



# Diagnostic accuracy of prostate-specific antigen below 4 ng/mL as a cutoff for diagnosing prostate cancer in a hospital setting: A systematic review and meta-analysis

Yan Jin<sup>1,\*</sup> , Jae Hung Jung<sup>2,3,\*</sup> , Woong Kyu Han<sup>4</sup> , Eu Chang Hwang<sup>5</sup> , Yoonmi Nho<sup>1</sup> , Narae Lee<sup>1</sup> ,  
Ji Eun Yun<sup>1</sup> , Kwang Suk Lee<sup>6</sup> , Sang Hyub Lee<sup>7</sup> , Hakmin Lee<sup>8</sup> , Su-Yeon Yu<sup>1</sup> 

<sup>1</sup>National Evidence-based Healthcare Collaborating Agency, Seoul, <sup>2</sup>Department of Urology, Yonsei University Wonju College of Medicine, Wonju, <sup>3</sup>Center of Evidence Based Medicine, Institute of Convergence Science, Yonsei University, Seoul, <sup>4</sup>Department of Urology, Yonsei University College of Medicine, Seoul, <sup>5</sup>Department of Urology, Chonnam National University Medical School, Gwangju, <sup>6</sup>Department of Urology, Gangnam Sevrance Hospital, Yonsei University College of Medicine, Seoul, <sup>7</sup>Department of Urology, Kyung Hee University Medical Center, Seoul, <sup>8</sup>Department of Urology, Seoul National University Bundang Hospital, Seongnam, Korea

**Purpose:** A prostate-specific antigen (PSA) cutoff of 4 ng/mL has been widely used for prostate cancer screening in population-based settings. However, the accuracy of PSA below 4 ng/mL as a cutoff for diagnosing prostate cancer in a hospital setting is inconclusive. We systematically reviewed the accuracy of PSA below 4 ng/mL cutoff in a hospital setting.

**Materials and Methods:** We systematically reviewed the literature by searching major databases until March 2020, and a meta-analysis and quality assessment were performed.

**Results:** A total of 11 studies were included at the completion of the screening process. The meta-analysis showed a sensitivity of 0.92 and a specificity of 0.16 for a PSA cutoff below 4 ng/mL. The area under the hierarchical summary receiver operating characteristic curve was 0.87, the positive likelihood ratio was 1.23, the negative likelihood ratio was 0.46, and the diagnostic odds ratio was 2.64. PSA sensitivities and specificities varied according to the cutoff range: 0.94 and 0.17 for 2 to 2.99 ng/mL, and 0.92 and 0.16 for 3 to 3.99 ng/mL, respectively. No significant differences in the sensitivity and specificity of PSA cutoffs in the range of 2 to 2.99 ng/mL and 3 to 3.99 ng/mL were found.

**Conclusions:** Although a PSA cutoff <3 ng/mL is relatively more sensitive and specific than PSA ≥3 ng/mL, no significant differences in sensitivity and specificity were found in the diagnosis of prostate cancer. Therefore, clinicians should choose an appropriate PSA cutoff on the basis of clinical circumstances and patients' characteristics.

**Keywords:** Diagnosis; Prostate-specific antigen; Prostatic neoplasms

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**Corresponding Author:** Su-Yeon Yu  <https://orcid.org/0000-0001-5488-5068>

National Evidence-based Healthcare Collaborating Agency, Namsan Square 7F, 173 Toegye-ro, Jung-gu, Seoul 04554, Korea

TEL: +82-2-2174-2761, FAX: +82-2-725-4917, E-mail: [suyeon.yu@neca.re.kr](mailto:suyeon.yu@neca.re.kr)

\*These authors contributed equally to this study and should be considered co-first authors.

## INTRODUCTION

Prostate cancer is one of the most common types of cancer worldwide and results in a large burden of morbidity and mortality. The incidence of prostate cancer is rapidly increasing, partly because of increased awareness of prostate cancer screening. During prostate cancer screening, the amount of prostate-specific antigen (PSA) in the blood, which is a glycoprotein formed by the prostate gland, is measured. In 1991, this test became popular in addition to digital rectal examination (DRE) because of the possibility for early detection of prostate cancer. The PSA test is simple, objective, quantitative, and feasible and is independent of the examiner's skill [1]. However, interpretation of PSA values requires an understanding of the clinical situation because other prostate-related conditions such as benign prostatic hypertrophy and prostatitis can also cause PSA elevation.

A PSA level  $\geq 4$  ng/mL has been widely accepted as a threshold for suggesting prostate biopsy to detect prostate cancer [2]. However, there is no consensus on the threshold value, and the risk for prostate cancer ranges from 6.6% to 12% in patients with PSA  $\leq 2$  ng/mL [3]. Two large randomized trials conducted in the United States and Europe evaluated the efficacy of population-based PSA screening for the detection of prostate cancer. The European Randomized Study of Screening for Prostate Cancer (ERSPC), a multicenter large-scale randomized controlled trial (RCT) initiated in 1993, aimed to investigate the effect of PSA screening on mortality related to prostate cancer. Since 1996, most centers have used a PSA level of  $\geq 3$  ng/mL instead of  $\geq 4$  ng/mL as an indicator of a positive finding on a screening test. Another screening RCT, the Prostate, Lung, Colorectal and Ovarian (PLCO) study, used a PSA cutoff of 4 ng/mL. Whereas ERSPC reported a survival benefit, PLCO and several meta-analyses indicated that PSA screening did not significantly improve prostate-specific mortality. Moreover, the US Preventive Services Task Force (USPSTF) recommended against PSA-based screening for prostate cancer in 2013, because it leads to unnecessary biopsy, resulting in adverse impacts due to overdiagnosis. Hence, the US [4] and European guidelines [5,6] do not recommend conducting an early prostate cancer screening program for the general population at the national level.

More recently, the USPSTF revised the recommendation and offered PSA screening selectively in men aged 55 to 69 years on the basis of clinical judgment and patient preferences. The American Cancer Society [4] recommends screening tests annually in people with a PSA level of 2.5 ng/mL

or more. For repeated PSA test results between 2.5 and 4.0 ng/mL, individual risk factors such as race, family history, age, and abnormal findings on a DRE should be considered to determine the need for prostate biopsy. The National Comprehensive Cancer Network recommended that prostate biopsy be conducted if the PSA exceeds 3 ng/mL or if the results of a DRE are very suspicious [7]. The UK National Health Service Guidelines recommended that even if PSA values increase, decisions about biopsy should be made in consideration of the patient's life expectancy.

Despite its high sensitivity and low specificity, the diagnostic performance of a PSA cutoff below 4 ng/mL remains inconclusive. Thus, instead of universally following a specific cutoff for all patients, it is necessary to judiciously decide on the need for a histologic examination based on patient characteristics such as age and prostate-related symptoms to reduce the rate of overdiagnosis and biopsy-related complications.

Therefore, this systematic review focused on the diagnostic accuracy of PSA with a cutoff of  $<4$  ng/mL for prostate cancer in participants with symptoms attending a health care facility.

## MATERIALS AND METHODS

### 1. Data sources and search strategy

The present study was registered with PROSPERO (no. CRD42020172239). We conducted a systematic search of articles published up to March 2020 in five literature databases: MEDLINE, EMBASE, the Cochrane Library, and the Korean databases KoreaMed and KMBASE. The search strategy is presented in Supplementary File 1.

### 2. Selection criteria

Articles based on studies that met the following criteria were included: 1) participants were not diagnosed with prostate cancer and biopsy was performed when the total PSA value was less than 4 ng/mL; 2) the diagnostic accuracy of a total PSA cutoff of  $<4$  ng/mL was compared with transrectal ultrasound (TRUS)-guided or magnetic resonance imaging (MRI)-guided biopsy with 10 or more cores; 3) at least one predetermined outcome was reported; 4) the study setting was a medical facility; and 5) the study design was a diagnostic accuracy study [8]. The exclusion criteria were as follows: 1) duplicate articles; 2) articles not published in English or Korean; 3) grey literature; 4) publications other than original research articles, such as reviews, editorials, letters, and comments; 5) a study not designed as a diagnostic accuracy study; 6) inclusion of only participants with prostate cancer;

7) inclusion of only participants with a total PSA cutoff >4 ng/mL; 8) performance of repeated biopsy; 9) missing total PSA result; 10) no inclusion of biopsy in the comparator arm; 11) report of a nonpredetermined outcome; and 12) full-text article not available. The PICO of the systematic review are presented in Supplementary File 2.

Two researchers independently selected the studies. Any disagreement was settled by discussion between the two reviewers or through a consensus meeting in consultation with a third reviewer until a final set of relevant studies was agreed on. The literature selection process was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [9] and the Cochrane Handbook for Systematic Reviews of Interventions [10]. The screening procedure was conducted using Covidence (Veritas Health Innovation, Melbourne, VIC, Australia).

### 3. Data extraction and methodologic quality assessment

According to a predefined data extraction format, pairs of researchers extracted information from the selected studies, including the research design, patient characteristics, characteristics of the index test (total PSA test) and reference test (biopsy), and test accuracy outcomes.

Two researchers independently assessed the risk of bias (ROB) of the selected studies using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) [11]. Any disagreement was resolved by discussion and consultation with a clinical expert group.

### 4. Outcome measures

The outcomes were sensitivity and specificity, positive and negative likelihood ratios (PLR and NLR), positive and negative predictive power, diagnostic accuracy, diagnostic odds ratio (DOR), and area under the curve below the PSA cutoff of 4 ng/mL. The outcomes for PSA values ranging from 2 to 2.99 ng/mL and from 3 to 3.99 ng/mL were also calculated, respectively.

### 5. Data synthesis and statistical analysis

We cross-tabulated the numerical information from the index test results (positive or negative) in 2×2 tables against the target disorder (positive or negative) to calculate the test accuracy outcomes.

We used visual inspection of the coupled forest plots of sensitivity and specificity to estimate heterogeneity. If significant heterogeneity was detected, then the relevant data were pooled using a random-effects coefficient bivariate

model and hierarchical summary receiver operating characteristic curve (HSROC) model; otherwise, a fixed-effects coefficient binary regression model was used. According to the Cochrane Handbook for Diagnostic Test Accuracy Reviews [12], the Spearman correlation coefficient was computed between the logit of sensitivity and logit of (1-specificity) to assess the threshold effect. If there were more than two PSA cutoff values in a single study, the PSA cutoff value with a higher diagnostic accuracy was used for the meta-analysis. Heterogeneity was assessed by using the  $I^2$  statistical method, with  $I^2 >50\%$  or a p-value <0.05 indicating significant heterogeneity.

Publication bias was assessed by creating a Deeks' funnel plot and performing an asymmetry test. Publication bias was considered present if there was a nonzero slope coefficient. Deeks' analysis was performed to evaluate the publication bias, with p <0.05 suggesting publication bias.

All statistical analyses were performed using Cochrane RevMan version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and Stata software (version 11; Stata Corp., College Station, TX, USA). Measurements with a p-value of <0.05 were considered statistically significant.

### 6. Ethics statement

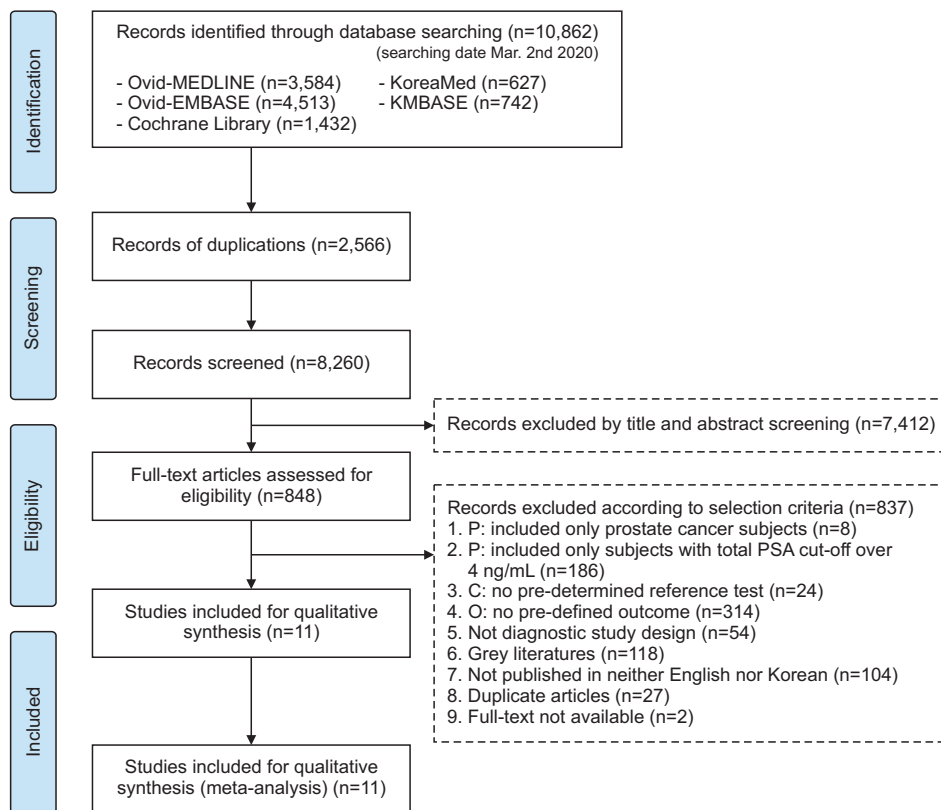
The present study protocol was reviewed and approved by the Institutional Review Board of the National Evidence-based Healthcare Collaborating Agency (approval no. NE-CAIRB20-024).

## RESULTS

### 1. Description of included studies

A total of 8,260 articles were retrieved from the database after excluding duplicates. According to the selection criteria, 848 articles were selected for full-text screening. All selection processes are presented in the PRISMA flowchart (Fig. 1). At the conclusion of screening, 11 studies (one in Korean) were included in this systematic review [13-23].

The included studies were those published in and after 2003, with five multicenter [15,16,19,21,22] and six single-center [13,14,17,18,20,23] studies. Of the included studies, nine and two studies had prospective [13-18,21-23] and retrospective [19,20] designs, respectively. The number of participants varied from 103 to 4,102, with a total participant number of 8,514. The majority of participants (4,341) were recruited from Europe [14,15,19]. The remaining studies with 4,173 participants were conducted in Asia [17,18,20,21], Brazil [13,23], and the United States [16,22]. The PSA cutoff values in the



**Fig. 1.** Flow diagram for identification of eligible studies. P, patient; PSA, prostate-specific antigen; C, comparator; O, outcome.

studies ranged from 2 to 10 ng/mL. All studies used the pathologic results of TRUS-guided biopsy with a minimum of 10 cores as a reference test. Two studies received funding from industry [16,22], and two received academic funding [19,23]. Three studies [13-15] reported no conflicts of interest, and four studies [17,18,20,21] did not report conflicts of interest. Baseline characteristics of the included studies are demonstrated in Table 1.

## 2. Quality of studies

Regarding the patient selection domain, eight studies were judged to have a low ROB [13-18,21,22]. However, one study [20] was rated as unclear, and the remaining [19,23] were rated as unclear with a high ROB because of inadequate information about the participants' recruitment (e.g., consecutive or random sample enrollment) and exclusion criteria, respectively. The ROB was rated as high in nine studies that did not prespecify the PSA cutoff [13-15,17-19,21-23]; two studies were rated as having low ROB in this respect [16,20]. All studies were rated as having low ROB with respect to the reference standard, flow, and timing domains. All studies were judged as having a low applicability of concerns of patient selection and index test domains. Although four studies [13,17,20,23] were rated as having a low ROB, seven studies [14-16,18,19,21,22] were rated as having a high

ROB owing to discrepancies in the number of participants in the study and the calculation of diagnostic accuracy regarding concerns of applicability of the reference standard. Supplementary Fig. summarizes the ROB according to the QUADAS-2.

## 3. Diagnostic test accuracy

A portion of the diagnostic performance results of PSA cutoffs below 4 ng/mL for each included study are shown in Table 1. The coupled forest plots of sensitivity and specificity with PSA cutoffs below 4 ng/mL are shown in Fig. 2, based on the threshold currently used in clinical practice.

The sensitivity of PSA cutoffs below 4 ng/mL ranged from 0.8 to 1, and the specificity ranged from 0.02 to 0.63. The pooled sensitivity was 0.92 (95% confidence interval [CI]: 0.86–0.95) with heterogeneity ( $I^2=92.57$ ,  $p<0.01$ ); the pooled specificity was 0.16 (95% CI: 0.09–0.28) with heterogeneity ( $I^2=98.04$ ,  $p<0.01$ ) (Fig. 2A). The area under the HSROC was 0.68 (95% CI: 0.05–0.99) (Fig. 2B); PLR was 1.23 (95% CI: 0.99–1.47); NLR was 0.46 (95% CI: 0.26–0.66); and DOR was 2.64 (95% CI: 1.11–4.17).

For PSA cutoffs in the range of 2 to 299 ng/mL, the sensitivity ranged from 0.9 to 1, and the specificity ranged from 0.05 to 0.55. The pooled sensitivity was 0.94 (95% CI: 0.92–0.96) and the pooled specificity was 0.17 (95% CI: 0.08–0.32), with

Table 1. Study characteristics of the included studies

Reference	Setting/country	Study design	Sample size	Inclusion criteria			Exclusion criteria
				Age (y)	PSA (ng/mL)	Others	
Castro et al., 2018 [13]	Single center/Brazil	Prospective	656	-	2.6–10	Referred to hospital	Previous prostate cancer, prostate surgery Hormonal manipulation Urinary tract infection, acute or chronic bacterial prostatitis Recent 5-alpha-reductase inhibitors use Previous 5-alpha-reductase inhibitors use Prostate surgical intervention A acute prostatitis, urinary tract infection, and previous androgen therapy Previous malignant disease An indwelling urinary catheter, a previous prostate cancer Previous 5-alpha-reductase inhibitors use A history of instrumental procedures An inconclusive histopathologic result A history of transurethral resection of the prostate or open prostatectomy and acute prostatitis
Vukovic et al., 2017 [14]	Single center/Serbia	Prospective	129	≥50	2–10	Normal DRE	
Osredkar et al., 2016 [15]	Two centers/Slovenia	Prospective	110	-	1.6–8	-	
Shakir et al., 2014 [16]	Multicenter/USA	Prospective	1,003	≥18	-	Multiparametric magnetic resonance imaging suspicious lesion	Altered mental status Patients unlikely able to hold reasonably still on a procedure table for the length of the procedure Patients with any known allergy to adhesives or latex or skin reactions to dressings (since the adhesive fiducials could theoretically induce a rash in these patients), if adhesive fiducials are to be used Inability to hold breath, if procedure will be performed with conscious sedation, and without general anesthesia Patients with pacemakers or automatic implantable cardiac defibrillators Gross body weight above the CT table limit (375 pounds), if CT table used Previous history of elevated PSA Established BPH, chronic prostatitis or prostate cancer Testosterone or finasteride therapy Underwent prior resection of prostate Rejected the biopsy Evidence of urinary tract retention Active infection or inflammatory disease Received previous medical treatment for any condition that may have affected serum PSA A previous malignancy (apart from skin cancer) Renal transplant or on renal dialysis Major cardiovascular or respiratory comorbidities, bilateral hip replacement An estimated life expectancy of less 10 years Rejected the biopsy
Mutlu et al., 2009 [17]	Single center/Turkey	Prospective	177	-	≥2.5	With lower urinary tract symptoms; or abnormal DRE	
Nishimura et al., 2008 [18]	Single center/Japan	Prospective	159	-	2.7–10	-	
Rosario et al., 2008 [19]	337 centers/United Kingdom	Retrospective	4,102	50–70	3.0–19.9	-	
Jeong et al., 2007 [20]	Single center/South Korea	Retrospective	1,063	60–79	≥3	Lower urinary tract symptoms; or regular medical check up	
Sözen et al., 2005 [21]	Four centers/Turkey	Prospective	408	-	2.5–20	Lower urinary tract symptoms	
Partin et al., 2003 [22]	7 centers/USA	Prospective	604	-	2–10	Recommender for biopsy by physician	Received testosterone or finasteride Undergone transurethral resection of the prostate Personal history of prostate cancer or transrectal prostate resection Requiring medication that could alter serum PSA, such as estrogen, finasteride or quinolone antibiotic therapy within 30 days of biopsy Patients on any medication or food supplement that can potentially alter serum PSA, such as but not limited to dehydroepiandrosterone or testosterone
Paschoalin et al., 2003 [23]	Single center/Brazil	Prospective	103	40–79	≥2	Abnormal DRE	

PSA, prostate-specific antigen; DRE, digital rectal examination; CT, computed tomography.



Table 1. Continued

Reference	Participants			Outcomes							Conflict of interest
	Age (y)	PSA (ng/mL)	PSA cutoff value (ng/mL)	Sensitivity	Specificity	LR (+)	LR (-)	DOR	Reference test		
Castro et al., 2018 [13]	Cancer: 69.4±6.87 Benign: 67.6±7.16	Cancer: 7.50±1.70* Benign: 6.29±1.81	3	1.000	0.017	1.02	0	-	TRUS-guided 12 <sup>3</sup> core biopsy	None	
Vukovic et al., 2017 [14]	Cancer: 65.3±6.6 Benign: 64.0±1.96	Cancer: 5.81±1.98 Benign: 6.24±1.96	3 3.47	0.923 0.906	0.063 0.092	0.98 1.00	1.23 1.02	0.80 0.98	TRUS-guided 12 <sup>3</sup> core biopsy	None	
Osredkar et al., 2016 [15]	Cancer: 67 (63.3–71.8)* Benign: 64 (60.8–68.0)	Cancer: 5.03 (3.85–7.60)* Benign: 4.34 (3.47–5.59)	2.7 3.3	0.950 0.900	0.068 0.189	1.02 1.11	0.74 0.59	1.23 1.87	TRUS-guided 10 core biopsy	None	
Shakir et al., 2014 [16]	62 (57–67)	6.7 (4.4–10.7)	2.5	0.947	0.105	1.06	0.51	2.08	TRUS-guided 12 <sup>3</sup> core biopsy	Industry	
Mutlu et al., 2009 [17]	Cancer: 65±7.2 Benign: 64.3±9.1	Cancer: 25.3±58.9* Benign: 8.53±14.28	2.13 2.83	0.950 0.900	0.461 0.550	1.76 2.02	0.10 0.17	17.79 12.17	TRUS-guided 12 <sup>3</sup> core biopsy	Not reported	
Nishimura et al., 2008 [18]	Cancer: 73.5 (62–92)* Benign: 68 (41–90)	Cancer: 6.24 (3.1–9.81) Benign: 6.11 (2.84–9.57)	3.064 3.917	1.000 0.950	0.017 0.140	1.02 1.10	0 0.35	- 3.17	TRUS-guided 10 <sup>3</sup> core biopsy	Not reported	
Rosario et al., 2008 [19]	Cancer: 63 (59–67)* Benign: 62 (58–66) 60–79	Cancer: 4.9 (3.7–7.6)* Benign: 4.1 (3.4–5.5) median, 6.8	3.5	0.833	0.273	1.15	0.61	1.87	TRUS-guided 10 core biopsy	Academy	
Jeong et al., 2007 [20]	Cancer: 65.0±7.8 Benign: 62.3±7.9	Cancer: 9.31±5.1* Benign: 7.45±3.9	2.91 3.86	0.950 0.900	0.059 0.154	1.01 1.06	0.85 0.65	1.17 1.57	TRUS-guided 12 core biopsy	Not reported	
Sözen et al., 2005 [21]	Cancer: 65 (59–71) Benign: 61 (55–68)	Cancer: 5.5 (4.0–7.5) Benign: 3.8 (2.1–5.9)	2.74 3.16	0.950 0.900	0.150 0.244	1.12 1.19	0.33 0.41	3.26 2.97	TRUS-guided 10 <sup>3</sup> core biopsy	Not reported	
Partin et al., 2003 [22]			3.37 3.72	0.850 0.800	0.290 0.363	1.20 1.26	0.52 0.55	2.33 2.28	TRUS-guided 10 <sup>3</sup> core biopsy	Industry	
Paschoalin et al., 2003 [23]	40–79	2–10	2	1.000	0.067	1.07	0	-	TRUS-guided 10 core biopsy	Academy	
			2.5	1.000	0.344	1.53	0	-			

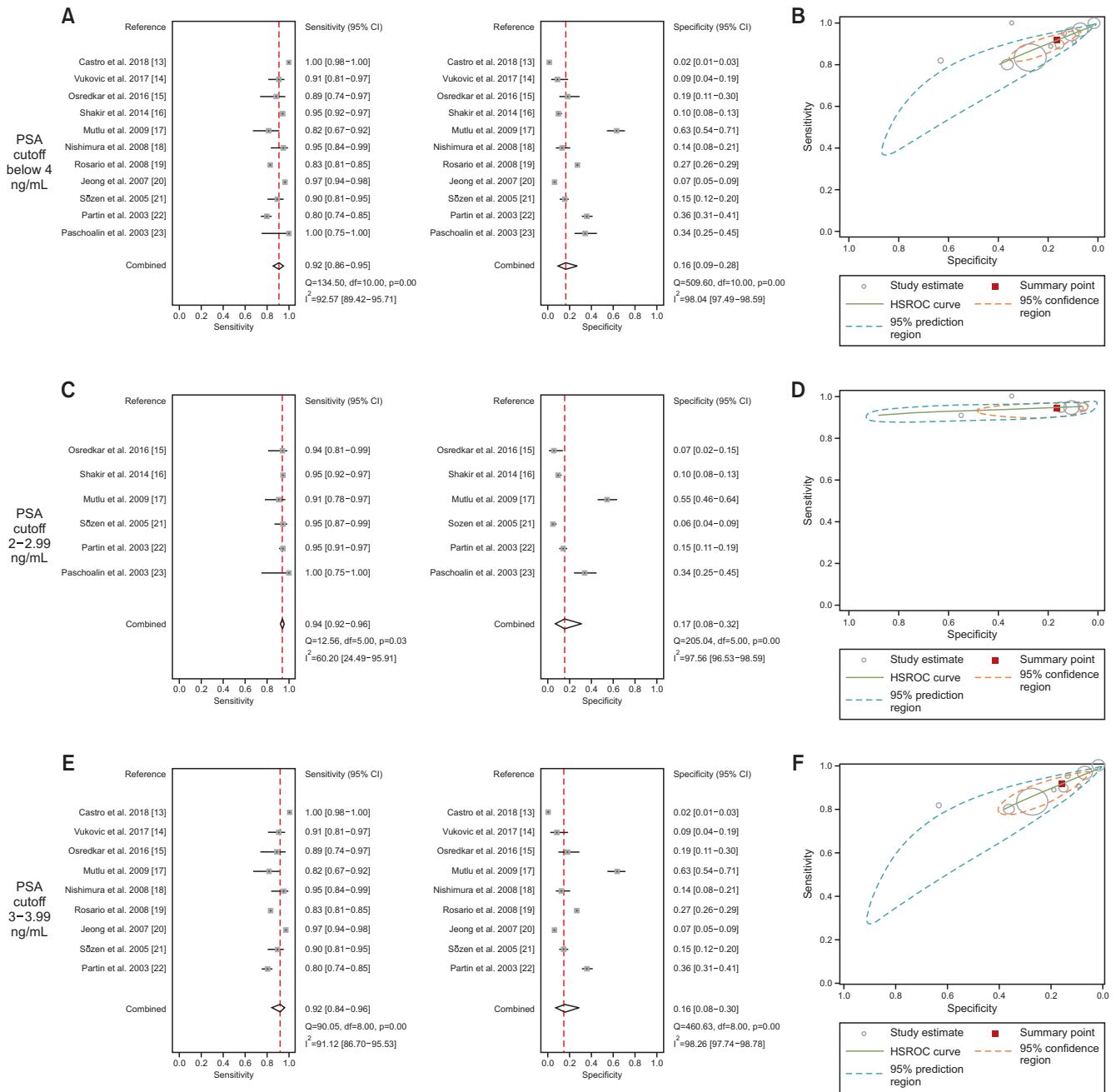
Values are presented as mean±standard deviation or median (interquartile range).

Exclusion criteria: Shakir et al. (2014) according to the information on clinical trial registration; Rosario et al. (2008) according to the ProtecT protocol; Partin et al. (2003) excluded three patients with PSA greater than 100 ng/mL from analysis; and Paschoalin et al. (2003) no exclusion criteria were mentioned in the study, while only patients with PSA less than 10 ng/mL were included in analysis.

PSA, prostate-specific antigen; LR, likelihood ratio; DOR, diagnostic odds ratio; TRUS, transrectal ultrasound.

\*Significant difference between two groups (p<0.05).

<sup>a</sup>.Additional core, if necessary, in biopsy setting.



**Fig. 2.** (A, C, E) Coupled forest plots of pooled sensitivity and specificity of different prostate-specific antigen (PSA) cutoffs. Numbers are pooled estimates with 95% confidence interval (CI) in parentheses. Corresponding heterogeneity statistics are provided at the bottom right corners. (B, D, F) Hierarchical summary receiver operating characteristic (HSROC) curve of the diagnostic performance of PSA for detecting prostate cancer.

heterogeneity of  $I^2=60.2$  ( $p<0.01$ ) and  $I^2=97.56$  ( $p<0.01$ ), respectively (Fig. 2C). The area under the HSROC was 0.93 (95% CI: 0.09–1.00) (Fig. 2D); PLR was 1.29 (95% CI: 0.86–1.71); NLR was 0.43 (95% CI: 0.09–0.78); and DOR was 3.98 (95% CI: 1.79–9.75).

The sensitivity and specificity of a PSA cutoff in the range of 3 to 3.99 ng/mL ranged from 0.8 to 1 and from 0.017 to 0.631, respectively. The pooled sensitivity was 0.92 (95% CI: 0.84–0.96) and the pooled specificity was 0.16 (95% CI: 0.08–

0.30) with significant heterogeneity, respectively ( $I^2=98.26$ ,  $p<0.01$ ;  $I^2=91.12$ ,  $p<0.01$ ) (Fig. 2E). The area under HSROC was 0.67 (95% CI: 0.06–0.99) (Fig. 2F); PLR was 1.22 (95% CI: 0.92–1.51); NLR was 0.50 (95% CI: 0.29–0.72); and DOR was 2.71 (95% CI: 0.94–4.48).

There were no significant differences in the sensitivity and specificity of PSA cutoffs in the range of 2 to 2.99 ng/mL or 3 to 3.99 ng/mL (sensitivity:  $t=2.14$ ,  $p>0.05$ ; specificity:  $t=0.02$ ,  $p>0.05$ ). For PSA cutoffs below 4 ng/mL, in the range

of 2 to 2.99 ng/mL and 3 to 3.99 ng/mL, the Deeks' funnel plot test ( $p=0.17, 0.46, \text{ and } 0.37$ , respectively) showed no evidence of publication bias.

## DISCUSSION

In this analysis, we reviewed the diagnostic accuracy of PSA with a cutoff of  $<4$  ng/mL for the diagnosis of prostate cancer in participants attending health care facilities with symptoms. We reviewed and quantitatively analyzed 11 studies, including a total of 8,512 participants. Our review showed that the PSA test seems to have a high sensitivity but a relatively low specificity. PSA with a cutoff in the range of 2 to 2.99 ng/mL showed a higher sensitivity, specificity, and area under the HSROC compared with cutoffs of from 3 to 3.99 ng/mL and  $>4$  ng/mL. The sensitivity and specificity of PSA cutoffs in the range of 2 to 2.99 ng/mL and 3 to 3.99 ng/mL did not show statistically significant differences. The DOR of PSA with cutoffs in the range of 2 to 2.99 ng/mL was higher than that of PSA with cutoffs in the range of 3 to 3.99 ng/mL.

A recently published study showed that prostate cancer was diagnosed in 25% of patients with PSA levels between 2.5 and 4 ng/mL [24], which is similar to the rate of diagnosis among those with a PSA level of 4 to 10 ng/mL [25]. Another study demonstrated that men older than 50 years with a PSA level higher than 2 ng/mL had a 27.8 times increased risk for prostate cancer [26]. Recently, Ross et al. [27] argued that PSA above 1.5 ng/mL should be used as a cutoff to consider further testing for all age groups, and the ERSPC risk calculator and adjunct variables (for example, PSA density, %fPSA) should be considered to further assess the risk for cancer. Public Health England released guidance in favor of a standard reference range of above 3 ng/mL for men aged 50 to 69 years [28]. Although our review supports the belief that a low PSA cutoff might be more sensitive to prostate cancer, the pooled DOR of each threshold was approximately 2 in addition to the low specificity; therefore, PSA screening tests appear to have low probabilities of confirming and ruling out prostate cancer based on a relatively small likelihood ratio. Moreover, the study by Mutlu et al. [17] showed the most beneficial results in DOR with PSA cutoffs of 2.13 and 2.83 ng/mL; however, the groups in that study had statistically different baseline PSA levels ( $25.3\pm 58.9$  ng/mL in the cancer group and  $8.53\pm 14.28$  ng/mL in the benign group). By contrast, the DOR in the study by Vukovic et al. [14] with PSA cutoffs of 3 and 3.47, which included only participants with normal DRE, was below 1. These results might reflect that a PSA cutoff below 4 ng/mL has a wide range of diag-

nostic accuracy as a screening test according to patient characteristics related to the risk for prostate cancer.

Although biopsy-detected prostate cancer, including high-grade cancer (clinically significant cancer with a Gleason score of 7 or higher), is not rare among men with PSA levels of 4.0 ng/mL or less [29,30], a previous study adopted a threshold of 4 ng/mL for prostate cancer screening and reported only a small absolute survival benefit with 9 years of follow-up [31]. In addition, the Prostate Cancer Intervention versus Observation Trial showed no survival benefit from radical prostatectomy in men with PSA  $\leq 10$  ng/mL (low-risk group) [32]. A low PSA cutoff increases the number of people who undergo prostate biopsy. Therefore, there are concerns about overdiagnosis and overtreatment of indolent and clinically insignificant prostate cancer as well as biopsy-related complications such as bleeding, difficulty in urination, and infection. In short, the choice between performing and not performing a prostate biopsy based on the PSA level is far from simple. However, noticing the distinction between diagnosing a significant or life-threatening cancer that needs to be treated and over-diagnosing a patient by detecting a clinically insignificant cancer that would otherwise have remained small and asymptomatic in the absence of any treatment during the lifetime of the patient is important in clinical practice.

Harvey et al. [33] systematically reviewed the diagnostic accuracy of PSA in a clinical setting, including studies from 1998 to 2008 conducted in Europe, and with a full range of PSA values from  $<4$  ng/mL to  $>10$  ng/mL. The results of that analysis showed that PSA sensitivity ranged from 0.78 to 1.00 and specificity from 0.06 to 0.66. Our results for sensitivity and specificity are consistent with those of the previous review. However, we believe that our study summarizes the results by use of the most updated data with rigorous methodology. The previous review did not assess ROB using QUADAS-2. More importantly, in most studies included in the previous review, TRUS-guided 12-core biopsy, which is a standard biopsy technique, was not performed. Moreover, we included studies with MRI-guided biopsy in addition to TRUS-guided biopsy as a reference test. Compared with the study by Harvey et al. [33], this led to a slightly higher sensitivity and a similar specificity in detecting prostate cancer in our review. Furthermore, our review included studies outside of Europe, such as Asia, Brazil, and the United States.

This study has several limitations. First, all included studies were conducted in a hospital setting, not in a community setting, which might lead to an increased possibility of biopsy being performed in the asymptomatic study population. Second, there was huge clinical heterogeneity



among the included studies. The source of clinical heterogeneity was the baseline differences in PSA levels and DRE findings among the study population. Including participants with or without lower urinary tract symptoms or abnormal DRE findings can be a source of clinical heterogeneity. In addition, studies performed in Brazil and the United States included participants with PSA values below 10 ng/mL, while several other studies from Asia and Europe included participants with PSA values up to 20 ng/mL. Some studies did not aim to evaluate the test performance of PSA but focused on diagnostic tools. Third, we were not able to perform subgroup analysis by patient characteristics to investigate the source of heterogeneity owing to small numbers of included articles. Finally, almost all studies were rated as having a high ROB in the index test domain, as the PSA cutoff threshold was not prespecified.

Although the issues of overdiagnosis and overtreatment of prostate cancer related to the use of a low PSA cutoff threshold continue, prostate cancer diagnostic rates of over 20% among those with PSA levels <4 ng/mL cannot be overlooked. In our review, no significant differences in sensitivity and specificity were found in the diagnosis of prostate cancer, although PSA with a cutoff value <3 ng/mL was relatively more sensitive and specific than PSA  $\geq 3$  ng/mL in addition to having a relatively small DOR. Therefore, clinicians should bear in mind that the diagnostic accuracy of PSA tests may vary according to patient characteristics and should choose a cutoff after discussing potential benefits and risks of screening with their patients to incorporate patient preferences in the decision.

## CONCLUSIONS

Although a PSA cutoff of <3 ng/mL is relatively more sensitive and specific than a PSA cutoff  $\geq 3$  ng/mL, no significant differences in sensitivity or specificity were found in the diagnosis of prostate cancer. Therefore, clinicians should choose a PSA cutoff with consideration of clinical circumstances, including patient characteristics related to the risk for prostate cancer.

## CONFLICTS OF INTEREST

The authors have nothing to disclose.

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## AUTHORS' CONTRIBUTIONS

Research conception and design: Jae Hung Jung, Woong Kyu Han, Eu Chang Hwang, and Su-Yeon Yu. Data acquisition: Kwang Suk Lee, Sang Hyub Lee, and Hakmin Lee. Statistical analysis: Yan Jin. Data analysis and interpretation: Yan Jin, Narae Lee, Ji Eun Yun, Kwang Suk Lee, Sang Hyub Lee, and Hakmin Lee. Drafting of the manuscript: Yan Jin and Jae Hung Jung. Critical revision of the manuscript: Woong Kyu Han, Eu Chang Hwang, and Su-Yeon Yu. Obtaining funding: Su-Yeon Yu and Woong Kyu Han. Administrative, technical, or material support: Yoonmi Nho. Supervision: Woong Kyu Han and Su-Yeon Yu. Approval of the final manuscript: all authors.

## SUPPLEMENTARY MATERIALS

Supplementary materials can be found via <https://doi.org/10.4111/icu.20210429>.

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