Review Article

Optimizing biopsy strategy for prostate cancer: Bayesian framework of network meta-analysis and hierarchical summary receiver operating characteristic model for diagnostic accuracy

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ABSTRACT

Overdiagnosis and overtreatment are well known problems in prostate cancer (PCa). The transrectal ultrasound (TRUS) Guided biopsy (GB) as a current gold standard investigation has a low positive detection rate resulting in unnecessary biopsies. The choice of optimal biopsy strategy needs to be defined. Therefore, we undertook a Bayesian network meta analysis (NMA) and Bayesian prediction in the hierarchical summary receiver operating characteristic (HSROC) model to present a method for optimizing biopsy strategy in PCa. Twenty eight relevant studies were retrieved through online databases of EMBASE, MEDLINE, and CENTRAL up to February 2020. Markov chain Monte Carlo simulation and Surface Under the Cumulative RAnking curve were used to calculate the rank probability using odds ratio with 95% credible interval. HSROC model was used to formulate the predicted true sensitivity and specificity of each biopsy strategy. Six different PCa biopsy strategies including transrectal ultrasound GB (TRUS GB), fusion GB (FUS GB), fusion + transrectal ultrasound GB (FUS + TRUS GB), magnetic resonance imaging GB (MRI GB), transperineal ultrasound GB (TPUS GB), and contrast enhanced ultrasound GB were analyzed in this study with a total of 7584 patients. These strategies were analyzed on five outcomes including detection rate of overall PCa, clinically significant PCa, insignificant PCa, complication rate, and HSROC. The rank probability showed that the overall PCa detection rate was higher in FUS + TRUS GB, MRI GB, and FUS GB. In terms of clinically significant PCa detection, FUS + TRUS GB and FUS GB had a relatively higher clinically significant PCa detection rate, whereas TRUS GB had a relatively lower rate for clinically significant PCa detection rate. MRI GB (91% and 81%) and FUS GB (82% and 83%) had the highest predicted true sensitivity and specificity, respectively, whereas TRUS GB (62% and 83%) had a lower predicted true sensitivity and specificity. MRI GB, FUS GB, and FUS + TRUS GB were associated with lower complication rate, whereas TPUS GB and TRUS GB were more associated with higher complication rate. This NMA and HSROC model highlight the important finding that FUS + TRUS GB, FUS GB, and MRI GB were superior compared with other strategies to avoid the overdiagnosis and overtreatment of PCa. FUS GB, MRI GB, and FUS + TRUS GB had lower complication rates. These results may assist in shared decision making between patients, carers, and their surgeons.

INTRODUCTION

Prostate cancer (PCa) is the second most common diagnosed malignancy in males worldwide.[1] and the fifth leading cause of cancer death in men.[2] In Indonesia, PCa is the third most common urologic cancer in men according to the GLOBOCAN 2012 study.[3]

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Currently, the worldwide usage of the diagnostic strategy of PCa consisting of serum prostate-specific antigen (PSA) measurement, digital rectal examination, and transrectal ultrasound-guided biopsies (TRUS-GB) has improved the detection rate of early PCa.[4] The European Association of Urology, the US Preventive Services Task Force, and the UK National Institute for Health and Care Excellence suggest transrectal ultrasound (TRUS)-guided biopsy (GB) as a standard investigation in the diagnosis of PCa.[5] However, this biopsy protocol resulted in a positive detection rate of only 17%–36%,[6,7] with low sensitivity of 27%–40.3% which could easily carry a high rate of missed cancer.[8] The dilemma being encountered by physicians was to decide whether or not to treat the patient in the initial setting of a negative prostate biopsy. Because PCa is often multifocal , the possibility exists that these patients may have cancer despite an initial negative biopsy. A significant number of patients (13%–41%) with persistently elevated PSA after an initial negative biopsy had a positive repeat biopsy suggesting that this method is associated with underdetection of high-grade PCa and overdetection of low-grade cancers. The ideal systematic biopsy strategy remains to be defined.[9-12]

With the problem of overdiagnosis and overtreatment of PCa, several imaging-GB strategies had been utilized in an effort to increase the PCa detection rate.[13] It is difficult to compare and provide the optimal biopsy strategy due to the absence of direct head-to-head statistical comparison and limited evidence. Therefore, we undertook the network meta-analysis (NMA) and anticipated it to provide a hierarchy of diverse methods in a wide spectrum of population.[14,15] Six different PCa biopsy strategies, consisting of TRUS-GB, transperineal ultrasound-GB (TPUS-GB), contrast-enhanced ultrasound-GB (CEUS-GB), magnetic resonance imaging-GB (MRI-GB), fusion-GB (FUS-GB), and FUS-GB plus TRUS-GB, and five clinical outcomes, consisting of overall PCa detection, significant PCa detection, insignificant PCa detection, complication rate, and hierarchical summary receiver operating characteristics (HSROC), were analyzed in this study.

METHODS

Literature search strategy and study selection

Eligible articles were extracted from online databases including EMBASE, MEDLINE, and CENTRAL up to February 2020. The search strategy included two parts (PCa and biopsy strategy) using certain keywords in combination with Medical Subject Headings terms and words: "prostate cancer," "biopsy strategy," "targeted biopsy," "systematic biopsy," "TRUS-GB," "TPUS-GB," "FUS-GB," "FUS + TRUS-GB," "CEUS-GB," and "MRI-GB." Full texts and abstracts were initially and independently screened by two reviewers and were assessed according to inclusion and exclusion criteria. Insignificant studies were excluded. Discrepancies between two reviewers were settled in a discussion with a third reviewer. Ethical approval was not required because it did not contain individual patient's data. The PICO of the study is explained in Table 1.

Data extraction and quality assessment

Studies included in this article met the following criteria: (1) subjects were patients with PCa; (2) the required data to formulate NMA and HSROC was available; (3) the comparison was between at least two different biopsy strategies; (4) the article was in English; and (5) studies were either randomized controlled trials (RCTs) or original studies. Two reviewers (IAR and IF) individually extracted and reviewed data based on study selection criteria using standardized, structured, and piloted extraction forms. The results were checked and discussed by IAR and IF to finalize the included studies. Any discrepancies were resolved in discussion with a third reviewer. For each included study, important information was extracted including author's name, publication year, number of sample sizes, mean age, prostate volume, mean PSA level, study design, intervention, overall PCa detection rate, clinical significant PCa detection rate, insignificant PCa detection rate, complication rate, true positive, false positive, false negative, and true negative. If the required data could not be directly acquired from articles, it was manually calculated using available data according to studies.[16,17] Table 2 demonstrates all of the above mentioned data. Cochrane Collaboration's risk of bias tool was used to assess the appropriateness of the included studies and the strength of the evidence. The investigations of risk of bias consisted of (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; and (7) other bias. Low, high, or unclear risk of bias was used for judgments. Risk of bias assessment is reported in Figure 1. Figure 2 shows a detailed literature search and selection process. Publication bias was examined by Begg's and Egger's tests.[18]

Outcomes

Overall PCa detection rate, clinically significant PCa detection rate, insignificant PCa detection rate, complication rate, and HSROC were ultimately analyzed as endpoints

Table 1: PICO of the study

PICO	Description
Patient	Patient with clinical suspicion of prostate cancer (high PSA or abnormal DRE)
Intervention	TRUS-GB (6, 8, 10, 12, 15, and 18 cores), TPUS-GB, CEUS-GB, FUS-GB, MRI-GB, and FUS + TRUS-GB
Control	TRUS-GB (6, 8, 10, 12, 15, and 18 cores), TPUS-GB, CEUS-GB, FUS-GB, MRI-GB, and FUS + TRUS-GB
Outcome	Overall prostate cancer, clinically significant, insignificant detection rate, complication rate, sensitivity, and specificity

PSA=Prostate-specific antigen, DRE=Digital rectal examination, TRUS=Transrectal ultrasound, GB=Guided biopsy, TPUS=Transperineal ultrasound, CEUS=Contrast-enhanced ultrasound, FUS=Fusion, MRI=Magnetic resonance imaging

Table 2: Baseline characteristics of selected studies

Author, year	Intervention	True Positive (TP)	False Positive (FP)	False Negative (FN)	True Negative (TN)	Pca detection rate		Clinical Significant Pca detection rate		Insignificant PCa detection rate		Mean Age	Prostate volume	Mean PSA level	Study design
						Event	Sample Size	Event	Sample Size	Event	Sample Size				
Ardeshir R Rastinehad, 2014	MRI+TRUS (FUS) GB	38	13	7	35	53	105	47	105	6	105	65.8	NA	9.2	RCT
	TRUS GB 12 cores	44	4	16	41	51	105	34	105	17	105				
	FUS+TRUS GB	NA	NA	NA	NA	66	105	51	105	19	105				
Arnout Alberts, 2017	TRUS GB 6 cores	19	30	NA	130	49	179	19	179	30	179	73.2	48	4.3	RCT
	MRI+TRUS (FUS) GB	24	47	4	87	71	158	24	158	47	158				
	TRUS GB 12 cores	19	45	5	94	64	158	19	158	45	158				
	MRI GB	17	11	7	20	28	48	17	48	11	48				
Christian Arsov, 2015	-MRI GB	31	8	NA	67	39	106	31	106	8	106	66	54	10	RCT
	MRI+TRUS (FUS) GB	27	8	6	69	35	104	27	104	8	104				
	FUS+TRUS GB	NA	NA	NA	NA	41	104	33	104	8	104				
	TRUS GB 12 cores	26	10	5	68	36	104	26	104	10	104				
Eduard Baco, 2015	MRI+TRUS (FUS) GB	38	13	7	35	51	86	38	86	13	86	65	43	7.4	RCT
	TRUS GB 12 cores	44	4	16	41	48	89	44	89	4	89				
Ethan J Halpern, 2005	CEUS GB	1	10	21	93	11	301	1	301	10	301	63	>4	9.5	RCT
	TRUS GB 6 cores	NA	NA	NA	NA	21	301	5	301	16	301				
F Delgado Oliva, 2016	CEUS GB	701	48	295	52	44	179	NA	NA	NA	NA	64.3	56.2	8.9	RCT
	TRUS GB 10 cores	NA	NA	NA	NA	75	179	NA	NA	NA	NA				
Francesco Porpiglia, 2016	MRI+TRUS (FUS) GB	47	7	NA	53	54	107	47	107	7	107	64	462	5.9	RCT
	TRUS GB 12 cores	19	12	NA	74	31	105	19	105	12	105				
Fransisco Rodriguez-Covarrubias, 2011	TRUS GB 12 cores	10	13	NA	52	23	75	20	75	3	75	64.78	53.56	8.65	RCT
	TRUS GB 18 cores	15	21	NA	39	36	75	27	75	9	75				
Geoffrey A. Sonn, 2014	MRI+TRUS (FUS) GB	26	10	NA	69	23	97	21	97	2	97	65	58	7.5	RCT
	TRUS GB 12 cores	NA	NA	NA	NA	28	102	15	102	13	102				
Gianlugi Taverna, 2011	TRUS GB 12 cores	NA	NA	NA	NA	29	100	NA	NA	NA	NA	65.9	NA	2.5-9.9	RCT
	CEUS GB	54	58	46	42	31	100	NA	NA	NA	NA				
Gianlugi Taverna, 2015	MRI GB	15	9	9	76	24	100	15	100	9	100	64	NA	12.63	RCT
	TRUS GB 12 cores	12	14	NA	74	26	100	12	100	14	100				
Haifeng Huang, 2016	TRUS-GB	NA	NA	NA	NA	32	100	NA	NA	NA	NA	64	33	10	Cohort
	TPUS-GB	NA	NA	NA	NA	40	100	NA	NA	NA	NA				
Jae Wook Kim, 2004	TRUS GB 6 cores	NA	NA	NA	NA	17	118	NA	NA	NA	NA	63.83	44.96	8.1	RCT
	TRUS GB 12 cores	NA	NA	NA	NA	21	122	NA	NA	NA	NA				
Jean JMCH de la Rosette, 2009	TRUS GB 8 cores	NA	NA	NA	NA	45	132	NA	NA	NA	NA	63	53.2	6.1	RCT
	TRUS GB 12 cores	NA	NA	NA	NA	49	128	NA	NA	NA	NA				
Kasta Taymoorian, 2007	CEUS GB	23	7	0	60	30	95	7	95	23	95	66	50	10	RCT
	TRUS GB 6 cores	1	7	22	87	8	95	5	95	3	95				
Le-Hang Guo, 2015	TPUS-GB	NA	NA	NA	NA	32	100	NA	NA	NA	NA	67	46	9	RCT
	TRUS-GB	NA	NA	NA	NA	40	100	NA	NA	NA	NA				
M.A. Rochester, 2008	TRUS GB 12 cores	38	25	NA	59	63	122	38	122	25	122	67.8	37	6.6	RCT
	TRUS GB 15 cores	31	19	NA	72	50	122	31	122	19	122				
Mahyar Ghafoori, 2015	TRUS GB 6 cores	NA	NA	NA	NA	8	60	NA	NA	NA	NA	58.2	NA	8.2	RCT
	TRUS GB 12 cores	NA	NA	NA	NA	21	60	NA	NA	NA	NA				
	TRUS GB 18 cores	NA	NA	NA	NA	24	60	NA	NA	NA	NA				
Michael Mitterberger, 2007	TRUS GB 12 cores	4	9	NA	37	13	50	4	50	9	50	52	35	3.2	RCT
	CEUS GB	8	8	NA	34	16	50	8	50	8	50				

Contd...

Table 2: Contd...

Author, year	Intervention	True Positive (TP)	False Positive (FP)	False Negative (FN)	True Negative (TN)	Pca detection rate		Clinical Significant Pca detection rate		Insignificant PCa detection rate		Mean Age	Prostate volume	Mean PSA level	Study design
						Event	Sample Size	Event	Sample Size	Event	Sample Size				
Nina Egbers, 2015	MRI-GB	NA	NA	NA	NA	32	100	NA	NA	NA	NA	NR	NR	NR	RCT
	TRUS-GB	NA	NA	NA	NA	40	100	NA	NA	NA	NA	NR	NR	NR	
Olivier Wegelin, 2019	MRI-GB	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	65	46	11.3	RCT
	FUS-GB	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR				
P. Emiliozzi, 2003	TPUS GB	19	22	2	66	41	107	19	107	22	107	68	NA	8.2	RCT
	TRUS GB 6 cores	15	19	9	73	34	107	15	107	19	107				
Roger Paul, 2006	TRUS GB 6 cores	NA	NA	NA	NA	32	100	NA	NA	NA	NA	64.3	50	5.7	RCT
	TRUS GB 10 cores	NA	NA	NA	NA	40	100	NA	NA	NA	NA				
Ryoei hara, 2008	TPUS GB	NA	NA	NA	NA	53	126	NA	NA	NA	NA	71	34	8.4	RCT
	TRUS GB 12 cores	NA	NA	NA	NA	58	120	NA	NA	NA	NA				
Sunao Shoji, 2017	MRI+TRUS (FUS) GB	137	8	3	105	148	250	138	250	113	250	68	34	6.7	RCT
	TRUS GB 12 cores	62	24	62	164	86	250	62	250	188	250				
Susanne Tewes, 2017	MRI+TRUS (FUS) GB	36	16	4	23	NA	NA	NA	NA	NA	NA	66	63	13	RCT
V. Kasivisvanathan, 2018	MRI-GB	95	23	0	134	118	252	95	252	23	252	64.4	NA	6.6	RCT
	TRUS GB 12 cores	64	55	NA	129	119	248	64	248	55	248				
Young Hyo Choi, 2019	TRUS GB 12 cores	323	199	NA	864	522	1786	323	1786	199	1786	64	35	4.55	RCT
	MRI GB	96	28	8	99	124	223	96	1786	28	223				
	MRI + TRUS (FUS) GB	34	13	9	43	47	90	34	90	13	90				

PSA=Prostate-specific antigen, TRUS=Transrectal ultrasound, GB=Guided biopsy, TPUS=Transperineal ultrasound, CEUS=Contrast-enhanced ultrasound, FUS=Fusion, MRI=Magnetic resonance imaging, TP=True positive, FP=False positive, TN=True negative, FN=False negative, NA=Not available, PCa=Prostate cancer

in this study. Clinically significant prostate cancer was defined as PCa that embodies a minimum Gleason score of 7, whereas insignificant PCa was defined as below or equal to Gleason score of 6.

Statistical analysis

We performed a Bayesian NMA model for each outcome separately,[19] combining direct evidence for each comparison (e.g., from studies comparing interventions A with B) with indirect evidence (e.g., from studies comparing A with C and studies comparing B with C). Network plots were generated to demonstrate the comparison scheme for each PCa biopsy strategy using Stata software (version 12.0; StataCorp LP, College Station, TX). The probability of one biopsy strategy being superior to all others, second best, the third best and so on, was calculated using Markov chain Monte Carlo (MCMC) simulation and Surface Under the Cumulative RAnking curve (SUCRA). For MCMC simulation, a Bayesian framework in NMA consisting of multiple treatments was conducted using R language (version 1.2.1335) and WinBUGS (MRC Biostatistics Unit, Cambridge, UK). The simulation was based on 40 000 iterations with a burn-in of 10 000 iterations. For SUCRA value, the summary numerical value was calculated. If SUCRA value is 100%, the intervention is certainly the best, and if SUCRA value is 0%, the intervention is certainly the worst. Odds ratio (OR) with 95% credible interval (CrI) was used for each intervention. A random-effects model was preferred instead of a fixed-effects model based on our model fit assessment. Furthermore, inconsistency was not found in all three outcomes analyses.

RESULTS

Search results and included strategies

A total of 248 citations retrieved by search strategy were included in this NMA study. Then, full-text screen was conducted, and 86 studies were excluded because of reviews, case report, duplicates, and non-English language. Thirty-two articles were excluded after titles and abstract reading. Thirteen articles were removed after full-text review. Finally, 28 studies[20-47] fulfilled the inclusion criteria consisting of a total of 6768 patients who were eligible and added for further analysis. All included studies were RCTs. Several different strategies consisted of TRUS-GB, MRI-GB, MRI + TRUS (FUS)-GB, FUS + TRUS-GB, CEUS-GB, and TPUS-GB. Five endpoints were ultimately analyzed including overall PCa detection, clinically significant PCa detection, insignificant PCa detection, complication rate, and HSROC. The flowchart of the study search and selection procedure is shown in Figure 2. The network structure graph is shown in Figure 3.

Overall prostate cancer detection rate

The results of overall PCa detection rate were analyzed by

calculating 17 studies[20-22,25,28,29,31-33,35-40,42,43] with the total of 7071 patients consisting of 6 biopsy strategies including TRUS-GB, FUS + TRUS-GB, MRI + TRUS (FUS)-GB, MRI-GB, TPUS-GB, and CEUS-GB, and network structure diagrams are shown in Figure 3a. The comparison of efficacy between different biopsy strategies for OR and 95% CI is presented in league table Figure 4a. As shown in the result with TRUS-GB as a comparator, FUS + TRUS-GB (RR: 1.35, 95% CrI: 0.8–2.2) was slightly better than MRI-GB (RR: 1.28, 95% CrI: 0.9–1.78) and FUS-GB (RR: 1.23, 95% CrI: 0.93–1.61). The cumulative rank probability based on SUCRA value showed that the biopsy strategies from best to worst in terms of overall PCa detection rate were FUS + TRUS-GB, MRI-GB, MRI + TRUS (FUS)-GB, TPUS-GB, CEUS-GB, and TRUS-GB. Figure 5a is a cumulative rank plot with the SUCRA of each strategy and its detailed ranking values are summarized in Table 3a.

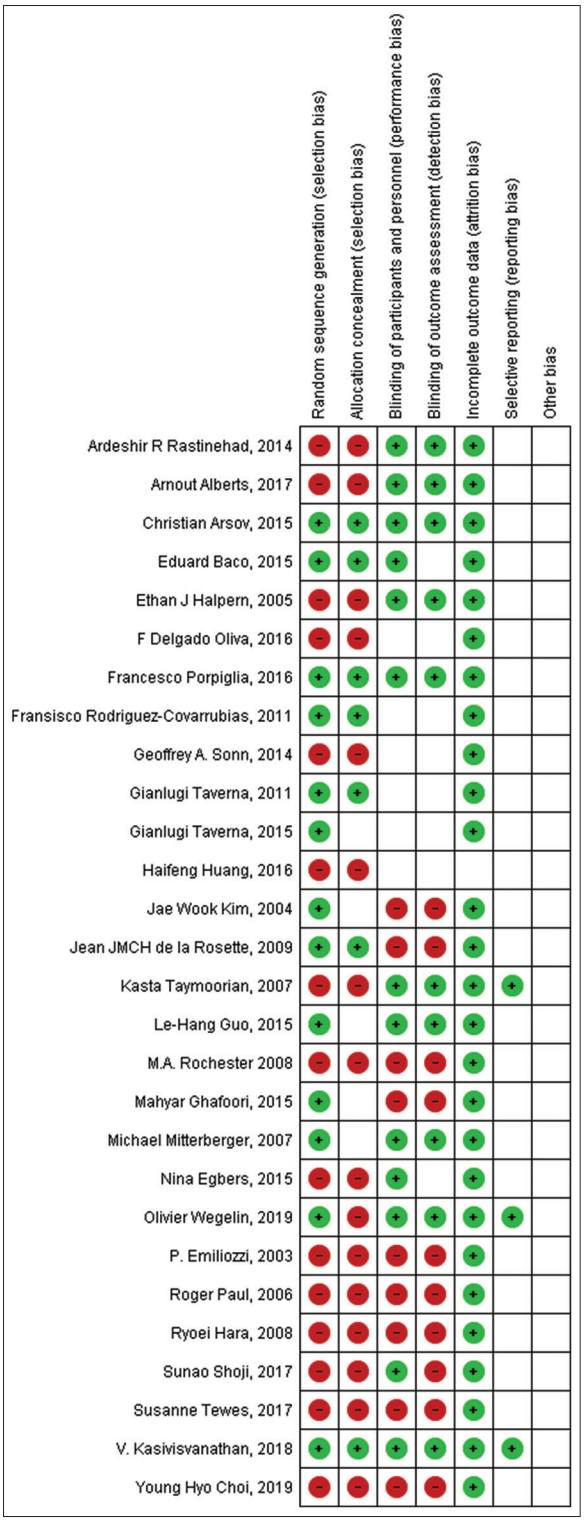

Figure 1: Risk of bias summary of 28 included studies. Green circle indicates low risk of bias and red circle indicates high risk of bias

Clinically significant prostate cancer detection rate

Fourteen studies[20-22,25,28,29,32,33,35-38,40,42] with a total of 7830 patients were used to contribute to the analysis of clinically significant PCa detection rate. Figure 3b presents the network structure diagrams. The efficacy of each biopsy strategy was compared to each other and is presented in league table Figure 4b. Our analysis showed that in the case of TRUS-GB as reference, FUS-GB (RR: 1.51, 95% CrI: 0.87–2.61) was better than FUS + TRUS GB (RR: 1.47, 95% CrI: 0.55–3.89), TPUS-GB (RR: 1.2, 95% CrI: 0.23–6.1), and MRI-GB (RR: 1.09, 95% CrI: 0.56–2.15). As indicated by

Table 3: Detailed rank probability based on Surface Under the Cumulative RAnking curve: (A) Rank probability for prostate cancer detection rate; (B) Rank probability for significant prostate cancer detection rate; (C) Rank probability for insignificant prostate cancer detection rate; (D) Complication rate

Biopsy Technique	SUCRA
A	
FUS + TRUS GB	75.66
MRI GB	70.76
MRI + TRUS (FUS) GB	65.36
TPUS GB	33.95
CEUS GB	29.15
TRUS GB	25.13
B	
MRI + TRUS (FUS) GB	74.63
FUS + TRUS GB	67.03
TPUS GB	51.56
MRI GB	43.63
TRUS GB	33.27
CEUS GB	29.88
C	
CEUS GB	75.14
TRUS GB	59.08
TPUS GB	59.06
FUS + TRUS GB	57.99
MRI + TRUS (FUS) GB	26.01
MRI GB	22.72
D	
TPUS-GB	91.98
TRUS-GB	63.06
FUS-GB	42.37
FUS + TRUS-GB	39.4
MRI-GB	13.2

SUCRA=Surface Under Cumulative RAnking curve, TRUS=Transrectal ultrasound, GB=Guided biopsy, TPUS=Transperineal ultrasound, CEUS=Contrast-enhanced ultrasound, FUS=Fusion, MRI=Magnetic resonance imaging

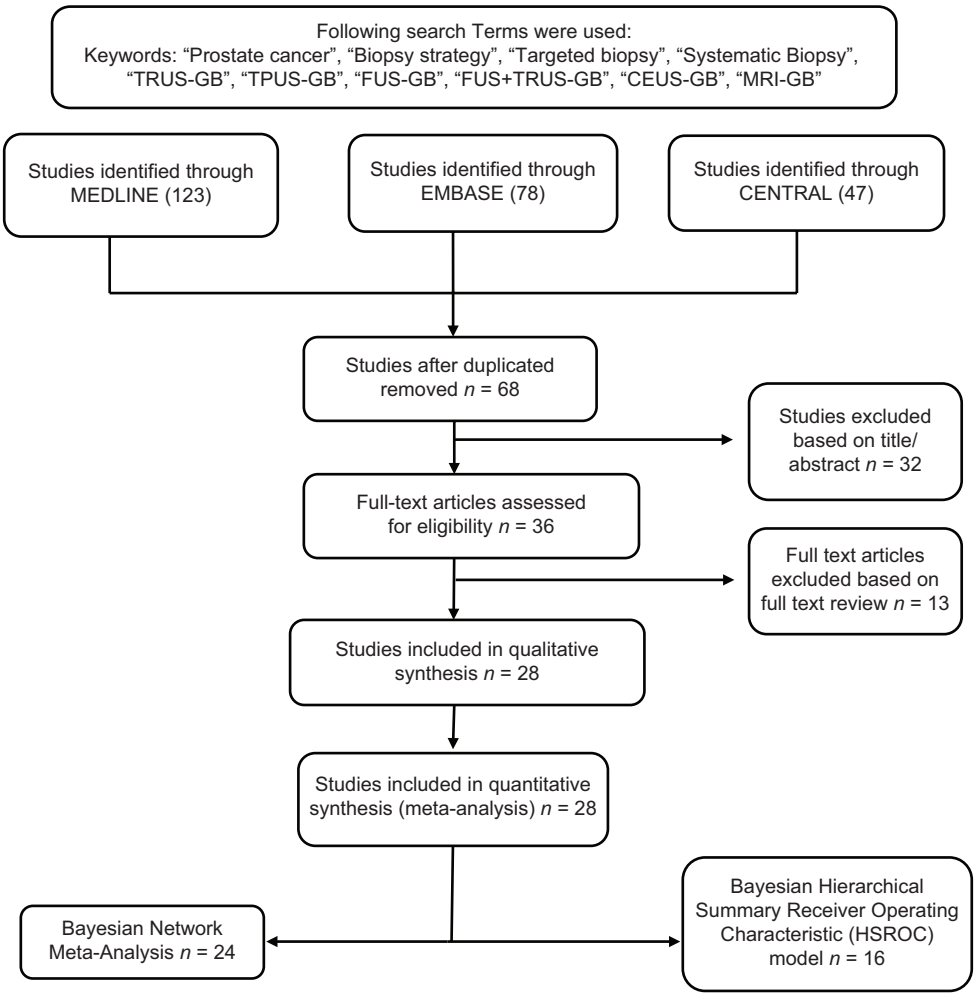

Figure 2: Flowchart of systematic literature identification and selection process implementing Preferred Reporting Items for Systematic Reviews and Meta-Analyses guide

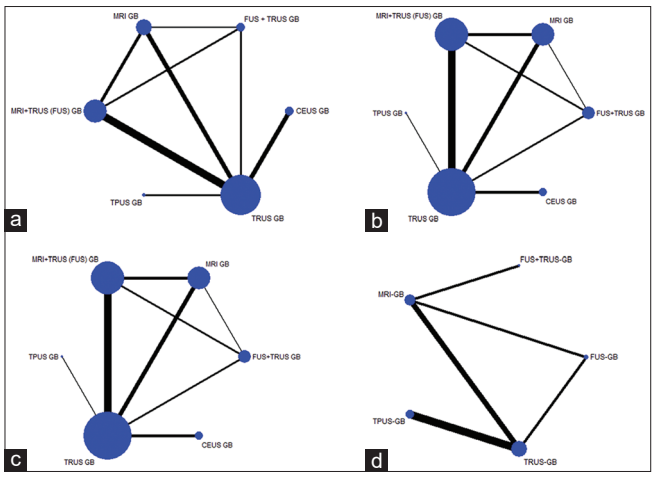

Figure 3: Network comparison structure diagrams of different biopsy strategies. (a) Prostate cancer detection rate; (b) Clinically significant prostate cancer detection rate; (c) Insignificant prostate cancer detection rate; (d) Complication rate. The size of every circle is proportional to the number of randomly assigned patients and indicates the sample size. The thickness of the line corresponds to the number of trials. Direct comparisons are linked with line

the results of ranking analysis based on SUCRA which is shown in Figure 5b and Table 3b, FUS-GB, FUS + TRUS-GB, TPUS-GB, MRI-GB, TRUS-GB, and CEUS-GB were ranked from best to worst, respectively.

Insignificant prostate cancer detection rate

The efficacy of each biopsy strategy in terms of insignificant PCa detection was also analyzed. Fourteen trials[20-22,25,28,29,32,33,35-38,40,42] with a total of 6267 patients were used to analyze this endpoint. The detailed comparison was served in network structure diagrams in Figure 3c. Moreover, the efficacy of different biopsy strategies was compared to each other and is shown in league table Figure 4c. It was found that for TRUS-GB as a comparator, CEUS-GB (RR: 1.3, 95% CrI: 0.50–3.63) and TPUS-GB (RR: 1.11, 95% CrI: 0.22–5.52) were more associated with insignificant PCa detection compared to MRI-GB (RR: 0.67, 95% CrI: 0.33–1.32) and FUS-GB (RR: 0.71, 95% CrI: 0.39–1.24) which were more less associated with insignificant PCa detection. The results of SUCRA rank probability Figure 5c sorting from more associated to less associated with insignificant PCa detection were CEUS-GB, TRUS-GB, TPUS-GB, FUS + TRUS-GB, FUS-GB, and MRI-GB. The detailed SUCRA values are shown in Table 3c.

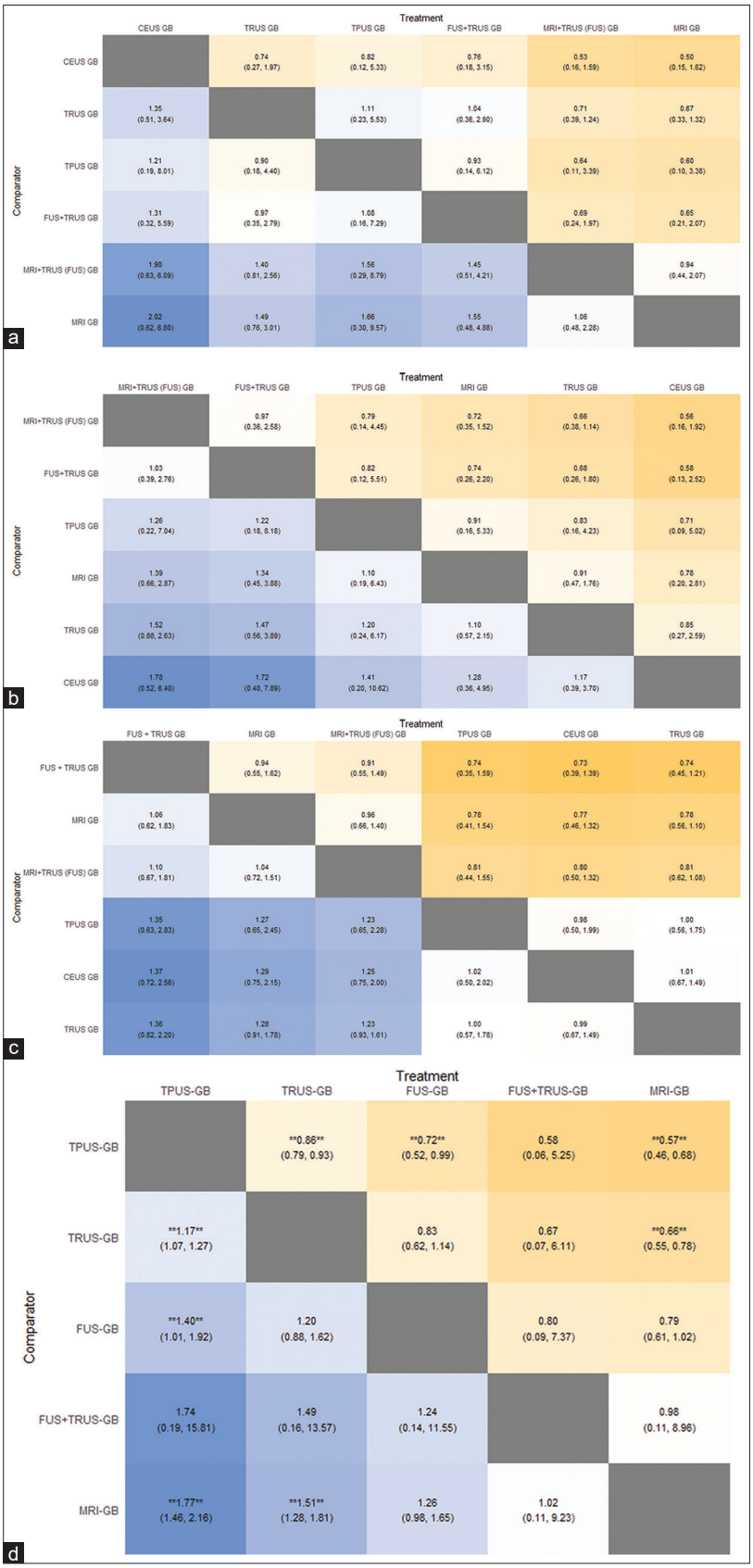

Figure 4: Network meta-analysis using odds ratio with 95% credible intervals of different biopsy strategies. A blue cell indicates that a treatment performed better than its comparator (estimate greater than 1), while an orange cell indicates that the treatment performed worse than its comparator (estimate smaller than 1). The strategy has been sorted from left to right according to Surface Under the Cumulative RAnking curve as from worst to best, respectively. (a) Overall prostate cancer outcome detection rate outcome, (b) Clinically significant prostate cancer detection rate outcome, (c) Insignificant prostate cancer detection rate outcome, (d) Complication rate

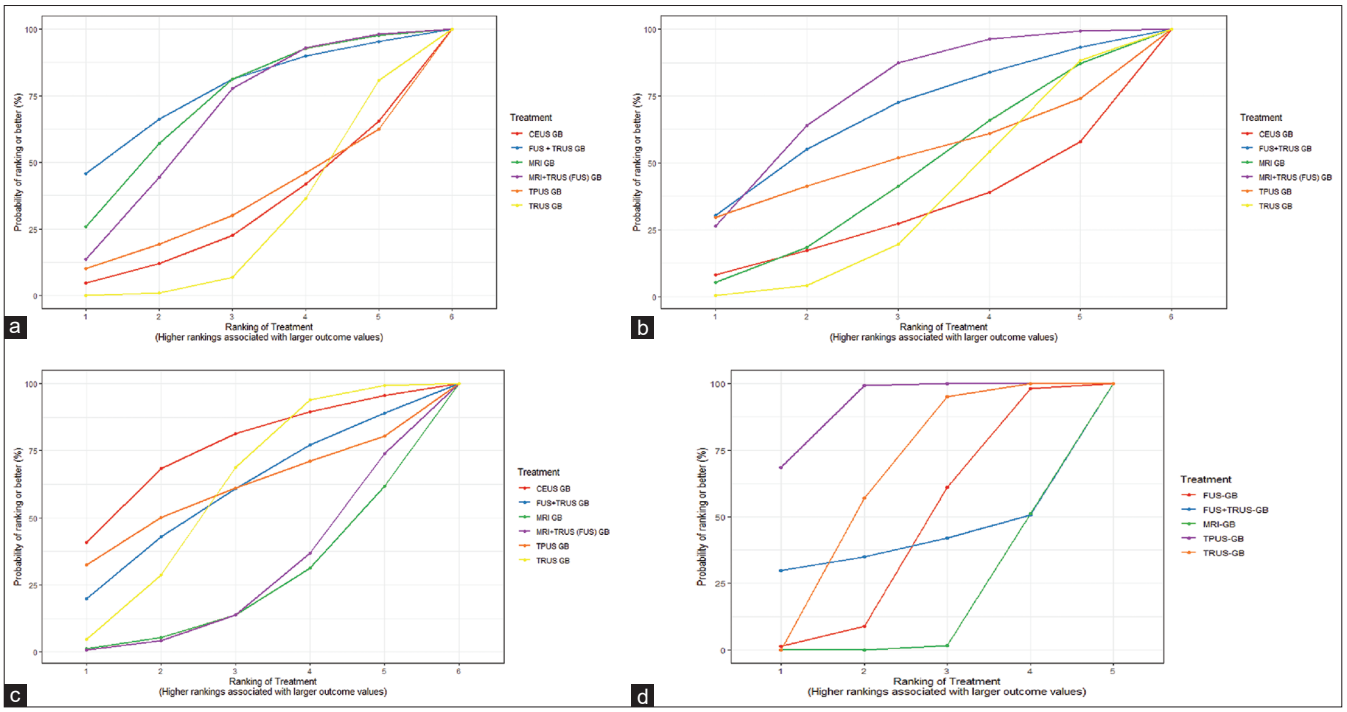

Figure 5: Surface Under the Cumulative RAnking curve plot for clinical outcomes. (a) Overall prostate cancer detection rate; (b) Clinically significant prostate cancer detection; (c) Insignificant prostate cancer detection; (d) Complication rate

Complication rate

The evaluation of complication rate in relation to different biopsy strategies was also analysed. Eight studies[21,31,32,35,44-47] with a total of 2073 patients contributed within the analysis of the results. The comparison of biopsy strategies was served in network structure diagram presented in Figure 3d and network league table presented in Figure 4d. Our analysis found that in TRUS-GB as reference, MRI-GB (RR: 0.66, 95% CrI: 0.55–0.78), FUS + TRUS-GB (RR: 0.67, 95% CrI: 0.07–6.1), and FUS-GB (RR: 0.83, 95% CrI: 0.61–1.13) were more related to lower complication rate compared to TPUS-GB (RR: 1.16, 95% CrI: 1.07–1.27) which was more related to high complication rate. Finally, the detailed rank probability showed that TPUS-GB, TRUS-GB, FUS-GB, FUS + TRUS-GB, and MRI-GB were ranked from higher to lower complication rate, respectively, with TPUS-GB and TRUS-GB related to higher complication, as presented in Table 3d and Figure 5d. The complications among the patients include infection/fever, pain, bleeding, rectal hemorrhage, hematuria, hemospermia, sepsis, and urinary retention, as shown in Table 4. Major complications of sepsis and urinary retention mostly occurred in TRUS-GB.

Hierarchical summary receiver operating characteristics

Data extraction showed a large heterogeneity in the reporting of diagnostic accuracy measures. For such reasons, the average operating points (summary of sensitivity and specificity) with the corresponding 95% CI were computed using the summary receiver operating characteristic curves using the hierarchical model proposed by Rutter and Gatsonis.[48] Due to limited primary data, only four HSROC curves consisting of TRUS-GB, FUS-GB, MRI-GB, and CEUS-GB were managed to be analyzed. It is easily found that MRI-GB (91% and 81%) and FUS-GB (82% and 83%) presented the highest predicted sensitivity and specificity for overall PCa detection. CEUS-GB had the sensitivity and specificity of 74% and 82%, respectively; meanwhile, TRUS-GB had the lowest predicted sensitivity of 62% and specificity of 83%. Figure 6 summarizes the HSROC curve.

DISCUSSION

A key issue in the diagnosis and treatment of PCa is the need to detect PCa which is clinically significant and requires treatment. Although the gold standard for PCa is TRUS-GB, it is beset with problems of overdiagnosis and overtreatment.[49]

To the best of our knowledge, this is the first study to combine Bayesian framework in NMA and HSROC model in biopsy strategy for PCa detection. Even in the case of limited primary evidence, all relevant evidences of biopsy strategy in PCa patients were integrated simultaneously by performing NMA. Moreover, to ensure a sustainable conclusion, we analyzed the sensitivity and specificity of biopsy strategy in the form of Bayesian prediction in HSROC. Bayesian framework was used to enhance the quality of our analysis so that it could provide results with more confidence for decision-making.[50,51]

In terms of overall PCa and clinically significant PCa detection rate outcome, FUS + TRUS-GB, MRI-GB, and

Table 4: Complication-related side effects in different biopsy strategies

Author, year	Intervention	Complications	Total patients	Bleeding	Rectal hemorrhage	Hematuria	Hemospermia	Fever	Pain	Urinary retention	Sepsis
Nina Egbers, 2015	MRI-GB	28	45	28	7	23	16	NA	NA	NA	NA
	TRUS-GB	36	45	35	6	34	7	NA	NA	NA	NA
Haifeng Huang, 2016	TRUS-GB	115	144	NA	2	47	NA	16	NA	13	1
	TPUS-GB	94	98	NA	0	35	NA	3	NA	10	0
Le-Hang Guo, 2015	TPUS-GB	73	161	NA	0	33	NA	2	58	NA	0
	TRUS-GB	76	167	NA	2	37	NA	9	26	NA	1
Olivier Wegelin, 2019	MRI-GB	40	77	NA	2	27	20	1	NA	0	NA
	FUS-GB	52	79	NA	2	40	28	2	NA	3	NA
Arnout R. Alberts, 2017	TRUS-GB	7	179	NA	NA	NA	NA	NA	NA	1	6
	FUS-GB	5	158	NA	NA	NA	NA	NA	NA	0	5
Christian Arsov, 2015	MRI-GB	2	106	0	0	0	0	2	0	NA	NA
	FUS + TRUS-GB	1	104	0	0	0	0	1	0	NA	NA
Ryoei hara, 2008	TPUS-GB	23	126	NA	NA	13	2	NA	NA	2	0
	TRUS-GB	18	120	NA	NA	11	NA	2	NA	3	0
V. Kasivisvanathan, 2018	MRI-GB	80	252	NA	30	64	68	NA	27	NA	NA
	TRUS-GB	129	248	NA	45	129	123	9	48	NA	NA

TRUS = Transrectal ultrasound, GB = Guided biopsy, TPUS = Transperineal ultrasound, CEUS = Contrast-enhanced ultrasound, FUS = Fusion, MRI = Magnetic resonance imaging, NA = Not available

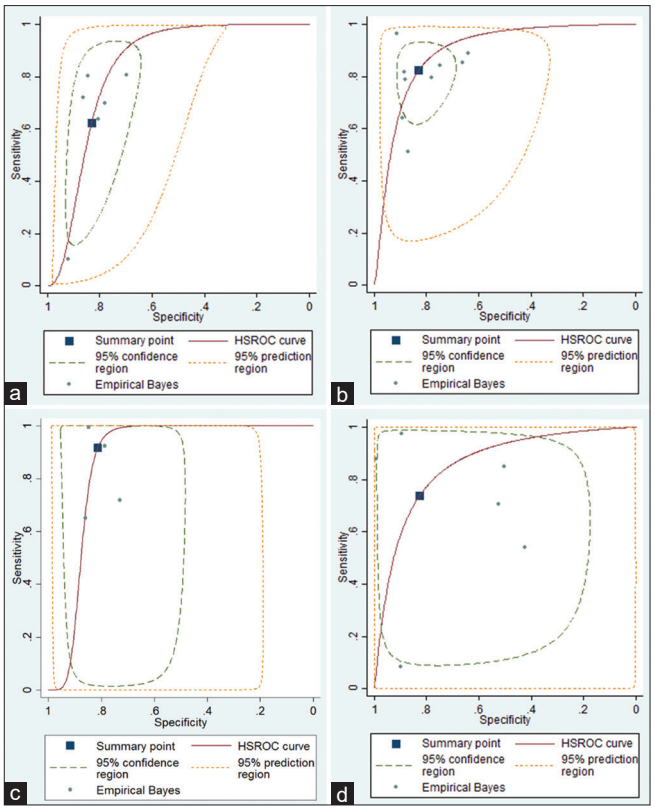

Figure 6: Bayesian prediction served in hierarchical summary receiver operating characteristic model by Rutter and Gatsonis for prediction of true sensitivity and specificity of (a) TRUS-guided biopsy; (b) magnetic resonance imaging + TRUS (fusion)-guided biopsy; (c) magnetic resonance imaging-guided biopsy; (d) contrast-enhanced ultrasound-guided biopsy

MRI + TRUS (FUS)-GB were ranked as the best. As for TRUS-GB, it was more associated with lower overall PCa detection and was more inferior in clinically significant PCa detection. MRI examination before prostate biopsy has the advantages of showing the location of the lesion; thus, it provides high sensitivity for detecting PCa.[52,53] Clinicians' choice of the appropriate biopsy might be influenced by MRI.[54] On T1-weighted images, PCa typically appears as a low signal within areas of homogeneous high signal.[55] On T2-weighted sequences, suspicious areas of the prostate could also be detected.[52] Another study has also emphasized the potential value of combining MRI with ultrasound-GB/FUS-GB.[56] High-resolution imaging and the better ability to detect cancer at a higher rate per core were shown in FUS-GB. FUS-GB digitally tracks the areas of lesions as well as trajectory and path of needle biopsies, enabling prior targets to be sampled and monitored. These benefits are not available in standard biopsy technique.[57, 58] An advantage of anatomical assessment of suspicious lesion size and the discriminative accuracy of detecting PCa with higher disease has been shown in Multi-parametric MRI (mp-MRI).[59] The mp-MRI is also associated with histopathological stability allowing detection of tumor progression.[60] A study by Von Beyme Cortés *et al.*[61] also reported that the combined approach of FUS + TRUS-GB revealed more Gleason score

upgrades compared to FUS-GB alone although the result was not significant.

As for TRUS-GB, TPUS-GB, and CEUS-GB, they were ranked lower compared to others regarding four efficacy endpoints (PCa detection, clinically significant PCa detection, insignificant PCa detection, and HSROC). CEUS-GB provided a statistically significant improvement in discrimination between benign and malignant biopsy sites. CEUS-GB can better detect PCa by utilizing the characteristic of neoangiogenesis in PCa.[62] It was showed that only tumor that has reached the size of 1 ml appears to have a high density of blood vessels, as smaller (<2 mm) tumours may be avascular.[63,64] This may be the reason for nonvisualization of small tumors which lower the overall PCa detection. As for TPUS-GB, the limitations of TPUS-GB lay in its difficulties in visualizing hypoechoic areas thus may be the reason for low sensitivity rate.[65]

In our review, we included 2109 patients undergoing prostate biopsy to analyze the complication and side effects related to procedure. Our results found that FUS-GB, MRI-GB, and FUS + TRUS-GB were more associated with less complication rate compared with TRUS-GB and TPUS-GB which had a higher risk for developing complications. MRI-GB was preferred because it is associated with lower pain intensity and fewer side effects. The samples which are taken are only from high suspicious areas on prior MRI. A fewer number of specimens are removed in a more directed technique based on prior MRI findings which eventually will reduce injury to surrounding structures.[66,67] Fewer complications using FUS-GB were also reported in a study by Siddiqui *et al*.[68] where they applied mp-MRI technology with ultrasound fusion-GB and confidently avoided side effects and complications, but at the same time, maintaining a high significant PCa detection rate.

Our results showed that the new biopsy techniques such as FUS-GB, MRI-GB, and FUS + TRUS-GB could result in a significantly higher rate for detecting PCa compared to random biopsy, translating to less biopsy related complications. This result leads us to believe that MRI-GB, FUS-GB, and FUS + TRUS-GB may become the first-line technique for detecting PCa in upcoming years.

There are several strengths of this review. First, the implementation of Bayesian framework in NMA as well as in HSROC model could provide better confidence in terms of decision-making results; therefore, it gives clarity for surgeons as well as patients for choosing the best strategy. Second, most of the studies included were RCTs, which permit a direct comparison between two diagnostic pathways with clinically relevant outcomes, as opposed to diagnostic cohort studies that can only inform us about test accuracy measures. Third, Regarding the suggestion from previous study,[69] we managed to analyze complication rates in our study. However, a cost-effectiveness analysis was not performed in this study which would be a limitation.

CONCLUSION

This NMA and HSROC model showed that FUS + TRUS-GB, FUS-GB, and MRI-GB are superior to other biopsy strategies in diagnosing PCa with fewer complications. These results will assist in shared decision-making between patients, carers, and their surgeons.

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