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The Micro-ultrasound Guided Prostate Biopsy in Detection of Prostate Cancer: A Systematic Review and Meta-Analysis

Chengyu You, Xianhui Li, Yuelin Du, Lei Peng, Hui Wang, Xiaojun Zhang, Anguo Wang*

Department of Urology, Nanchong Central Hospital, The Second Clinical College, North Sichuan Medical College, Nanchong, 63700, Sichuan, China.

*Correspondence: Anguo Wang, MD, Department of Urology, Nanchong Central Hospital, The Second Clinical College, North Sichuan Medical College, Nanchong, 63700, Sichuan, China. (Tel: 15583030887, Fax: 0817-2222009, E-mail: wanganguo2019@163.com).

Abstract

Background: To compare the detection rate of micro-ultrasound with multiparametric magnetic resonance imaging targeted biopsy (mpMRI-TB) for prostate cancer diagnosis.

Methods: The studies on micro-ultrasound prostate biopsy for prostate cancer diagnosis were searched in PubMed, Cochrane library and EMBASE databases from inception to April.2021. we performed a systematic review and cumulative meta-analysis based on search results using Software Rev-Man 5.3.

Results: A total of 11 studies involving 1081 patients were included. The Meta-analysis showed that no significant difference was found between micro-ultrasound and mpMRI-TB in the total detection of prostate cancer(OR:1.01, 95%CI:0.85~1.21, p=0.89), of Grading Groups(GG)=1(OR: 0.92, 95%CI:0.68~1.25, p=0.59),of GG≥2(OR:1.01, 95%CI:0.83~1.22, p=0.92), and of GG≥3(OR: 1.31, 95%CI:0.95~1.81, p=0.10).

Conclusions: Micro-ultrasound guided prostate biopsy provides comparable detection rates for prostate cancer diagnosis with the mpMRI-TB, which is expected to challenge mpMRI-TB in the diagnosis of prostate cancer.

Key Words: micro-ultrasound, magnetic resonance imaging, prostate cancer, biopsy, detection

Introduction

Prostate cancer (PCa) is the most common urinary tumor, of which incidence is the second worldwide, and which is the sixth cause of cancer death in men[1]. According to International Society of Urological Pathology (ISUP) 2014 grade group (GG) system, the GG≥2 was regarded as clinically significant PCa. Inversely, the GG=1 was considered as clinically insignificant PCa[2]. Prostate biopsy is a reliable diagnosis of PCa, including systematic biopsy and magnetic resonance imaging targeted prostate biopsy(MRI-TB)[3].Among them, the ultrasound guided systematic biopsy is classical, but its reliability is poor since major accuracy of prostate lesions are isoechoic which are invisible[4]. Therefore, multiparametric MRI-TB (mpMRI-TB) recently has been widely carried out because of its reliability, accuracy and lower complications, including in-bore MRI-TB, MRI ultrasound fusion (FUS-TB) and cognitive registration[5, 6]. For clinically significant PCa, the sensitivity and specificity of mpMRI-TB was 91% and 37%, respectively[7].

Due to the contraindications, cost and renal injury risk caused by contrast agents of MRI[8, 9], many new ultrasonic technologies are emerging including shear wave elastography, contrast-ultrasound, and high resolution micro-ultrasound[10-12]. Among them, the micro-ultrasound is the most outstanding, whose detection rate of PCa is higher than traditional systematic biopsy, and even comparable to mpMRI-TB[13, 14]. In addition, current studies showed that its sensitivity and specificity was up to 91% and 49%, which is on a par with mpMRI-TB[15]. Hence, we performed a systematic review and meta-analysis to discuss differences in prostate cancer detection rate between micro-ultrasound and mpMRI-TB.

METHODS

According to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Statement**,** this review was registered prospectively (CRD 42021266952) in the PROSPERO database.

Literature Search

A comprehensively systematic literature search was performed in April 2021 using PubMed, the Cochrane Library, EMBASE databases by using search terms, including “micro-ultrasound”, “prostate”, and “biopsy”. Restriction that publication language was imposed in the English. No restrictions to publication date. Then references that come from relevant studies were manually retrieved using PubMed database.

The studies focused on patients who underwent consecutively micro-ultrasound and mpMRI-TB, and reported their corresponding results were included. Besides, we did not include letters, cases, reviews, and studies which are irrelevant to the theme or lack complete data.

Quality Assessment and Data Extraction

The Quality Assessment of Diagnostic Accuracy Studies-2(QUADAS-2) tool was used to evaluate the risk of bias and applicability concerns of the included studies[16]. For the data of interest, the following items were included: the author, publication year, age, prostate specific antigen (PSA), prostate volume, number of patients abnormal digital rectal examination (DRE), type of mpMRI-TB, number of patients underwent consecutively two biopsy techniques, number of cores and number of detection.

The above steps (literature search, quality assessment and data extraction) were independently completed by two of us (CY.Y and XH.L). All disagreements were resolved by a senior author (AG.W) after public discussion.

Statistical analysis

The odds ratios (OR) were calculated for continuous and dichotomous variables respectively, with 95% confidence intervals (CIs). The heterogeneity between studies was assessed by using the chi-squared and I- squared test. Random-effects models were used for cumulative analyses which were high heterogeneity(I^2>50%). Otherwise, fixed-effects models were used.

A subgroup analysis was performed according to the type of mpMRI-TB. Finally, P value of <0.05 was considered as a statistical significance. Analysis was accomplished by The Review Manager software (RevMan) Version 5.3.

Results

In the end, a total of 11 studies were included[17-27]. Among them, 4 studies were conference abstract[18, 22, 24, 26], and the remaining were prospective[17, 19-21, 23, 25, 27]. The specific process was shown in Fig.1. The characteristics of included studies were shown in Table 1. Bias risk assessment and applicability results showed that the quality of 6 included studies were high, and of 5 included studies were moderate, which were shown in Table 2.

Detection Rate of Pca

No significant difference between micro-ultrasound and mpMRI-TB was found for clinically insignificant PCa(GG=1) (OR: 0.92, 95%CI:0.68~1.25, p=0.59,Fig.2), clinically significant Pca(GG≥2) (OR:1.01, 95%CI:0.83~1.22, p=0.92,Fig.3), GG≥3(OR: 1.31, 95%CI:0.95~1.81, p=0.10,Fig.4), and overall PCa detection rate(OR:1.01, 95%CI:0.85~1.21, p=0.89, Fig.5).

Publication bias

The potential publication bias was analyzed by funnel plots. There was publication bias in most of the outcomes. For example, the funnel plot of overall PCa detection rate showed the obvious asymmetry (Fig.6).

Subgroup Analysis

Whether compared with FUS-TB or cognitive registration, the subgroup analysis indicated that there was no significant difference between two techniques in the clinically insignificant PCa(GG=1) (OR:0.79,95%CI:0.51~1.21, p=0.28, and OR: 1.04,0.62~1.74, p=0.90, respectively, Fig.2), clinically significant Pca(GG≥2) (OR:1.09, 95%CI:0.84~1.41, p=0.51, and OR:0.88,95%CI:0.65~1.20,p=0.43, respectively, Fig.3), GG≥3(OR:1.33, 95%CI:0.95~1.86, p=0.09, and OR:1.00, 95%CI:0.11~9.23,p=1.00, respectively, Fig.4), and overall PCa detection rate(OR:1.00, 95%CI:0.78~1.28, p=1.00, and OR:0.99, 95%CI:0.75~1.31, p=0.94, respectively, Fig.5).

Discussion

Owing to the characteristics of accuracy, detection, cost and learning curve, micro-ultrasound technology has been widely concerned. The results of Meta-analysis suggested that there was no significant difference between micro-ultrasound and mpMRI-TB in the detection rate of PCa. The results of subgroup analysis results were consistent.

Although mpMRI-TB has achieved excellent performance in prostate cancer diagnosis, its limitations still exist. On the one hand, the applicability of mpMRI-TB was restricted because of contraindications on MRI, including claustrophobia, pacemakers, and renal failure[9, 28]. Meanwhile, the cost of mpMRI-TB was controversial[29]. Fortunately, the bi-parametric MRI improved above limitations, with similar diagnostic efficacy in diagnosing PCa[30, 31].On the one hand, the false positive rate and false negative rate of mpMRI-TB were 5%-15% and 16-35%, respectively[32, 33]. In addition, the results of mpMRI-TB were statistically different among interobservers. It was proved by previous study, which explored the concordance among experienced radiologists and found that the kappa for peripheral zone and transition zone prostate lesions were respectively only 0.59 and 0.509[34]. What's more, Wegelin et al. claimed that registration errors were associated with biopsy results because FUS-TB and cognitive registration are both executed by transrectal ultrasound probe[35]. Klotz et al. also noted the challenges of post mpMRI-TB care management[21].

Recently, the micro-ultrasound developed by Exact Imaging emerges as focal points in prostate cancer diagnosis. Rather than the traditional 8 MHz, it runs under the frequency of 29 MHz. Besides, its resolution down to 70 mm, which is 300% higher than the conventional ultrasounds[36]. Obviously, it can clearly show the microstructures and tissue which well explains our Meta-analysis results. Moreover, the learning curve of micro-ultrasound is observably shorter than mpMRI-TB, whose learning curve is stable after 15 cases, far lower than 40 cases for mpMRI-TB[21, 37]. The prostate risk identification using micro-ultrasound (PRI-MUS) protocol is used for micro-ultrasound to identify suspicious prostate lesions[38]. For sensitivity, the PRI-MUS is comparable to prostate imaging reporting and data system version 2.1(PI-RADS 2.1) for mpMRI.(80% versus 86.8%)[38, 39]. Regrettably, the current version PRI - MUS may cause some amount of missed diagnosis, because it only identifies suspicious prostate lesions in peripheral zone accounting for 70%-80% of PCa[20]. However, mpMRI-TB could identify suspicious region both in peripheral and transition zone, which worked for the risk bias. Therefore, mpMRI-TB can be a supplement to micro-ultrasound biopsy in the clinic. Lughezzani et al. stated that micro-ultrasound diagnosis accuracy was associated with prostate volume and tumor location, especially in the transition zone[40]. Socarras et al. supported it and thought that micro-ultrasound performance is inferior to mpMRI because of penetration limitation[25]. Socarras et al. also indicated that micro-ultrasound could replace conventional ultrasound in mpMRI-TB to further improve the diagnostic efficacy, especially in high suspicion of PCa with negative MRI and indeterminate lesions[25]. Claros et al. confirmed it by comparing MRI cognitive guided micro-ultrasound biopsies with robotic ultrasound MRI fusion biopsies[19]. By the way, Saita et al. found that micro-ultrasound technology can also be appropriate for bladder cancer, and manifested that the detection rate of bladder cancer in lamina propria and in muscular layer reached 100% and 71.4%, respectively[41].

Some inherent limitations cannot be avoided, although rigorous methodology of review and quantitative synthesis were performed. First, the included studies contain conference abstract and journal articles and lack of high quality randomized controlled studies. Second, the patients included suspicion of PCa, biopsy naïve, and previous negative biopsies, but there was no subgroup analysis on patients or on the type of study. Third, all included patients underwent MRI before micro-ultrasound biopsy, which obviously caused the information bias of detection rate. But some included studies ignored the blind. Finally, there is publication bias for included studies.

Conclusions

Micro-ultrasound guided prostate biopsy provides comparable detection rates for prostate cancer diagnosis with the mpMRI-TB. Due to high sensitivity, accurate positioning, low cost, and short learning curve, micro-ultrasound is expected to challenge mpMRI-TB in the diagnosis of prostate cancer. However, further quality studies are needed to compare the diagnostic efficacy of micro-ultrasound and mpMRI-TB.

Declarations

Compliance with Ethics Standards

Not applicable

Conflict of Interest

None declared.

Availability of Data and Materials

All data generated and analyzed during this study are included in this published article.

Authors' Contributions

Conceived and designed the experiments: Anguo Wang. Analyzed the data: Chengyu You, Yuelin Du, Xianhui Li and Hui Wang. Contributed reagents/materials/analysis: Yuelin Du, Xianhui Li, Lei Peng, and Xiaojun Zhang. Wrote the manuscript: Chengyu You and Xianhui Li. All authors have read and approved the final manuscript.

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Abbreviations

Pca: prostate cancer

ISUP: International Society of Urological Pathology

GG: grade group system

MRI-TB: magnetic resonance imaging targeted prostate biopsy

mpMRI-TB: multiparametric magnetic resonance imaging targeted prostate biopsy

FUS-TB: MRI ultrasound fusion

PSA: prostate specific antigen

DRE: digital rectal examination

OR: odds ratio

Cis: confidence intervals

PRI-MUS: prostate risk identification using micro-ultrasound protocol

PI-RADS 2.1: prostate imaging reporting and data system version 2.1

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Table 1: Characteristics of included studies.

Author,year	Age(years)	PSA(ng/dl)	prostate volume(ml)	NO. of abnormal DRE	type of mpMRI-TB	NO. of underwent consecutively two biopsy techniques	NO. of cores(micro-ultrasound/mpMRI-TB)
Abouassaly et al.2020	66(59.5-68.5)[a]	5.39(4.13-8.74)	38(24-50)	7	FUS-TB	19	2（2-3）/3(2.5-3)
Astobieta et al.2018	NA	NA	NA	35	cognitive	35	NA
Claros et al.2020	68(65-72)	7.8(5.6-11.4)	57(37-69.3)	47	cognitive	47	3(2-4)
Eure et al.2019	65.6±4.4[b]	6±1.1	38.8±8.2	9	cognitive	9	2-3[c]
Klotz et al.2021	67(61-72)	7(5.1-10)	38(28-53)	NA	Site G cognitive	77	NA
					Site J FUS-TB	62	
					Site K cognitive	14	

Lopez et al.2019	NA	NA	NA	51	NA	51	NA
Lughezzani et al.2020	65(59-70)	7.3(5.2-9.9)	45(30-70)	72	FUS-TB	320	4(3-6)
Perez et al.2019	NA	8.5(4.2-40)	NA	NA	cognitive	55	NA
Socarras et al.2020	62(58-68)	6.5(4.7-9.2)	47(32-67)	31	cognitive	194	2(1-5)/1(0-4)
Staerman et al.2019	NA	NA	NA	NA	NA	39	NA
Wiemer et al.2020	70(64-74)	7.59(5.78-11.5)	53(35.5-76.5)	42	FUS-TB	159	2-3

[a]: Median(Interquartile range,IQR); [b]: Mean±Standard; [c]:range; PSA: prostate specific antigen; DRE: digital rectal examination; mpMRI-TB: multiparametric magnetic resonance imaging targeted prostate biopsy; FUS-TB: magnetic resonance imaging ultrasound fusion; NA: not available;

Table 2: Bias risk and applicability concerns of included studies.

Study	Risk of Bias				Applicability Concerns			Quality
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard	
Abouassaly et al.2020	L	U	H	L	L	L	L	H
Astobieta et al.2018	L	U	U	U	L	U	U	H
Claros et al.2020	L	H	H	L	L	L	L	H
Eure et al.2019	L	L	L	U	L	L	L	M
Klotz et al.2021	L	H	L	U	L	U	U	H
Lopez et al.2019	L	U	H	U	L	L	L	H
Lughezzani et al.2020	L	L	U	L	L	L	L	M
Perez et al.2019	L	H	U	U	L	L	L	H
Socarras et al.2020	L	L	U	L	L	L	L	M
Staerman	L	U	L	U	L	L	L	M

et al.2019								
Wiemer et al.2020	L	L	U	L	L	L	L	M

L:Low;U:Unclear;H:High;M:moderate.

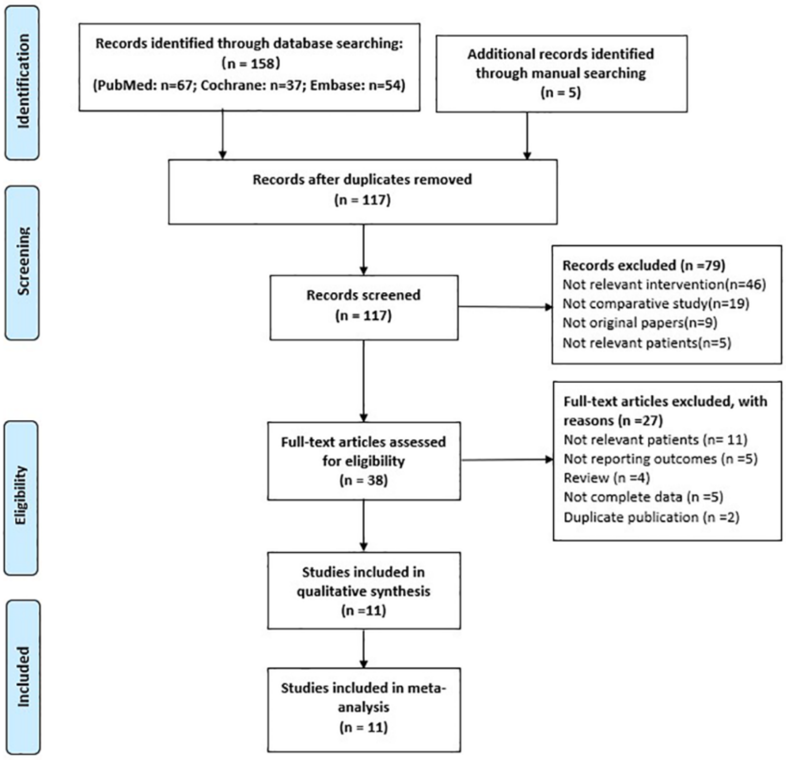

Fig.1: PRISMA flow diagram.

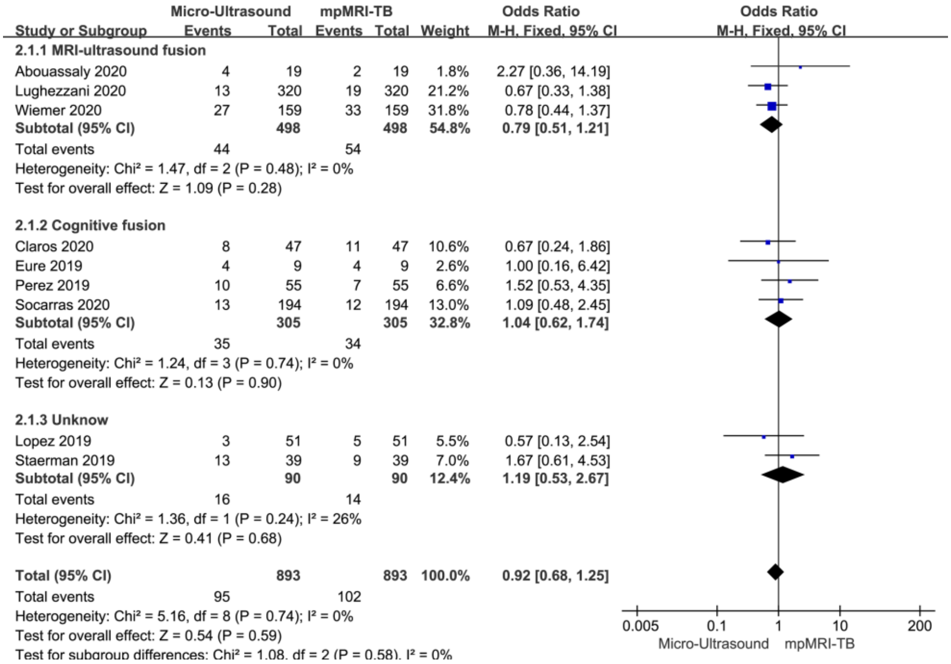

Fig.2: Forest plot and meta-analysis of detection rate for clinically insignificant PCa (GG=1).

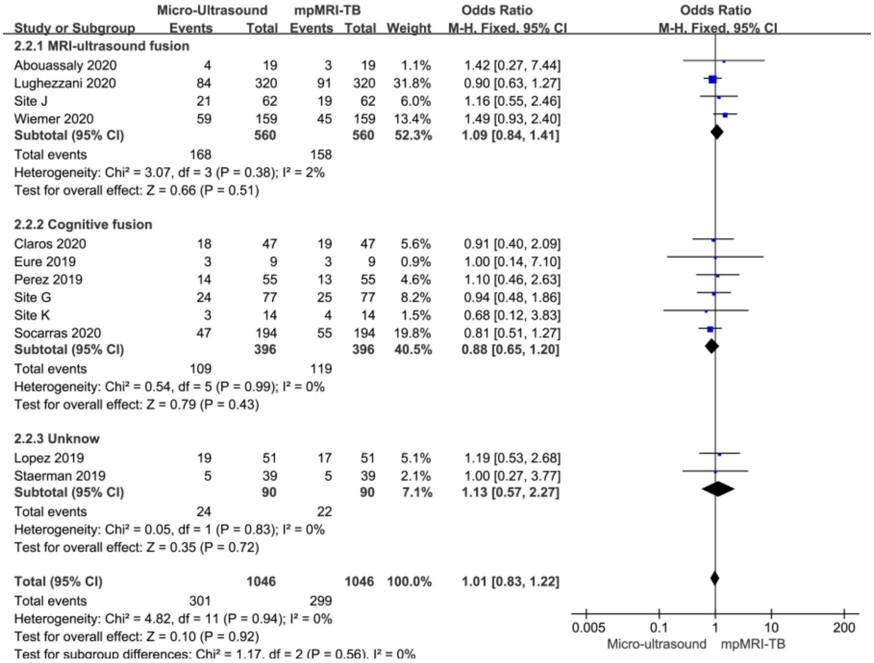

Fig.3: Forest plot and meta-analysis of detection rate for clinically significant Pca (GG≥2).

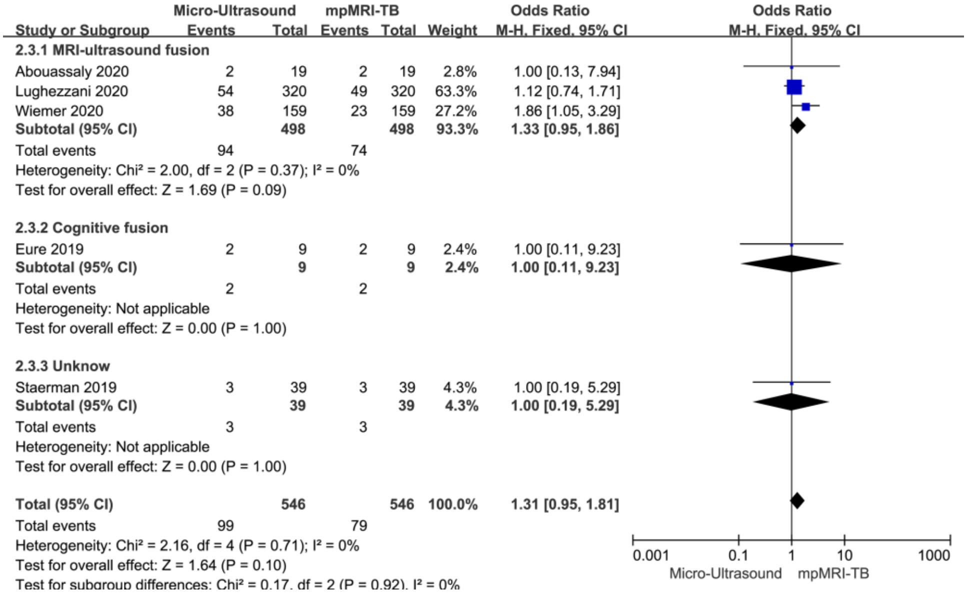

Fig.4: Forest plot and meta-analysis of detection rate for GG≥3.

Study or Subgroup	Micro-Ultrasound Events	Micro-Ultrasound Total	mpMRI-TB Events	mpMRI-TB Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.4.1 MRI-ultrasound fusion						
Abouassaly 2020	8	19	5	19	1.2%	2.04 [0.52, 8.00]
Lughezzani 2020	97	320	110	320	31.2%	0.83 [0.60, 1.16]
Site J	21	62	19	62	5.1%	1.16 [0.55, 2.46]
Wiemer 2020	86	159	78	159	14.6%	1.22 [0.79, 1.90]
Subtotal (95% CI)		**560**		**560**	**52.0%**	**1.00 [0.78, 1.28]**
Total events	212		212			
Heterogeneity: Chi² = 3.20, df = 3 (P = 0.36); I² = 6%						
Test for overall effect: Z = 0.00 (P = 1.00)						
2.4.2 Cognitive fusion						
Astobieta 2018	20	35	12	35	2.1%	2.56 [0.97, 6.72]
Claros 2020	26	47	30	47	5.4%	0.70 [0.31, 1.60]
Eure 2019	7	9	7	9	0.6%	1.00 [0.11, 9.23]
Perez 2019	24	55	20	55	4.6%	1.35 [0.63, 2.91]
Site G	24	77	25	77	7.0%	0.94 [0.48, 1.86]
Site K	3	14	4	14	1.3%	0.68 [0.12, 3.83]
Socarras 2020	60	194	67	194	18.8%	0.85 [0.56, 1.30]
Subtotal (95% CI)		**431**		**431**	**39.8%**	**0.99 [0.75, 1.31]**
Total events	164		165			
Heterogeneity: Chi² = 5.71, df = 6 (P = 0.46); I² = 0%						
Test for overall effect: Z = 0.07 (P = 0.94)						
2.4.3 Unknow						
Lopez 2019	22	51	22	51	5.1%	1.00 [0.46, 2.19]
Staerman 2019	18	39	14	39	3.1%	1.53 [0.62, 3.79]
Subtotal (95% CI)		**90**		**90**	**8.2%**	**1.20 [0.66, 2.17]**
Total events	40		36			
Heterogeneity: Chi² = 0.48, df = 1 (P = 0.49); I² = 0%						
Test for overall effect: Z = 0.60 (P = 0.55)						
Total (95% CI)		**1081**		**1081**	**100.0%**	**1.01 [0.85, 1.21]**
Total events	416		413			
Heterogeneity: Chi² = 9.74, df = 12 (P = 0.64); I² = 0%						
Test for overall effect: Z = 0.13 (P = 0.89)						
Test for subgroup differences: Chi² = 0.35, df = 2 (P = 0.84), I² = 0%						

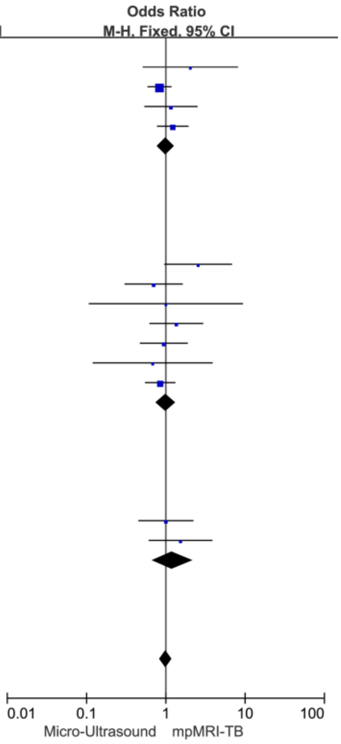

Fig.5: Forest plot and meta-analysis of overall PCa detection rate (GG≥1).

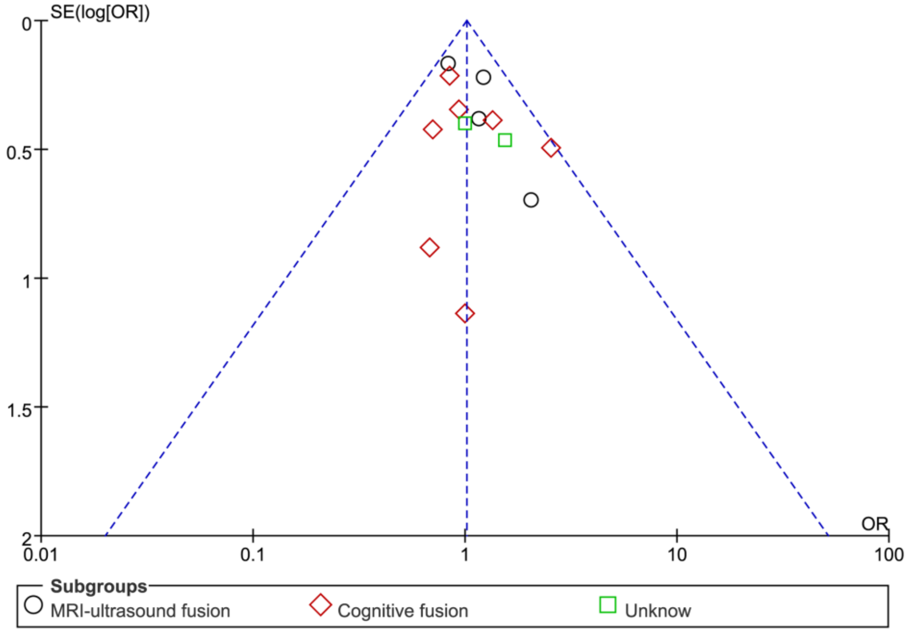

Fig.6: Funnel plots of publication bias for overall PCa detection rate.