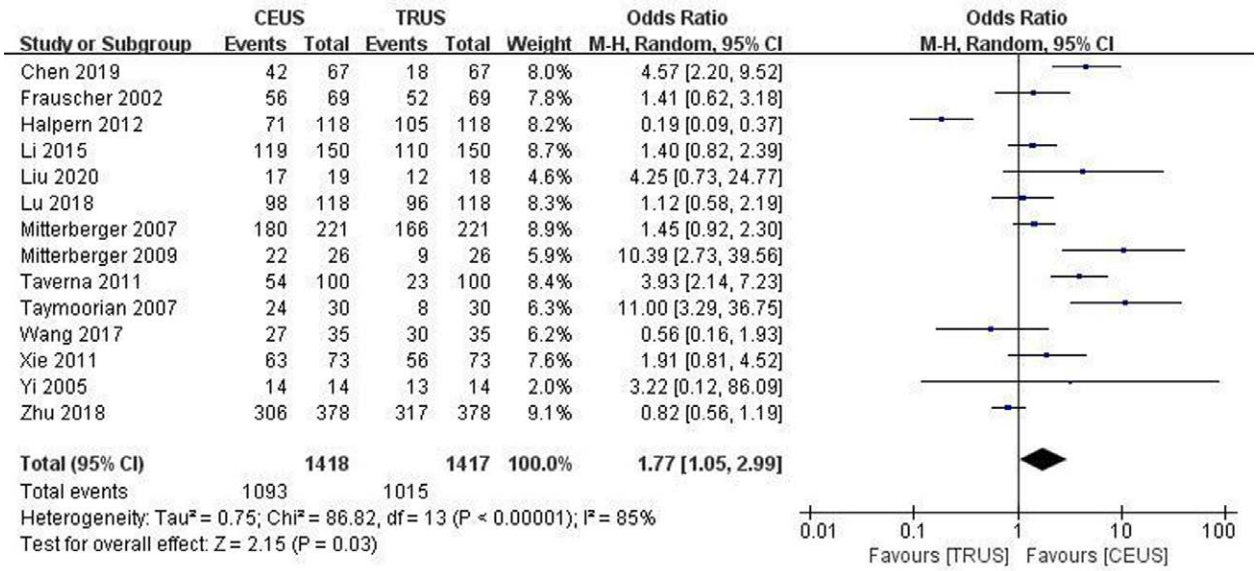

Figure 2. Forest plot and meta-analysis of diagnostic sensitivity comparing CEUS targeted with TRUS guided systematic biopsy. CEUS = contrast-enhanced ultrasound, TRUS = transrectal ultrasonography.

Table 2

Subgroup analyses in terms of diagnostic sensitivity comparing CEUS targeted and TRUS guided prostate biopsy.

Subgroups	No. of studies	OR (95% CI)	*P* value	Study heterogeneity			
				Chi^2	df	I^2	*P* value
China vs other countries							
China	8	1.51 [0.91, 2.51]	.11	21.93	7	68%	**.003**
Other countries	6	2.19 [0.74, 6.48]	.16	63.86	5	92%	**<.001**
Retrospective vs prospective							
Retrospective	3	2.70 [1.05, 6.94]	**.04**	7.14	2	72%	**.03**
Prospective	11	1.58 [0.85, 2.93]	.15	73.66	10	86%	**<.001**
Before 2010 vs after 2010							
Before 2010	5	3.35 [1.30, 8.60]	**.01**	16.20	4	75%	**.003**
After 2010	9	1.34 [0.70, 2.58]	.38	64.67	8	88%	**<.001**

CEUS = contrast-enhanced ultrasonography, OR = odds ratio, TRUS = transrectal ultrasonography.
The p value is bold when <0.05.

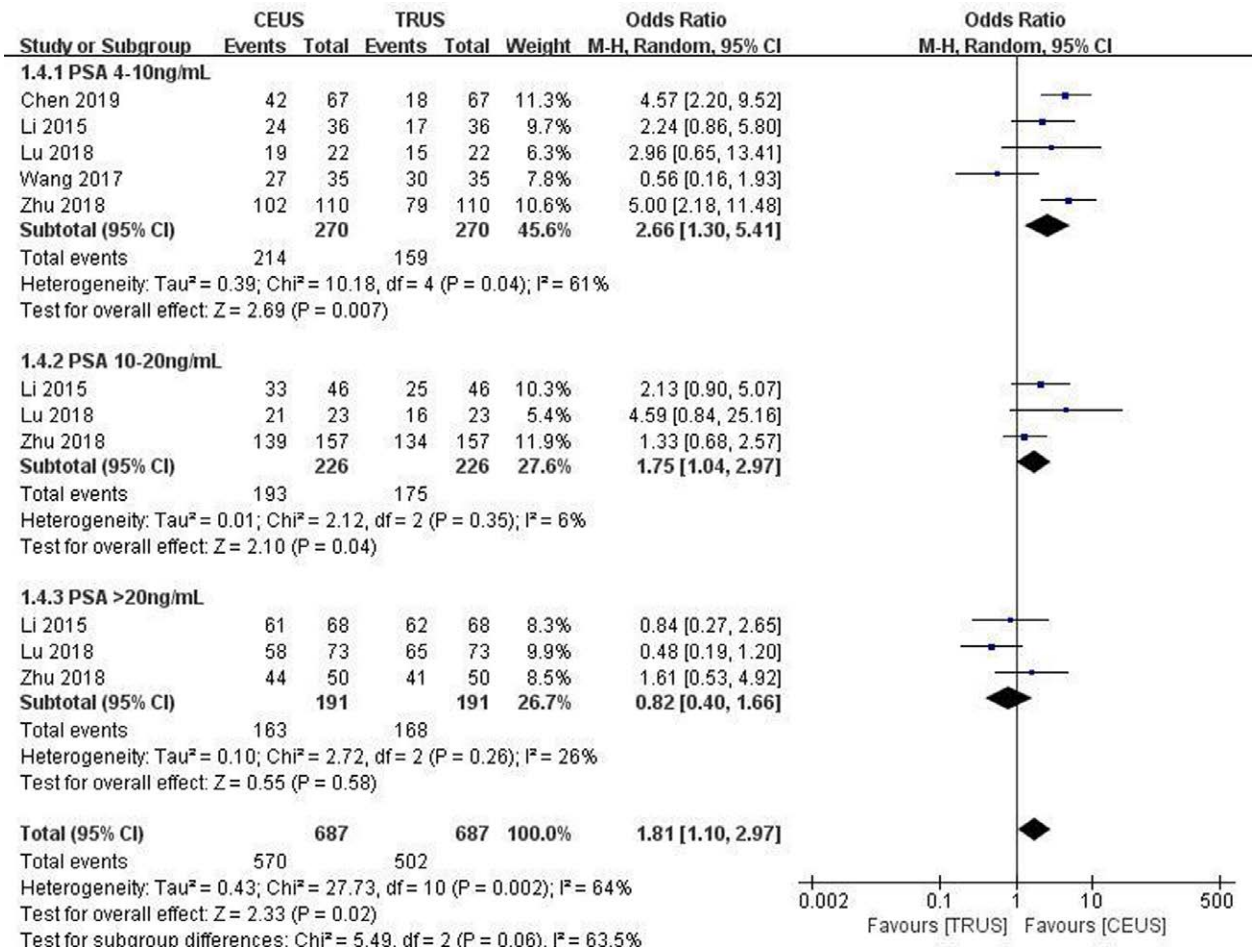

Figure 3. Forest plot and meta-analysis of diagnostic sensitivity comparing CEUS targeted with TRUS guided systematic biopsy at different PSA levels. CEUS = contrast-enhanced ultrasound, PSA = prostate specific antigen, TRUS = transrectal ultrasonography.

Moreover, Chen et al developed a scoring system based on the performance of multiparametric ultrasound to predict peripheral zone PCa and clinically significant PCa, which was found comparable to PI-RADS V2.[31] Despite the promising findings, considering the lack of large-scale trials, the advantages of CEUS only over conventional TRUS remain uncertain. Therefore, we performed this meta-analysis to confirm the diagnostic efficiency of CEUS in patients underwent naïve prostate biopsies.

In the meta-analyses we found that CEUS-guided biopsy had a higher chance of diagnosing PCa in abnormal imaging areas of the prostate gland. CEUS achieved a greater sensitivity than TRUS, especially for patients with a PSA value of 4 to 10 ng/mL. Moreover, the proportion of positive cores and accuracy was higher in the CEUS-guided biopsy. The results indicated that CEUS-targeted biopsy had significant advantages over systematic biopsy in terms of detection rate for patients with PSA values in the gray area, simultaneously decreasing the associated morbidity. However, noticeable heterogeneity in meta-analyses is worthy of concern. According to our subgroup analyses, CEUS-targeted biopsy seemed insufficient to eliminate the need for systematic biopsy. This might be explained by the fact that

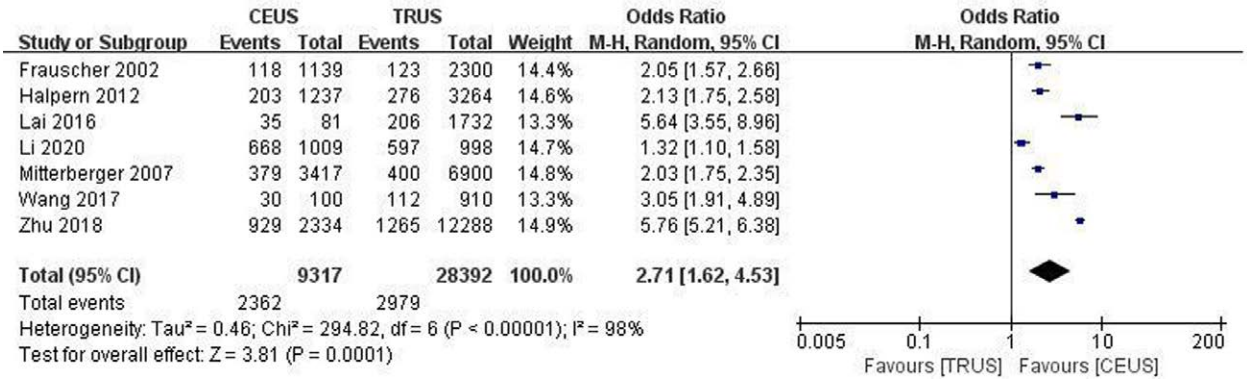

Figure 4. Forest plot and meta-analysis of positive rate of each core comparing CEUS targeted with TRUS guided systematic biopsy. CEUS = contrast-enhanced ultrasound, TRUS = transrectal ultrasonography.

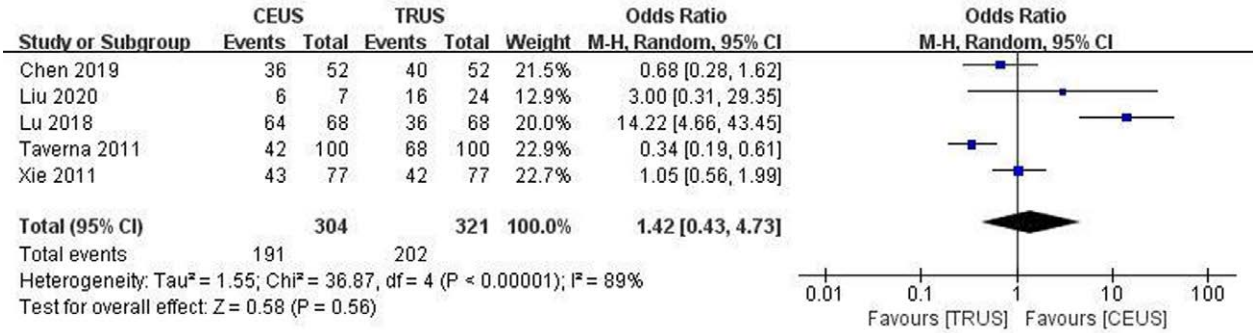

Figure 5. Forest plot and meta-analysis of diagnostic specificity comparing CEUS targeted with TRUS guided systematic biopsy. CEUS = contrast-enhanced ultrasound, TRUS = transrectal ultrasonography.

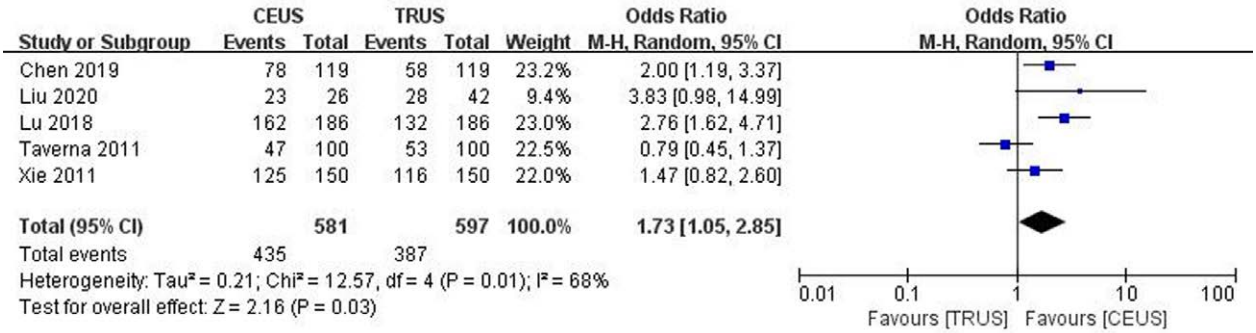

Figure 6. Forest plot and meta-analysis of diagnostic accuracy comparing CEUS targeted with TRUS guided systematic biopsy. CEUS = contrast-enhanced ultrasound, TRUS = transrectal ultrasonography.

hypervascularity is not a direct marker of cancer lesions, and biopsy samples obtained from hypervascular areas were possibly negative, but positive for samples in non-hypervascularized areas of the gland.[26] On the other hand, given the cost-benefit ratio of CEUS in the gray PSA area, Halpern et al also recommended a limited CEUS-targeted biopsy following PSA screening.[16]

For patients with a positive biopsy result, the Gleason score is a well-established indicator of prognosis. Based on previous clinical studies, there was no lethal risk of PCa with a Gleason score of 2 to 4, and only a modest risk with scores of 5 and 6 for patients who underwent conservative treatment.[32–34] In other words, only the clinically significant PCa (Gleason score > 6) requires aggressive management, and active surveillance alone may be reasonable for low-grade PCa.[35] Therefore, it is important to define the grading of PCa for the choice of therapeutic applications. We investigated the sensitivity of CEUS to clinically significant PCa in the present meta-analysis, showing that CEUS was more capable of discovering PCa with higher Gleason scores. This is because lesions with higher Gleason scores are usually associated with growing small vessels.[36,37] The ability to detect more aggressive lesions may enhance the clinical application prospects of CEUS for predicting PCa prognosis.

In recent years, a number of meta-analyses have demonstrated that multiparametric magnetic resonance imaging (mpMRI) informed targeted prostate biopsy is superior to systematic biopsy alone in diagnostic pathways for PCa.[4,38] According to current guidelines, mpMRI combined with targeted biopsy is strongly recommended, and ultrasound plays a minor role in

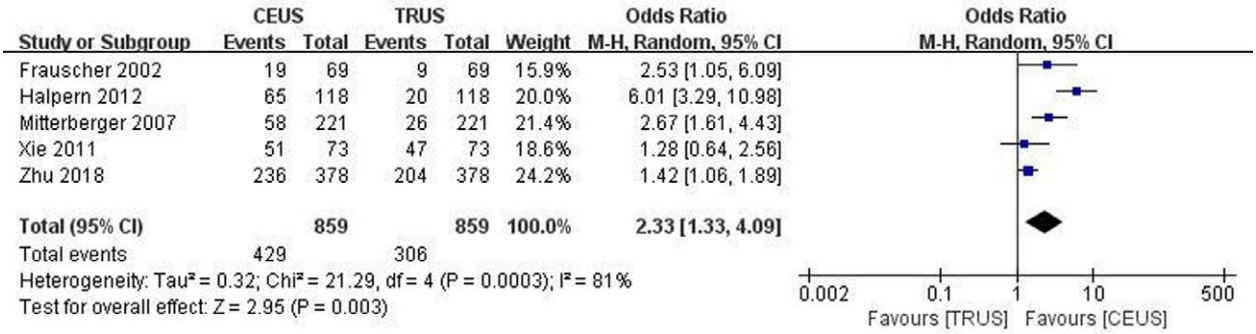

Figure 7. Forest plot and meta-analysis of detection rate of clinical significant PCa comparing CEUS targeted with TRUS guided systematic biopsy. CEUS = contrast-enhanced ultrasound, PCa = prostate cancer, TRUS = transrectal ultrasonography.

the accurate diagnosis of PCa.[39] However, mpMRI-targeted biopsy requires specific devices and is relatively expensive and time consuming. Moreover, MRI is contraindicated for patients with implants, pacemakers, or claustrophobia. Lately, a population-based trial showed that, biopsy performed only in men with positive MRI was noninferior to standard biopsy for detecting clinically significant PCa.[40] In addition, a prospective multicenter study indicated ultrasound directed prostate biopsy detected clinical significant PCa equally well comparing with MRI targeted biopsy.[41] Therefore, the ultrasound-based imaging including CEUS still plays a valuable role for PCa screening.

To the best of our knowledge, this is the first meta-analysis to include a comprehensive search strategy that compared CEUS-targeted and the currently widely used systematic biopsy. However, we acknowledge the inherent limitations of this study. First, there is no standard procedure for CEUS-guided biopsies. Significant variability probably existed across the involved studies with regard to the definition of suspicious lesions, the number of target cores, and the experiences of the radiologists who interpreted the images and the different facilities or agents used. Second, the heterogeneity among the studies in the comparisons compelled us to use random-effect models. Third, sensitivity and specificity were analyzed in our study, but the interference of missing diagnoses was not ruled out. Finally, the different designs of each study did not allow us to address an established conclusion, considering the inconsistent results from subgroup analyses.

5. Conclusions

Although the role of systematic biopsy is still far from obsolete, our findings suggests that CEUS-guided prostate biopsy helped improve the diagnostic sensitivity, especially in the PSA gray area, with fewer cores. Furthermore, patients could benefit from CEUS in terms of diagnostic efficiency to detect clinically significant PCa, leading to more individual management. In light of these limitations, further randomized controlled trials focusing on the accuracy of CEUS-targeted prostate biopsies are still warranted.

Author contributions

XW, DBW and CBQ designed the meta-analysis. QSM, LLF, HT and JHJ performed the paper search and data extraction. QLG and JHJ performed the data analyses. MZ wrote the manuscript. DBW and CBQ supervised the whole process of the draft.
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Writing – review & editing: Qinglu Gao.

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