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Review

Comparison on Diagnostic Accuracy of Prostate Cancer Detection Tools: A Systematic Review and Meta-Analysis

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HIGHLIGHTS

- Some tests and markers have proved to improve the diagnosis of prostate cancer (PCa).
- PI-RADS is superior in the diagnosis of PCa with high sensitivity, specificity, and AUC compared to PHI and PCA3.
- Fagan's nomograms showed that the post-test probability of cancer subjects.

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ABSTRACT

Introduction
Some tests and markers have proved to improve the diagnosis of prostate cancer (PCa). This meta-analysis aimed to review the diagnostic accuracy of three commercial tests, prostate health index (PHI), prostate cancer antigen 3 (PCA3), and prostate imaging reporting & data system V2 (PI-RADS) for detecting of PCa.

Methods
We did a comprehensive literature search of international databases including Scopus, Web of Science, and PubMed from January 2000 to Feb 2018. We included three groups of diagnostic accuracy studies that used PCA3, PHI, and PI-RADS to assess PCa. The l quality of the study was measured by the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) criteria.

Results
Twenty-six studies on PHI, 24 articles on PI-RADS, and 26 papers on PCA3 were included for the meta-analysis. For the diagnosis of PCa, the sensitivity and specificity were 0.76 and 0.84 for PI-RADS, 0.48 and 0.85 for PHI, 0.49 and 0.79 for PCA3. Also, the derived area under curves (AUC) from the hierarchic summary ROCs (HSROCs) were 0.86 (95% CI, 0.83-0.89) for PI-RADS, 0.72 (0.68-0.76) for PCA3, and 0.70 (0.66-0.74) for PHI. Fagan's nomograms showed that the post-test probability of cancer subjects with a positive test was 53%, 63%, and 45%, for PHI, PI-RADS, and PCA3 respectively.

Conclusions
Currently, available evidence suggests that the PI-RADS is superior in the diagnosis of PCa with high sensitivity, specificity, and AUC compared to PHI and PCA3.

Keywords: Prostate Cancer; Prostate Imaging Reporting & Data System; Prostate Health Index; Prostate Cancer Antigen 3; Diagnosis

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Introduction

Prostate cancer (PCa) is one of the most prevalent cancers and is the second source of death in American men with a global incidence of 49.6 per 10000 persons (1). Prostate-Specific Antigen (PSA) is being commonly used for the detection of PCa as it is cheap and easy to access; however, its sensitivity and specificity are not adequate as an ideal tumor marker (2). Other diagnostic modalities including PSA density, prostate health index (PHI), prostate imaging reporting and data system (PI-RADS), and prostate cancer antigen3 (PCA3) have gained a great deal of attention as accurate diagnostic tests (3-5). PCA3 is a urinary biomarker that is overexpressed in PCa and has been shown to have more specificity compared to PSA, especially in repeated biopsy patients (6). PHI is a combination formula of total PSA, free PSA, and proPSA and enjoys greater specificity than PSA especially for clinically significant PCa detection. Also, increased PHI is an index of cancer recurrence after radical prostatectomy (7, 8). PI-RADS is another diagnostic method for PCa with good accuracy, though it has a significant heterogeneity (9). PI-RADS is a scoring system for each MRI sequence and is reported as a per lesion score. Investigations of early PCa diagnosis have indicated different methods with each having limitations despite good accuracy (9, 10). A prostate biopsy is a gold standard for PCa diagnosis (11) and many papers have been published comparing its accuracy versus diagnostic accuracy of PCA3, PHI, and PI-RADS individually (6, 12, 13). The object of this study was to compare three methods together based on their sensitivity, specificity, and accuracy to determine an overall picture of accurate PCa diagnosis.

Methods

The protocol of the study was saved in PROSPERO; International Prospective Register of Systematic Reviews, with ID= CRD42018089099.

Search strategy

The systematic search was conducted in the international databases including PubMed, Scopus, and Web of Science from January 2000 to Feb 2018 according to PRISMA guideline (14). The search terms were: (prostate or prostatic) AND (cancer or carcinoma or neoplasm or malignancy or tumor) AND (assessment or diagnosis or (sensitivity and specificity) or detection) AND (biopsy or pathology or histopathology) AND [("Prostate Imaging Reporting and Data System") or PI-RADS or PIRADS) OR ("Prostate Cancer Antigen3" or PCA3 or dd3 or upm3 or "differential display code 3 antigen") OR (Prostate Health Index or PHI or "[-2] proPSA). Additionally, the reference list of each relevant article was reviewed. Furthermore, gray literature, such as reports and conference presentations were checked.

Study selection

We included three groups of articles in this systematic review to evaluate the diagnostic tests of PCa. The common criteria included 1) enrolled patients with suspected or early diagnosis PCa; 2) for comparison, a gold standard based on the histopathological examination of biopsy; 3) sufficient data to calculate true positive (TP), false negative (FN), false positive (FP) and true negative (TN) values for PCa diagnosis; and 4) studies that were original articles. On the other hand, the specific criteria were: a) for PI-RADS V2 test, MRI of the prostate including all sequences performed and assessed by a PI-RADS scoring system; 2) for PCA3 test, all patients undergoing PCA3 testing before biopsy; and 3) for PHI test, calculating of this index using the formula of serum levels of fPSA, tPSA, and p2PSA.

Studies with no usable data, receiving therapy, aggressive PCa, non-English full-text papers, and studies with overlapping patient populations were excluded. Also, review articles, letters to editors, animal studies, and case-report studies were excluded. Two researchers independently performed the screening process based on titles, abstracts, and then full texts of selected papers. Possible disagreements were resolved by consensus.

Data extraction and quality evaluation

We extracted the following data from each paper: the name of the first author, the year of publication, country of data collection, study design, patient age, number of PCa, descriptions of the diagnostic tests, and cut-off values. For each study, values of TP, FN, FP, TN, sensitivity, specificity, and area under the curve (AUC) were extracted if available.

The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) was used for the quality assessment of included studies (15). Data extraction and quality assessment were performed by two separate researchers and all disagreements were resolved by a third reviewer.

According to each diagnostic test (PIRADS, PCA3, and PHI), the sensitivity, specificity, and diagnostic odds ratio (DOR) were obtained for every study and subsequently pooled. The heterogeneity of included studies was assessed by Q test and I^2 statistic. If the results of the Q test were significant and I^2>50%, the random effect model was selected. We also assessed the test performance using the summary receiver operation characteristics (SROC) curve and AUC. The Deeks funnel plot was used to assess potential publication bias. We used Fagan's nomogram to estimate the clinical value of the diagnostic test.

All meta-analysis methods were performed by STATA (Release 14. statistical software. College Station, Texas: STATA Corp LP).

Results

Literature search and study selection

As displayed in Figure 1, the literature searches initially identified 1702 articles. According to inclusion criteria, we assessed titles and abstracts, where 485 articles (PHI=90, PI-RADS=254, and PCA3=141 papers) were selected. After reviewing the full texts, a total of 151 articles (PHI=33, PI-RADS=71, and PCA3=45 papers) remained and finally, 26 studies on PHI, 24 articles on PI-RADS, and 26 papers on PCA3 were eligible for the meta-analysis. The general characteristics of the included studies are presented in Table 1.

Study characteristics

The individual characteristics of the included studies are summarized in Table 1-1 to 1-3. The mean/median age, sample size, TP, TN, FN, FP, and AUC are reported in the tables. A total of 5931 patients (2656 PCa and 3275 non-PCa), 8491 patients (3307 PCa and 5184 non-PCa), and 7487 subjects (2362 PCa and 5125 non-PCa) were included in the pooled analyses for PI-RADS, PHI, and PCA3, respectively.

Quality assessment

All studies in each group (PI-RADS, PHI, and PCA3) were assessed using the QUADAS-2. The results of this assessment are shown in Figure 2. Overall, the quality of the studies was moderate.

Diagnostic accuracy of tools for overall PCa

The combined sensitivity and specificity were 0.76 (95% CI, 0.71–0.81) and 0.84 (0.78–0.90) for PI-RADS, 0.48 (0.43–0.54) and 0.85 (0.80–0.89) for PHI, and 0.49 (0.44–0.54) and 0.79 (95% CI, 0.76–0.82) for PCA3, respectively (Figure 3).

Also, diagnostic odds ratio was 17.57 (11.52-26.80) for PI-RADS, 3.70 (3.14-4.36) for PCA3 and 5.28 (4.03-6.93) for PHI. Figure 4 illustrates the hierarchic summary ROCs (HSROC) plot with 95% CI area and summary points of tools. The derived AUC from the HSROCs were 0.86 (0.83-0.89) for PI-RADS, 0.72 (0.68-0.76) for PCA3, and 0.70 (0.66-0.74) for PHI.

To find the posttest probability, we used Fagan's nomogram for which we performed a simulation of a set with a prevalence of 26% for PCa based on the studies (16). Accordingly, in this model, the probability of someone having PCa and not being detected by the

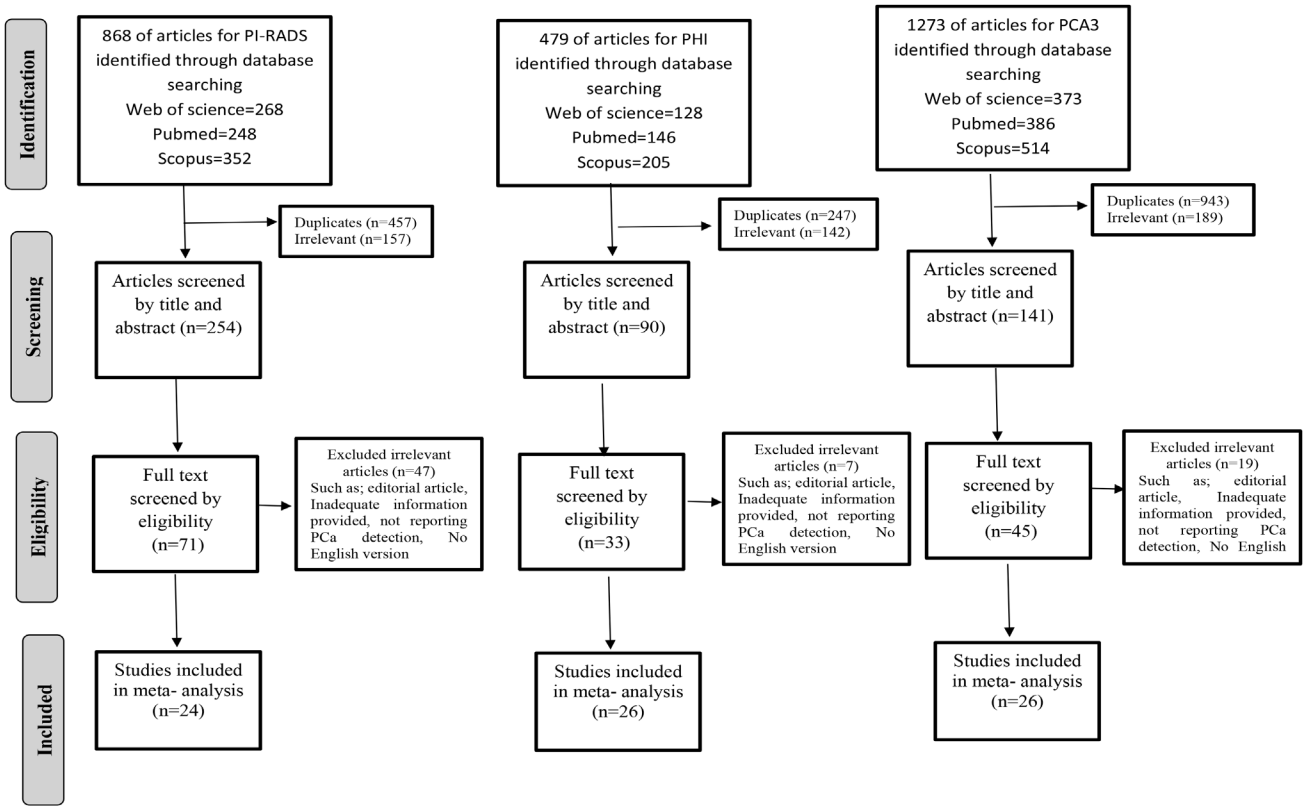

Figure 1. Flow diagram of the study selection process

Table 1-1. Characteristics of studies included in the meta-analysis according to PI-RADS

First Author	Year	Country/ Region	Sample Size	PCa number	Patient Age (Yr) (mean/ median)	Cut-off value	TP	FP	FN	TN	AUC (95% CI)
Garcia-Reyes, K (12)	2013-2016	USA	178	152	64.7(44-83)	NA	95	4	57	22	0.830
Xu, N (17)	2015-2017	China	528	137	65(52-82)	3.0	122	148	15	243	0.836±0.03
Borkowetz, A (18)	2015	Germany	214	111	63(40-75)	4.0	92.	38	19	65	NA
Rosenkrantz, A. B.(19)	NA	USA	60	30	NA	3.0	20	9	10	21	NA
Kuhl, C. K (20)	2013-2016	Germany	542	180	64.8(42-80)	NA	156	43	24	319	NA
Kim, S. H (21)	2014-2016	Korea	295	160	67(51-79)	4.0	144	27	16	108	NA
Gao, G (22)	2008-2010	China	71	35	68.8±8.9	4.0	30	2	5	34	0.906±0.03
Nougaret, S (23)	2007-2014	France	371	292	60(41-81)	4.0	95	44	12	220	NA
Wang, R (24)	2002-2009	China	1478	507	70(65-75)	3.0	412	100	95	871	0.931
Furuya, K(25)	2012-2013	Japan	50	33	68.5 (53-82)	NA	21	8	12	9	0.5830(0.435-0.731)
Kasel-Seibert, M (26)	2013-2015	Germany	82	31	65(48-88)	4.0	24	10	7	41	0.83±0.08
El-Samei, H (27)	2014-2015	Egypt	55	38	62(51-79)	3.0	35	1	3	16	NA
Feng, Z. Y (28)	2013-2015	China	401	150	64.4(34-88)	3.0	144	40	6	211	0.942±0.03
Wang, X (29)	2011-2013	Italy	133	60	68±7.9	5.0	32	8	28	65	0.749±0.02
Polanec, S (30)	2011-2015	Austria	65	33	65.3(62-87)	3.0	32	20	1	12	0.75
Sahibzada, I(31)	2008-2011	UK	200	111	69.8(59-86)	NA	41	13	70	76	NA
Radtke, J. P (32)	2013	Germany	294	150	64(60-71)	3.0	112	48	38	103	NA
Rastinehad, A. R (33)	2012-2014	USA	312	202	65.1(60-70)	3.0	191	75	11	35	0.702
Wang R (34)	2002-2014	China	142	55	68.6(26-91)	3.0	50	20	5	67	0.90±0.05
Grey, A .D.R (35)	2012-2013	UK	201	77	64.5±7.1	3.0	74	50	3	74	0.89
Baur, A .D. J (36)	2008-2012	Germany	55	18	66(54-78)	4.0	14	3	4	34	0.93
Roethke, M. C (37)	2011-2012	Germany	64	27	64.5(49-77)	NA	18	3	9	34	0.848±0.11
Junker, D (38)	2011-2013	Austria	73	39	62±7.8	NA	35	13	4	21	0.86±0.08
Schimmöller, L (39)	2011-2012	Germany	67	28	66.8±7.5	10.0	24	13	4	26	NA

TP: True Positive; FN: False Negative; FP: False Positive; TN: True Negative; AUC: Area Under the Curve; PI-RADS: Prostate Imaging Reporting & Data System; PCa ;Prostate Cancer

Table 1-2. Characteristics of studies included in the meta-analysis according to PHI

First Author	Year	Country/ Region	Sample Size	PCa number	Patient Age (Yr) (mean/ median)	Cutoff value	TP	FP	FN	TN	AUC (95% CI)
Catalona, W.J (40)	2003-2009	USA	892	430	62.8±7	24.1	387	334	53	118	0.72
Seisen, T (41)	2013	France	138	39	63.4(44-83)	40	26	26	13	73	0.8
Lazzeri, M (13)	NA	European	262	136	67.3±8.1	43.7	123	76	13	50	0.81(0.75-0.85)
Filella, X (42)	2011-2013	Spain	354	175	68(38-88)	31.94	158	135	17	49	0.73
Stephan, C (43)	2009-2012	Germany	246	110	65(41-81)	NA	99	107	11	29	0.68(0.62-0.74)
Al Saidi, S.S (44)	2014-2015	Oman	136	28	66(45-90)	41.9	23	21	5	87	NA
Porpiglia, F(5)	2011-2013	Italy	170	52	65(60-70)	48.9	21	26	31	92	NA
Loeb, S (45)	2004-2009	USA	658	324	63(50-84)	27	292	220	32	104	0.707(0.665-0.73)
Ng, C.F (46)	2008-2013	China	230	21	65.9(50-79)	26.54	19	105	2	104	0.781(0.67–0.897)
Osredkar, J (47)	2013-2014	Slovenia	110	36	67(63-72)	25.6	32	53	4	21	0.742(0.65-0.82)
Lazzeri, M(48)	2011-2012	European	646	264	64.2±7.2	27.6	238	308	26	74	0.67(0.64–0.71)
Friedl, A (49)	2014-2016	Austria	112	62	67(61-72)	40	57	34	5	16	0.79
Na, R (50)	2013-2014	China	660	136	66.95±8.89	28.0	127	259	9	265	0.87(0.83-0.90)
Ferro, M (51)	NA	Italy	300	108	65(50-73)	31.6	97	115	11	77	0.77(0.72 - 0.83)
Tan, L.G.L (52)	2012-2014	Singapore	157	30	65.4±6.46	26.75	27	53	3	74	0.7937(0.71–0.88)
Vukovic, I (53)	2012-2014	Serbia	129	65	64±6.6	27.48	59	47	6	17	0.68(0.59-0.77)
Ferro, M(54)	2010	Italy	151	48	64.5(48-87)	38.7	41	40	7	63	0.77
Fuchsova, R (55)	2010-2013	Czech	263	113	66.5(50-83)	37.0	102	71	11	79	0.79
Yu, G.P (56)	2012-2013	China	261	97	67(25-91)	38.59	88	71	9	93	0.85 (0.79–0.91)
Lughezzani, G (57)	NA	European	883	365	64.5±7.7	NA	328	418	37	100	0.68(0.64-0.72)
Furuya , K (25)	2012-2013	Japan	50	33	68.5(53-82)	38.7	21	4	12	13	0.79 (0.67–0.92)
Scattoni ,V(58)	2011-2012	Italy	211	73	67.5±7.5	28.3	66	95	7	43	0.69(0.59–0.79)
Mearini, L (59)	2012	Italy	275	86	65.4±6.8	37.1	79	116	7	73	0.76(0.71 – 0.81)
Park, H (60)	2015-2016	Korea	246	125	69.6±8.7	22.9	112	38	13	83	0.76(0.69–0.84)
Lazzeri, M (61)	2010-2011	Italy	222	71	63.9±7.1	28.8	64	113	7	38	0.67(0.61–0.73)
Lughezzani, G (62)	2010-2011	Italy	729	280	64.3±7.8	NA	252	328	28	121	0.70(0.66-0.73)

TP: True Positive; FN: False Negative; FP: False Positive; TN: True Negative; AUC: Area Under the Curve; PHI: Prostate Health Index; PCa: Prostate Cancer

Table 1-3. Characteristics of studies included in the meta-analysis according to PCA3

First Author	Year	Country/Region	Sample Size	PCa number	Patient Age (Yr) (mean/ median)	Cutoff value	TP	FP	FN	TN	AUC (95% CI)
Haese, A(63)	2008-2009	European	463	128	64.4±6.6	35	60	94	68	241	0.66
Salami, S.S (64)	NA	USA	45	15	64.5	NA	14	19	1	11	0.65 (0.54–0.76)
Marks, L.S (65)	2004-2006	USA	233	60	64(45-83)	35	35	48	25	125	0.67 (0.60–0.76)
Van Gils, M.P.M.Q (66)	NA	Netherland	534	174	64.3±7.2	58	113	122	61	238	0.65 (0.58-0.72)
Panebianco, V(67)	2009-2010	Italy	41	28	60.3(48-69)	35	20	4	8	9	0.75 (0.60–0.87)
Salagierski , M(68)	2011	Poland	80	24	66.2(50-81)	35	18	25	6	31	0.72
Adam, A(69)	2010	South African	105	44	67(35-89)	35	30	20	14	41	0.70 (0.60–0.81)
Deras, I.L (70)	NA	North American	507	206	64(32-89)	35	111	78	95	223	0.70
Aubin, S.M.J (71)	NA	USA	1072	190	NA	35	92	189	98	693	0.69(0.65-0.74)
Goode, R.R (72)	NA	New York	456	88	66(41-90)	35	64	76	31	285	0.77
Hessels, D (73)	2003-2006	Netherland	336	134	63(38-83)	35	82	53	52	149	0.72 (0.66–0.77)
De Luca, S (74)	2011	Italy	432	114	68(41-82)	35	92	228	22	90	NA
Gittelman, M.C (3)	2013	USA	466	102	NA	25	79	156	23	208	0.74
Nyberg, M (75)	2008	Sweden	62	18	63	35	12	24	6	20	0.74
Ochiai, A(76)	2009-2011	Japan	633	264	67(42-89)	35	176	105	88	264	0.74
Ramos, C.G (77)	2009-2010	chile	64	25	62.1(44-83)	35	13	5	12	34	0.77
Pepe, P (78)	2009-2011	Italy	74	27	NA	35	19	27	8	20	0.66
Wu, A.K (79)	2012	USA	103	37	63.5±7.4	35	14	15	23	51	0.64 (0.53–0.75)
Wang, R (80)	2006-2007	USA	187	87	62(44-86)	35	46	20	41	80	NA
Busetto, G.M (81)	2010-2012	Italy	163	68	66.4±5.3	35	46	48	22	47	0.59 (0.51–0.66)
De la Taille, A (82)	2008-2009	European	515	207	63±7.6	35	132	74	75	234	0.76
Stephan, C (43)	2009-2012	Germany	246	110	65(41-81)		99	91	11	45	0.74
Ferro, M (54)	2010	Italy	151	48	64.5(48-87)	32.5	39	44	9	59	0.71
Scattoni, V (58)	2011-2012	Italy	211	73	67±7.5	31.5	66	106	7	32	0.57
Porpiglia, F(5)	2011-2013	Italy	170	52	65(60-70)	32.5	34	29	18	89	NA
Seisen, T (41)	2013	France	138	39	63.4(44-83)	35	24	41	15	58	0.55

TP: True Positive; FN; False Negative; FP; False Positive; TN: True Negative; AUC: Area Under the Curve; PCA3: Prostate Cancer Antigen3; PCa: Prostate Cancer

PHI tool was 18%. In the same vein for the PI-RADS, a negative result was associated with 9% of individuals with PCa. Eventually, for PCA3, it was 18% (Figure 5). On the other hand, the posttest probability of cancer patients with a positive test was 53%, 63%, and 45% for PHI, PI-RADS, and PCA3 respectively. All these suggest that among these tests, PI-RADS is more specific in the diagnosis of PCa.

Publication bias

The asymmetry of Deek's plot was used to detect possible publication bias. The results revealed no publication bias for PCA3 and PI-RADS (Figure 6).

Discussion

In this meta-analysis, we assessed the diagnosis of PCa by three tools, PI-RADS, PHI, and PCA3. The results of this study showed that these techniques have acceptable validity indices to detect PCa.

The diagnostic value of common tests in PCa detection is still challenging. Despite the widespread use of PSA as a biomarker for unnecessary biopsies and detection of PCa, its use is far from ideal due to its low specificity (83). Therefore, a US preventive services task force recommends other biomarkers and tools with high sensitivity and specificity for diagnosis (84). Meanwhile, it should be noted that biopsy may be related to a few problems, such as bleeding, urinary retentions, or infections despite antibiotic prophylaxis (85, 86). Therefore, it is necessary to evaluate the diagnostic value of tools for reducing useless biopsies.

Although studies showed that there are many tests to diagnose PCa, three tests with high sensitivity and accuracy are used for early detection of prostate cancer. Recently, multi-parametric MRI, which includes anatomical T2-weighted imaging (T2WI), diffusion-weighted imaging (DWI), dynamic contrast-enhanced (DCE) imaging, and magnetic resonance spectroscopy (MRS), is becoming increasingly popular for detection, staging, and treatment planning of PCa (87). To decrease variability and establish wide acceptance and implementation in practice, the European Society of Urogenital Radiology (ESUR) published a guideline known as PI-RADS (88). In 2015, an updated version (PI-RADS V2) was developed that improved the sensitivity and specificity of V1 for assessing PCa (89). In our meta-analysis, we only included studies employing PI-RADS V2 for detecting overall PCa.

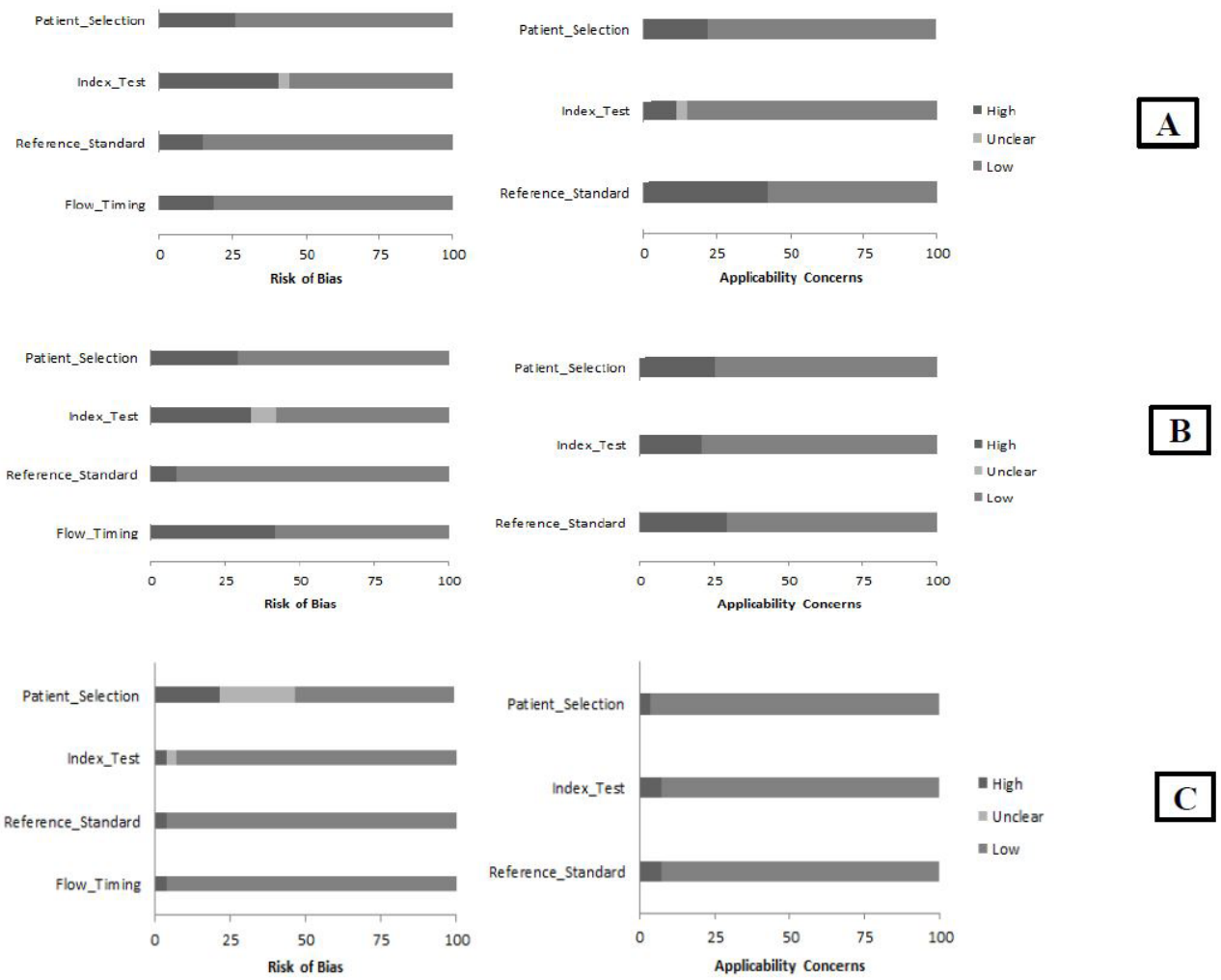

Figure 2. The assessment of methodological quality of the graph for all included studies according to diagnosis tests, A= PHI, B=PI-RADS, C= PCA3

Other methods for diagnosing PCa are serum markers. It has been proposed that measurement of the precursor PSA isoform and its derivatives might improve the detection of PCa. The PHI is a comprehensive test that includes serum p2PSA, free PSA, and total PSA, and can increase the diagnostic accuracy of tPSA in detecting PCa (90). Some studies demonstrate that PHI may be better than tPSA alone in initial or repeat setting (91, 92). Another diagnostic tool is a urine marker called PCA3 that is a non-coding RNA with an over-expressed in PCa cells (93, 94). A few studies have found that PCA3 is valuable for PCa screening and in decreasing the number of negative biopsies (82, 95).

In 2013, a systematic review showed that the pooled sensitivity and specificity of PHI were 90% and 31.6%, respectively. The results of this study indicated that the accuracy of PCa detection improved using PHI (96).

Another meta-analysis study suggested that the urine PCA3 has acceptable sensitivity (62%), specificity (75%), and a moderate level of accuracy (AUC=0.75) in PCa diagnosis (97). The finding of a meta-analysis revealed that PI-RADS version 2 has (9) good precision in PCa with great sensitivity and modest specificity (9).

Our results showed approximately high specificity of three tests, PI-RADS, PHI, and PCA3 ranging between 0.79 and 0.85. Few studies are assessing the prognostic performance of these three tests in patients with PCa. In a cohort study, PI-RADS resulted in the highest value in the accuracy for predicting PCa compared with PCA3 and PHI (AUC=0.78) (98). In another study, the results showed that PI-RADS has a high diagnostic value in identifying PCa compared with PCA3 and PHI (AUC=0.936) (5).

To the best of our knowledge, our study is the first systematic review and meta-analysis to evaluate and

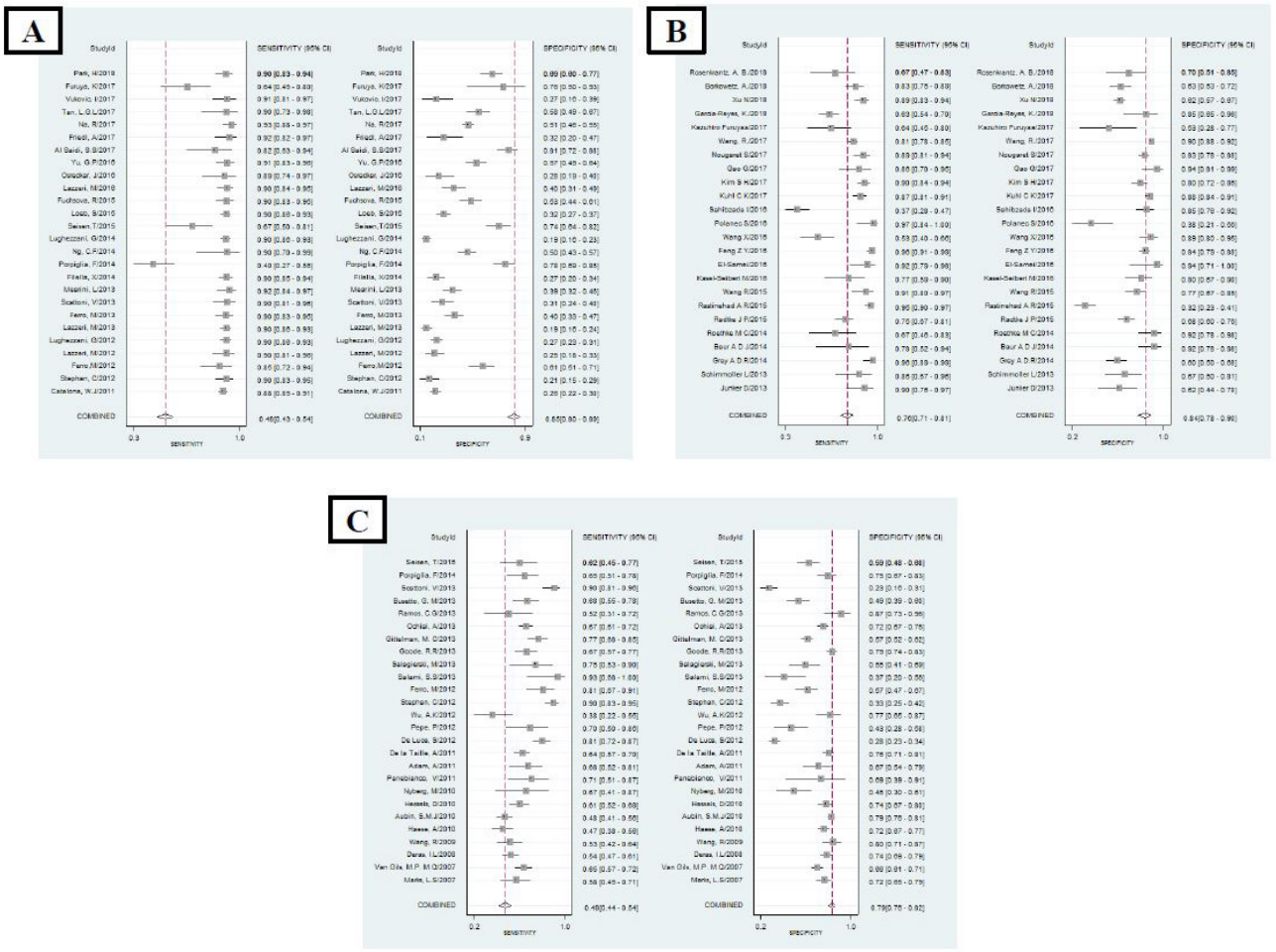

Figure 3. Forest plots of pooled sensitivities and specificities of PHI(A), PI-RADS(B) and PCA3(C) for the diagnosis of PCa

compare the performance of PI-RADS, PHI, and PCA3 with each other. Our results suggested that PI-RADS V2 yielded the highest AUC value (0.86) and that this model is superior to the other models in terms of performance including PCA3 or PHI (DOR= 17.57 for PI-RADS, 3.70 for PCA3, and 5.28 for PHI). Indeed, the high variations of values for sensitivity and specificity have been revealed in the DOR, with greater values indicating a better discriminatory diagnostic test (99). Also, the post-test probability of PI-RADS was higher than that of PCA3 or PHI, indicating a relatively good clinical value of the PI-RADS test. On the other hand, if the patient test is negative, the post-test probability of having PCa would be 9% and if the patient test is positive, the post-test probability of having PCa would be 63% for PI-RADS.

It is important to note that although MRI requires expert interpretation and has high inter-observer variability and is expensive, it offers spatial information on tumors.

Our meta-analysis had some limitations which should be taken into account. The results of this study showed heterogeneity compromising the overall accuracy.

Although there is one gold-standard (biopsy) and studies were included only based on the number of patients in all studies, lack of blinding, not selecting patients with the same criteria across all studies, and different cut-off points for tools caused heterogeneity. Also, we expanded our searches in several databases to avoid publication bias. Another limitation was a potential publication bias, as non-English studies were excluded. The small number of trials and the marked differences between the methodology of tests may have yielded moderate quality. Nevertheless, our study provided the most up-to-date evidence on the important tests of PCa diagnosis. However, the large multicenter randomized trials or cohort studies with similar methodologies should be performed to evaluate the diagnostic value of PI-RADS, PHI, and PCA3 in predicting PCa in the future.

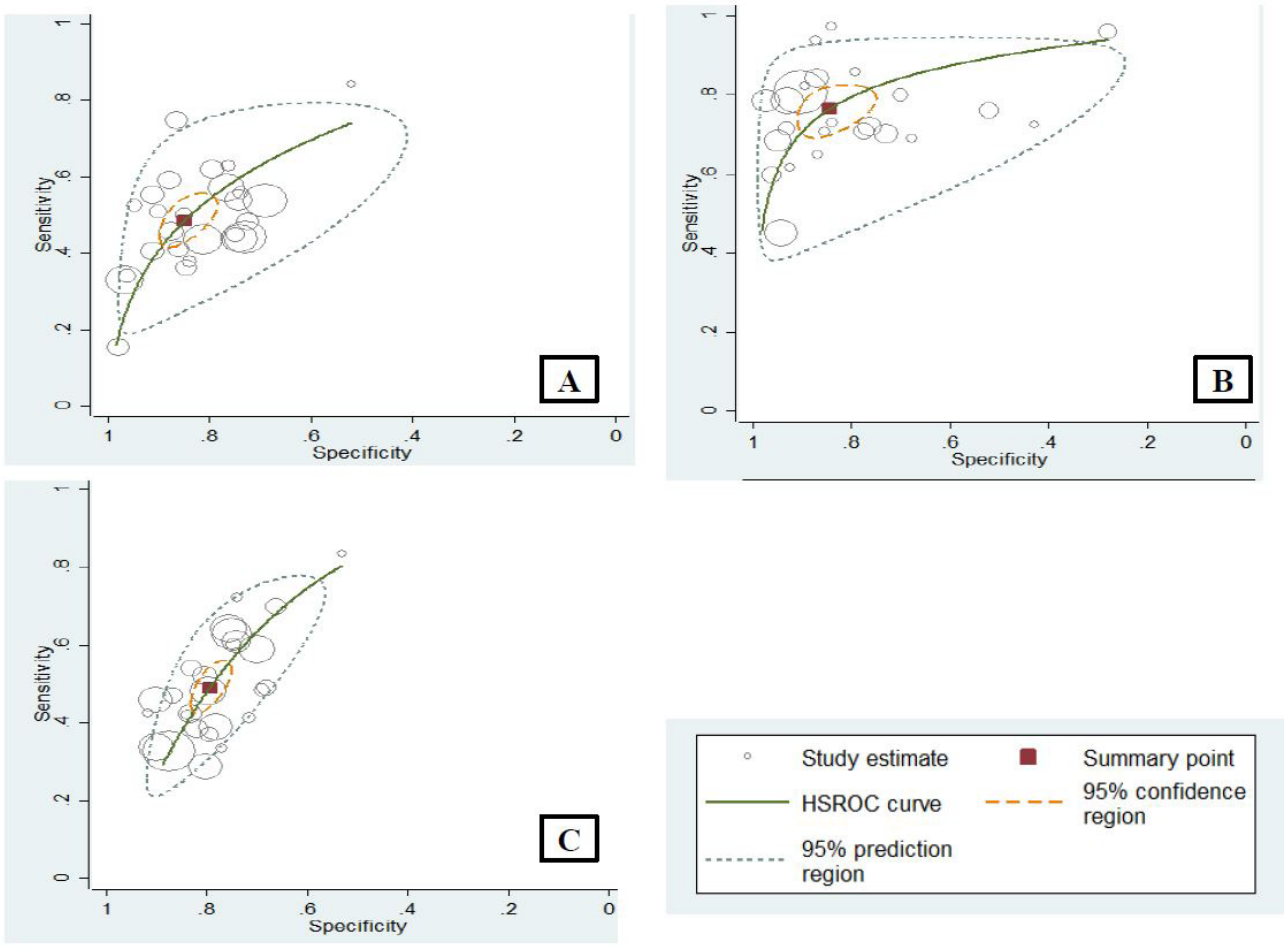

Figure 4. The SROC curve of diagnostic tests for PCa. A= PHI, B=PI-RADS, C= PCA3

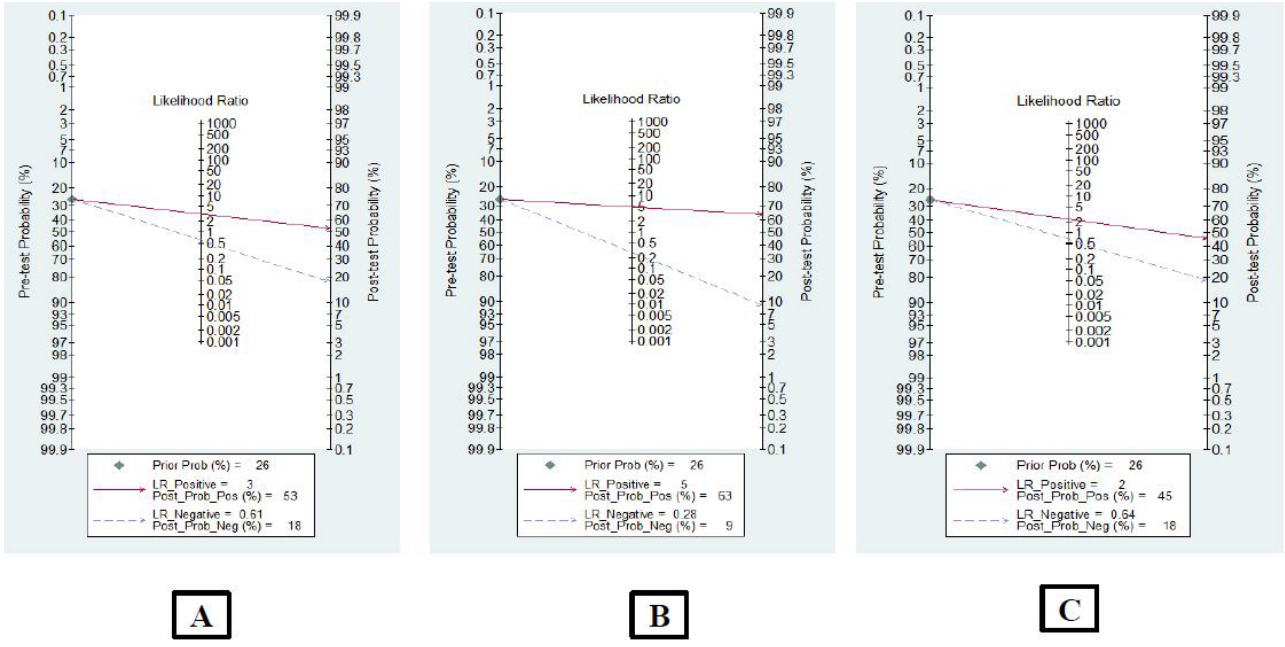

Figure 5. Fagan diagram assessing the diagnostic value of tests for PCa. A= PHI, B=PI-RADS, C= PCA3

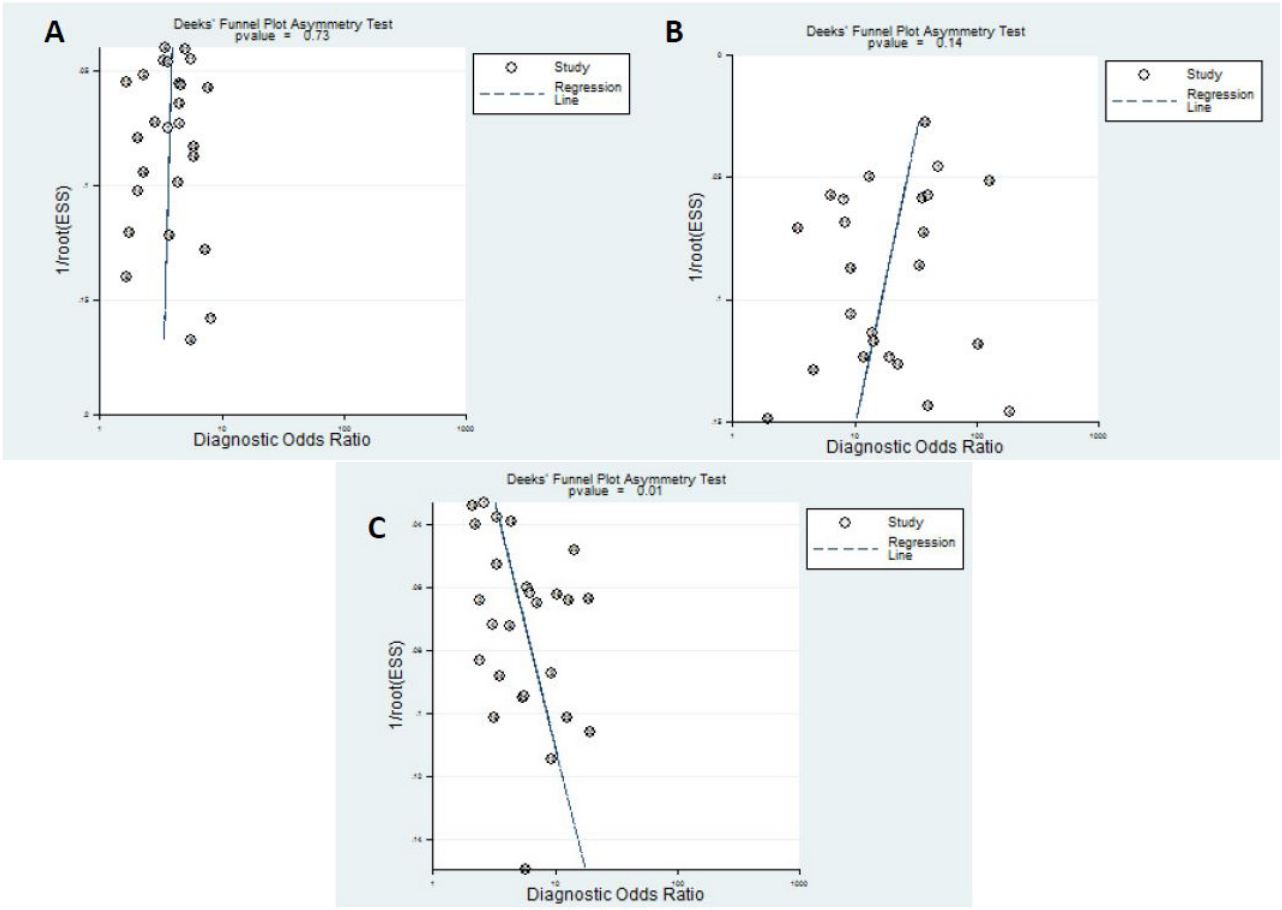

Figure 6. Linear regression test of funnel plot asymmetry for PCA3 (A), PI-RADS (B) and PHI(C)

Conclusions

Based on the results of this review, the clinical application of these non-invasive methods of early detection of PCa would reduce unnecessary biopsies. Currently, available evidence suggests that the PI-RADS is superior in PCa diagnosis with high sensitivity, specificity, and AUC compared to PHI and PCA3.

Authors' contributions

All authors contributed equally.

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Conflict of interest

All authors declare that there is not any kind of conflict of interest.

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Ethical statement

Not applicable.

Data availability

Data will be provided by the corresponding author on request.

Abbreviation

AUC	Area under curves
DCE	Dynamic contrast-enhanced
DOR	Diagnostic odds ratio
DWI	Diffusion-weighted imaging
ESUR	European Society of Urogenital Radiology
FN	False negative
FP	False positive

HSROCs	Hierarchic summary ROCs
MRS	Magnetic resonance spectroscopy
PCa	Prostate cancer
PCA3	Prostate cancer antigen 3
PHI	Prostate health index
PI-RADS	Prostate imaging reporting & data system
PSA	Prostate-specific antigen
QUADAS	Quality assessment of diagnostic accuracy studies
SROC	Summary receiver operation characteristics
TN	True negative

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