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Prostate health index (PHI) as a reliable biomarker for prostate cancer: a systematic review and meta-analysis

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Abstract

Objectives: Prostate cancer (PCa) represents the second most common solid cancer in men worldwide. In the last decades, the prostate health index (PHI) emerged as a reliable biomarker for detecting PCa and differentiating between non-aggressive and aggressive forms. However, before introducing it in clinical practice, more evidence is required. Thus, we performed a systematic review and meta-analysis for assessing the diagnostic performance of PHI for PCa and for detecting clinically significant PCa (csPCa).

Methods: Relevant publications were identified by a systematic literature search on PubMed and Web of Science from inception to January 11, 2022.

Results: Sixty studies, including 14,255 individuals, met the inclusion criteria for our meta-analysis. The pooled sensitivity and specificity of PHI for PCa detection was 0.791 (95%CI 0.739–0.834) and 0.625 (95%CI 0.560–0.686), respectively. The pooled sensitivity and specificity of PHI for csPCa detection was 0.874 (95%CI 0.803–0.923) and 0.569 (95%CI 0.458–0.674), respectively. Additionally, the diagnostic odds ratio was 6.302 and 9.206, respectively, for PCa and csPCa detection, suggesting moderate to good effectiveness of PHI as a diagnostic test.

Conclusions: PHI has a high accuracy for detecting PCa and discriminating between aggressive and non-aggressive PCa. Thus, it could be useful as a biomarker in predicting patients harbouring more aggressive cancer and guiding biopsy decisions.

Keywords: biomarker; clinically significant prostate cancer (csPCa); diagnosis; PCa; prostate health index (PHI); prostate tumor; screening.

Introduction

Prostate cancer (PCa) represents the most common solid tumour in men over 60 years and the second leading cause of cancer death in men, after lung cancer [1].

PCa is a very heterogeneous disease characterised by a wide spectrum of clinical manifestations, ranging from clinically insignificant forms to lethal castration-resistant ones. It has been estimated that more than 50% of patients has a low risk of progression [2]. In these patients, active surveillance instead of a radical surgery procedure is recommended. Noteworthy, the over-diagnosis and over-treatment of indolent tumours is major trouble associated with PCa. Thus, the early identification and the appropriate management of the patients is fundamental. In this scenario, laboratory medicine has a key role. Worldwide, the PCa screening is based on the use of the prostate-specific antigen (PSA). It is a serine protease, which physiologically dissolves seminal clots. The circulating PSA consists of 80–95% complexed forms and the small remaining proportion of free form. The test for measuring total PSA (tPSA) levels, including both complexed and free PSA (fPSA), was developed and approved by the Food and Drug Administration for PCa over 30 years ago [3]. However, the PSA-based screening has several drawbacks. First, PSA is

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organ-specific and not cancer-specific. Although it has high sensitivity, it has poor specificity and low positive predictive value (PPV), resulting in unnecessary biopsies. Additionally, PSA cannot accurately identify aggressive PCa [4], leading to over-diagnosing and over-treatment in patients with low-risk disease that may not require active clinical intervention. Indeed, up to 42% of PCa detected based on PSA are clinically insignificant. Consequently, the identification of patients with clinically significant PCa (csPCa), which requires treatment, is one of the main concerns in daily practice. Finally, PSA levels are influenced by several factors, such as benign prostatic hyperplasia, infection, age, and drug [5, 6]. Thus, there is active research for identifying reliable biomarkers to guide Clinicians in the detection of PCa and its aggressive forms to appropriately treat the patient.

In the last decades, a role for the different forms of PSA has emerged. In the early 1990s, literature evidence showed that increased levels of fPSA are commonly associated with benign conditions [7, 8]. Noteworthy, fPSA consists of three different forms: benign PSA, intact inactive PSA, and proPSA. Among these, proPSA is the form associated with PCa. proPSA has several molecular isoforms, including [–2], [–4], and [–5, –7] [9]. The [–2] proPSA (p2PSA) is the most stable in serum. In 2010, the Beckman Coulter introduced an automated immunoassay for its detection and developed an index, namely the prostate health index (PHI), which is calculated by a mathematical combination of the values of tPSA, fPSA, and p2PSA, according to the following formula: (proPSA/fPSA)$\times\sqrt{}$tPSA. In 2012, the FDA approved PHI for PCa detection in men with the following characteristics: (i) older than 50 years; (ii) PSA between 4 and 10 µg/L; (iii) or a non-suspicious digital rectal examination (DRE) [10]. Additionally, some Authors showed that PHI outperforms tPSA and fPSA in the detection of csPCa [11, 12].

Although several Authors showed that PHI has good analytical performance for detecting PCa, the European Association of Urology stated that there is too limited evidence to implement these tests into routine screening programs [13]. Also, the American Urological Association has declared that more evidence is required to confirm the reliability of PHI to decrease the number of unnecessary biopsies while keeping the capacity to detect csPCa [14].

The aim of this study was to assess the accuracy of PHI for detecting PCa and identifying csPCa.

Materials and methods

We followed the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines 2020 [15]. All studies investigating the diagnostic efficacy of PHI for PCa detection were searched for inclusion.

Literature search strategy

Two reviewers systematically and independently (LA and MV) performed a comprehensive electronic search of PubMed and Web of Science. The following Medical Subject Heading (MeSH) terms "Prostate Health Index", "PHI", "cancer prostate" and "tumor prostate" were used to search articles. No publication date restriction was applied, and the date of our search was until January 11, 2022.

Study selection

The inclusion criteria were: (i) retrospective and prospective study design; (ii) English language; (iii) sufficient data provided to calculate the outcome; (iv) PCa diagnosis confirmed on biopsy.

Exclusion criteria were: (i) evaluation of only the prognostic role of PHI; (ii) lack of evaluation of PHI accuracy; (iii) letters, case reports, animal studies, reviews, and meta-analysis (vi) other languages than English; (v) full-text not found.

Data collection

Two authors (LA and MV) independently collected data referring to studies and patient characteristics. The extracted information from each study included the first author's name and year of publication, study design, inclusion criteria, study population, nr of positive biopsy, nr of csPCa, the calibration system used (WHO vs. Hybritech), PHI cut-off value, outcome data [sensitivity, specificity, true positive (TP), false negative (FP), true negative (TN), false positive (FP)].

Statistical analysis

Meta-analytical summaries of PHI performance were calculated following the bivariate binomial approach by fitting a generalized linear mixed model (GLMM) [16–18]. Summary pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio and diagnostic odds ratio (DOR) were calculated by R Language v. 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) and RStudio IDE v.1.3.1093 (RStudio, PBC, Boston, MA) with the lme4, mada and meta packages [19]. Pooled results were confirmed by importing data into the interactive application MetaDTA (Diagnostic Test Accuracy Meta-Analysis v. 2.01) hosted on the shinyapps server and available at https://crsu.shinyapps.io/dta_ma/ [20, 21]. Hierarchical summary receiver operating characteristic (HSROC) model parameters estimated by MetaDTA (lambda or accuracy parameter, theta or cut-point parameter, beta or shape parameter, the variance of the accuracy parameter and the variance of threshold parameter) were imported into the software Review Manager (RevMan) v. 5.4.1 (The Cochrane Collaboration, 2020) to obtain the HSROC plots [22]. Heterogeneity across the studies was evaluated by plotting sensitivities and specificities, together with their 95%CI, by Forest and Crosshair plots [23] and by inconsistency index (I2), calculated as 100%*(Q – df)/Q, where Q is Cochran's heterogeneity statistic and df the degrees of freedom. Publication bias was evaluated by funnel plot and Deeks's formal test.

Results

Study selection

The process of study selection is schematically presented in the PRISMA flow diagram (Figure 1). After the removal of duplicates, a total of 371 articles were obtained. After screening the title and abstracts, 273 studies were excluded because they were literature review, case reports, letters, or meta-analysis; they did not measure PHI; they did not evaluate the diagnostic accuracy of PHI for PCa detection. The full text of 92 studies was further evaluated. Finally, a total of 60 studies were included, 42 for PCa and 18 for csPCa analysis.

Study characteristics and quality assessment

The main characteristics of all the studies included in the meta-analysis are reported in Table 1.

The diagnostic performances of the studies for PCa and csPCa analysis are described in Tables 2 and 3, respectively.

For PCa studies (n=42), the sample size included was between 50 and 1,538, with cut-off, sensitivity and specificity ranging, respectively, from 21.3 to 63.9, from 0.380 to 0.945 and from 0.213 to 0.963 (Table 2). For csPCa studies (n=18), the sample size included was between 43 and 1,538, with cut-off, sensitivity and specificity ranging, respectively, from 17.8 to 67.6, from 0.533 to 1.000 and from 0.211

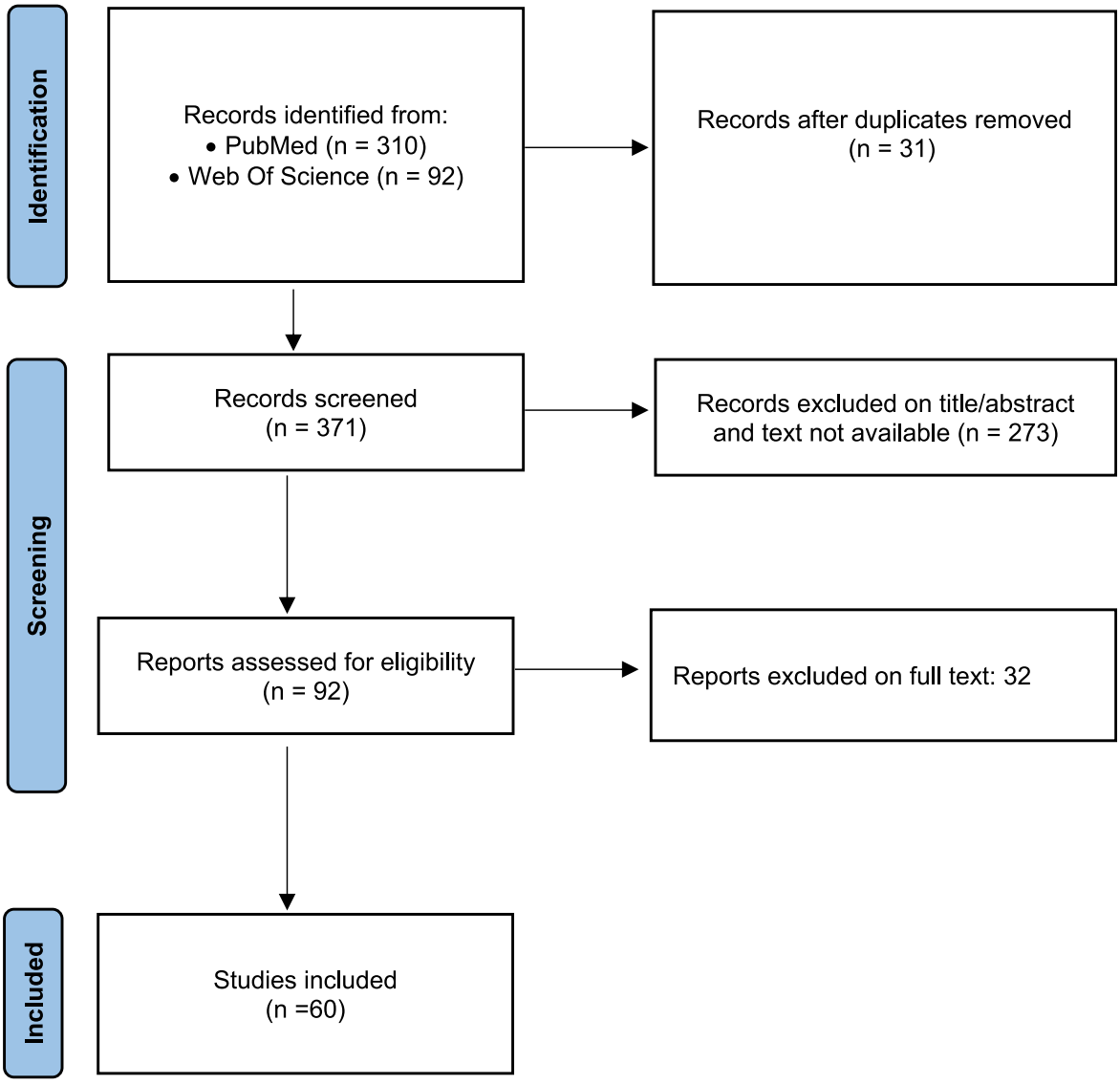

Figure 1: PRISMA 2020 study selection flow diagram.

Table 1: Characteristics of all the studies included in the meta-analysis.

Authors [ref]	Study design	Country	Inclusion criteria	Study population	Positive biopsy	csPCa	Calibrators
Chiu et al. 2021 [24]	Monocentric prospective observational	Taiwan	PSA 2–10 µg/L, and/or a suspicious DRE	412	134	94	Hybrithech
Ferro et al. 2021 [25]	Monocentric prospective observational	Italy	PSA 2–10 µg/L, and/or a suspicious DRE	196	142	90	WHO
Garrido et al. 2021 [26]	Monocentric prospective observational	Portugal	PSA between 2 and 10 µg/L and no previous history of PCa, irrespective of the DRE findings	237	118	100	Hybritech
Stejskal et al. 2021 [27]	Multicentric prospective observational	Czech republic	Men planned for a prostate biopsy for elevated total PSA levels with negative DRE at four different hospitals	395	296	–	NA
Kim et al. 2020 [28]	Multicentric prospective observational	UK	Increased PSA and mpMRI	545	395	256	NA
Nassir et al. 2020 [29]	Monocentric retrospective observational	Saudi Arabia	tPSA of 4–10 µg/L, who were initially underwent prostate biopsy	194	71	–	NA
Othman et al. 2020 [30]	Monocentric prospective observational	Malaysia	Consecutive men undergoing TRUS prostate biopsy for suspected PCa with tPSA level of ≤20 µg/L	84	25	8	Hybritech
Barisiene et al. 2020 [31]	Multicentric prospective observational	Lithuania	Males older than 50 years old with tPSA range from 2 to 10 µg/L and normal DRE referred for prostate biopsies	210	112	81	Hybritech
Ito et al. 2020 [32]	Multicentric prospective observational	Japan	(1) serum PSA higher than the age stratified cut-offs of 3 ng/mL at ages 50–64 years, 3.5 µg/L at 65–69 years and 4 ng/mL at 70 years old or older, and 10 ng/mL or less; (2) an initial prostate systematic biopsy within 3 months after informed consent; (3) the number of biopsy cores restricted to 12 to 20 with acceptance of an additional target biopsy of a hypoechoic region by transrectal ultrasound or a suspicious region by MRI; (4) men between ages 50 and 79 years; (5) TRUS findings of abnormality, and total and transition zone prostate volume within 6 months before prostate biopsy; and (6) optional MRI before prostate biopsy	363	179	–	NA
Kopecký et al. 2020 [33]	Monocentric prospective observational	Poland	Patients suspected of having PCa	55	31	–	NA
Stojadinovic et al. 2020 [34]	Monocentric retrospective observational	Serbia	Men with PSA ≤10.0 µg/L who underwent transrectal, ultrasound guided prostate biopsy and PHI testing	200	88	35	NA
Hsieh et al. 2020 [35]	Monocentric prospective observational	Asian	Patients who were more than 40 years and underwent prostate biopsy for suspicious PCa due to elevated serum PSA level (PSA >4 µg/L) and/or abnormal findings on DRE	102	39	24	NA
Lopes et al. 2019 [36]	Monocentric retrospective observational	NA	Patients with PHI test and 3 T MR exam with at least one suspicious MR identified lesion with a PI-RADS score of ≥3 prior to biopsy.	233	82	–	NA

Table 1: (continued)

Authors [ref]	Study design	Country	Inclusion criteria	Study population	Positive biopsy	csPCa	Calibrators
Jagalarmudi et al. 2019 [37]	Monocentric prospective observational	NA	Suspicion of PCa owing to a serum PSA level between 2 and 10 µg/L	140	49	–	WHO
Cheng et al. 2019 [38]	Monocentric prospective observational	Taiwan	Patients underwent TRUSP biopsy for suspected prostate cancer, including patients with abnormal tPSA >4 µg/L <10 µg/L, or patients with abnormal DRE findings, whose tPSA <10 ng/mL	121	33	21	Hybritech
Sriplakich et al. 2018 [39]	Monocentric prospective observational		All patients with a serum PSA of 4 and 10 ng/mL and nonsuspicious DRE of prostate cancer	101	16	–	NA
Hsieh et al. 2018 [40]	Monocentric prospective observational	China	Patients aged 50–75 years and a serum total PSA level 4.0 and 10.0 µg/L, with or without an abnormal DRE	154	36	26	NA
Dolejsova et al. 2018 [41]	Monocentric prospective observational	Czech republic	Patients with the biopsy and following radical prostatectomy	320	320	225	NA
Park et al. 2018 [42]	Multicentric prospective observational	Korea	Consecutive men aged 60–75 years with tPSA ≥3.5 µg/L who underwent their first prostate biopsy for suspected PCa	246	125	–	NA
Al Saidi et al. 2017 [43]	Multicentric prospective observational	Oman	All men scheduled for prostate biopsy in their workup management during the study period	136	28	17	Hybritech
Na et al. 2017 [44]	Multicentric prospective observational	China	(1) tPSA level >10.0 µg/L;(2) tPSA level >4.0 µg/L with confirmation after 2–3 months; (3) %fPSA<0.16 when patients had a total PSA level >4.0 µg/L; and (4) suspicious lesions detected by DRE or ultrasound at any level of tPSA	1,538	618	–	NA
Vukovic et al. 2017 [45]	Monocentric prospective observational	Serbia	Patients with age over 50 years, no previous history of PC, normal DRE findings, serum PSA in interval between 2 and 10 µg/L, and minimally 12 biopsy cores taken from patient	129	65	–	NA
Furuya et al. 2017 [46]	Monocentric prospective observational	Japan	tPSA values of 2.0–10.0 µg/L and the performance of MRI before the biopsy	50	33	–	NA
Friedl et al. 2017 [47]	Monocentric retrospective observational	Austria	Suspicious prostate MRI	112	62	31	NA
Tan et al. 2017 (A) [48]	Monocentric prospective observational	Japan	Patients with at least one PI-RADS 3 or higher lesion on mpMRI and who underwent both targeted and systematic prostatic biopsies in the same session	115	51	40	NA
Tan et al. 2017 (B) [49]	Multicentric prospective observational	Malaysia	Patients 50–75 years of age with normal DRE in a total PSA range of 4–10 µg/L	157	30	19	NA
Chiu et al. 2016 [50]	Monocentric prospective observational	China	Patients with PSA 4–10 µg/L and non-suspicious DRE, with or without lower urinary tract symptoms, who consented before prostate biopsy.	569	62	16	Hybritech
Morote et al. 2016 [51]	Monocentric retrospective observational	Spain	Men younger than 75 and tPSA between 3 and 10 µg/L, scheduled to their first TRUS guided biopsy	183	68	45	NA

Table 1: (continued)

Authors [ref]	Study design	Country	Inclusion criteria	Study population	Positive biopsy	csPCa	Calibrators
Lazzeri et al. 2016 [52]	Multicentric retrospective observational	Italy, France, Spain, Germany, UK	Patients >45 years of age with or without a positive DRE, with or without a previous negative biopsy with a tPSA 4–10 µg/L	262	136	106	NA
Yu et al. 2016 [53]	Multicentric prospective observational	China	(1) tPSA >4.0 µg/L; (2) %fPSA ratio <0.16; (3) PSAD >0.15; or (4) presence of prostate nodules detected by DRE or ultrasound	261	67	30	NA
Fuchsova et al. 2015 [54]	Monocentric prospective observational	Czech republic	Patients suspected of having PCa, with total PSA ranging from 0 to 20 µg/L, and underwent TRUS biopsies.	263	113	–	NA
Mearini et al. 2015 [55]	Monocentric prospective observational	Italy	NA	43	43	14	NA
Loeb et al. 2015 [56]	Multicentric prospective observational	USA	Men 50 years old or older with PSA 2–10 µg/L and benign findings on DRE	658	324	160	NA
Seisen et al. 2015 [57]	Monocentric prospective observational	France	Consecutive patients undergoing a first prostate biopsy for suspected PCa, based on at PSA ranging from 4 to 20 µg/L and/or an abnormal DRE	138	62	39	Hybritech
Fossati et al. 2015 [58]	Multicentric retrospective observational	Italy, France, Spain, Germany, UK	Patients undergoing prostate biopsy for suspected PCa according to indications from their referring physicians, enrolled in the PROMEtheuS project who were aged<60 years	238	67	–	NA
Mearini et al. 2014 [59]	Monocentric prospective observational	Italy	Patients with a tPSA between 2.0 and 10 µg/L	275	86	–	NA
Filella et al. 2014 [60]	Monocentric prospective and retrospective observational	Spain	Patients selected for biopsy because of an elevated serum PSA level and/or abnormal DRE, as well as patients diagnosed of prostate cancer and referred to our hospital for treatment	354	175	70	NA
Porpiglia et al. 2014 [61]	Monocentric prospective observational	Italy	Persistently increased PSA and/or positive DRE	170	52	24	Hybritech
Ng et al. 2014 [62]	Monocentric retrospective observational	China	Patients who are suspected of having PCa, because of either an elevated level of serum PSA or an abnormal DRE	320	21	–	WHO
Lazzeri et al. 2014 [63]	Monocentric prospective observational	Italy, France, Spain, Germany, UK	Patients >45 yr of age with or without a positive DRE in a total PSA range of 2–10 µg/L	646	264	–	NA
Scattoni et al. 2013 [64]	Multicentric prospective observational	Italy	PSA between 2 and 15 µg/L, and/or positive DRE, who performed PBx	211	70	–	Hybritech
Ferro et al. 2013 [65]	Monocentric prospective observational	Italy	Men aged over 50 years, no prior prostate surgery and biopsy, no bacterial acute or chronic prostatitis, no use of 5-a reductase inhibitors, PSA values included between 2 and 10 µg/L, availability of serum samples and corresponding clinical data and completion of at least a 16 core template biopsy after enrolment	300	108	–	WHO

Table 1: (continued)

Authors [ref]	Study design	Country	Inclusion criteria	Study population	Positive biopsy	csPCa	Calibrators
Lazzeri et al. 2013 [66]	Multicentric retrospective observational	Italy, France, Spain, Germany, UK	Sub-analysis of PRO-PSA multicentric European study (PROMEtheuS). The overall study population included patients undergoing prostate biopsy for suspected PCa according to indications from their referring physicians. Inclusion was limited to patients enrolled in thePROMEtheuS project who had a first-degree relative(father, brother, son) with PCa	158	71	47	NA
Stephan et al. 2013 (A) [67]	Multicentric prospective and retrospective observational	France, Germany	tPSA results between 1.6 and 8.0 µg/L	1,362	668	228	WHO
Stephan et al. 2013 (B) [68]	Multicentric prospective observational	Germany	Men scheduled for prostate biopsy owing to suspicious DRE, suspicious TRUS, or increased PSA concentration or PSA velocity	246	110	43	WHO
Perdonà et al. 2013 [69]	Monocentric prospective observational	Italy	Men undergoing first biopsy	160	47	19	–
Ferro et al. 2012 [70]	Monocentric prospective observational	Italy	Men aged over 50 years, no prior prostate surgery and biopsy, no bacterial acute or chronic prostatitis, no use of 5-α reductase inhibitors in the previous six months, PSA values included between 2 and 20 µg/L, negative DRE	151	48	36	–
Guazzoni et al. 2011 [71]	Monocentric prospective observational	Italy	Men with tPSA 2.0–10 µg/L and negative DRE who were scheduled for prostate biopsy	268	107	52	–
Liang et al. 2011 [72]	Monocentric retrospective observational	USA	PSA exceeding 2.5 µg/L, abnormal DRE or a family history of PCa	474	227	69	–

csPCA, clinically significant prostate cancer; DRE, digital rectal exam; PSA, prostate specific antigen; tPSA, total PSA; mpMRI, multiparametric magnetic resonance imaging; TRUS, transrectal ultrasound; PHI, prostate health index; PI-RADS, prostate imaging reporting and data system; TRUSP, transrectal ultrasound-guided prostate biopsy; PSAD, PSA density; PBx, prostate biopsy; NA, not available information

to 0.885 (Table 3). The forest plots and the crosshair plots for sensitivity and specificity across the studies for PCa and csPCa, are reported in Figures 2–6. The plots suggest high variability for both sensitivity and specificity. No publication bias was detected by inspection of the funnel plot and formal Deeks's test (p=0.659 and p=0.065, respectively for PCa and csPCa studies).

Diagnostic accuracy of PHI for detecting PCa and csPCa

Due to the high heterogeneity observed in the sensitivity and specificity data [respectively, I2 93.6% (95%CI 92.1%–94.7%) and 95.3% (95%CI 94.4%–96.1%) for PCa studies; 92.3% (95%CI 89.3%–94.5%) and 95.4% (95%CI 94.0%–96.6%) for csPCa], a random-effects model was applied. Meta-analytical summaries of PHI performances were obtained following a bivariate binomial method by fitting a GLMM.

For PCa studies, penalized or unpenalized goodness-of-fit measures were AIC=688.1, BIC=700.2, LogLikelihood=−339.0 and deviance=678.1. The variance-covariance matrix of parameter estimates showed, respectively, variance of the logit(sensitivity)=0.0213, variance of the log (specificity)=0.0190 and covariance=−0.0129. Pooled results were as follows: sensitivity 0.791 (95%CI 0.739–0.834), specificity 0.625 (95%CI 0.560–0.686), positive likelihood ratio 2.110 (95%CI 1.838–2.424), negative likelihood ratio

Table 2: Characteristics of the studies included in the meta-analysis for PCa analysis.

First author and year of publication [ref]	PHI cut-off	Se	Sp	n	PCa	TP	FN	TN	FP
Guazzoni et al. 2011 [71]	48.5	0.429	0.9	268	107	46	61	145	16
Liang et al. 2011 [72]	39.09	0.38	0.8	474	227	86	141	198	49
Ferro et al. 2012 [70]	38.7	0.85	0.61	151	48	41	7	63	40
Ferro et al. 2013 [65]	31.6	0.9	0.4	300	108	97	11	77	115
Lazzeri et al. 2013 [66]	40.3	0.648	0.713	158	71	46	25	62	25
Perdonà et al. 2013 [69]	43.77	0.66	0.72	160	47	31	16	81	32
Scattoni et al. 2013 [64]	28.3	0.9	0.31	116	40	36	4	24	52
Stephan et al. 2013 (A) [67]	NA	0.9	0.354	1,362	668	601	67	246	448
Stephan et al. 2013 (B) [68]	27.5	0.9	0.213	246	110	99	11	29	107
Filella et al. 2014 [60]	46.89	0.663	0.715	354	175	116	59	128	51
Lazzeri et al. 2014 [61]	41.5	0.629	0.623	646	264	166	98	238	144
Mearini et al. 2014 [59]	37.1	0.919	0.386	275	86	79	7	73	116
Ng et al. 2014 [62]	26.54	0.9	0.4976	230	21	19	2	104	105
Porpiglia et al. 2014 [61]	48.9	0.409	0.78	170	52	21	31	92	26
Fossati et al. 2015 [58]	41.2	0.642	0.632	238	67	43	24	108	63
Fuchsova et al. 2015 [54]	40	0.84	0.63	263	113	95	18	95	55
Loeb et al. 2015 [56]	31.3	0.8	0.461	658	324	259	65	154	180
Seisen et al. 2015 [57]	40	0.435	0.671	138	62	27	35	51	25
Chiu et al. 2016 [50]	35	0.613	0.822	569	62	38	24	417	90
Lazzeri et al. 2016 [52]	63.9	0.728	0.731	262	136	99	37	92	34
Morote et al. 2016 [51]	28.98	0.9	0.278	183	68	61	7	32	83
Yu et al. 2016 [53]	38.59	0.91	0.567	261	67	61	6	110	84
Al Saidi et al. 2017 [43]	41.9	0.821	0.806	136	28	23	5	87	21
Tan et al. 2017 [48]	26.75	0.9	0.5827	157	30	27	3	74	53
Friedl et al. 2017 [47]	40	0.92	0.33	112	62	57	5	17	33
Furuya et al. 2017 [46]	38.7	0.636	0.765	50	33	21	12	13	4
Na et al. 2017 [44]	32	0.945	05,228	1,538	618	584	34	481	439
Vukovic et al. 2017 [45]	41.67	0.641	0.625	129	65	42	23	40	24
Hsieh et al. 2018 [40]	29.6	0.778	0.678	154	36	28	8	80	38
Park et al. 2018 [42]	22.9	0.9	0.683	246	125	113	12	83	38
Sriplakich et al. 2018 [39]	34.14	0.75	0.753	101	16	12	4	64	21
Cheng et al. 2019 [38]	21.62	0.9	0.273	121	33	30	3	24	64
Jagalarmudi et al. 2019 [37]	21.33	0.9	0.24	140	49	44	5	22	69
Lopes et al. 2019 [36]	45.9	0.73	0.77	121	33	24	9	68	20
Barisiene et al. 2020 [31]	44.49	0.563	0.837	210	112	63	49	82	16
Ito el a. 2020 [32]	NA	0.9	0.358	363	179	161	18	66	118
Kopecky et al. 2020 [33]	36.4	0.774	0.667	55	31	24	7	16	8
Othman et al. 2020 [30]	30.2	0.76	0.641	84	25	19	6	38	21
Nassir et al. 2020 [29]	33.14	0.831	0.797	194	71	59	12	98	25
Ferro et al. 2021 [25]	42.7	0.908	0.963	196	142	129	13	52	2
Garrido et al. 2021 [26]	37.96	0.7034	0.7899	237	118	83	35	94	25
Stejskal et al. 2021 [27]	40.775	0.657	0.763	395	296	194	102	76	23

Se, sensitivity; Sp, specificity; n, number; PCa, prostate cancer; TP, true positive; FN, false negative; TN, true negative; FP, false positive; NA, not available information.

0.335 (95%CI 0.280–0.401) and DOR 6.302 (95%CI 4.976–7.980).

For csPCa studies, penalized or unpenalized goodness-of-fit measures were AIC=281.6, BIC=289.5, LogLikelihood=−135.8 and deviance=271.6. The variance-covariance matrix of parameter estimates showed, respectively, variance of the logit(sensitivity)=0.0752, variance of the log(specificity) =0.0517 and covariance=−0.0460. Pooled results were as follows: sensitivity 0.874 (95%CI 0.803–0.923), specificity 0.569 (95%CI 0.458–0.674), positive likelihood ratio 2.030 (95%CI 1.647–2.502), negative likelihood ratio 0.220 (95%CI 0.155–0.314) and DOR 9.206 (95%CI 6.384–13.276).

Table 3: Characteristics of the studies included in the meta-analysis for csPCa analysis.

First author and year of publication [ref]	PHI cut-off	Se	Sp	n	csPCa	TP	FN	TN	FP
Loeb et al. 2015 [56]	33.8	0.8	0.455	639	160	128	32	218	261
Mearini et al. 2015 [55]	67.6	0.8667	0.857	43	14	12	2	25	4
Seisen et al. 2015 [57]	40	0.667	0.737	138	39	26	13	73	26
Chiu et al. 2016 [50]	35	0.813	0.754	569	16	13	3	417	136
Morote et al. 2016 [51]	17.83	0.95	0.244	183	45	43	2	34	104
Tan et al. 2017 [48]	26.75	0.9	0.551	157	19	17	2	76	62
Tan et al. 2017 [49]	27	1	0.44	115	40	40	0	33	42
Furuya et al. 2017 [46]	30.7	0.857	0.345	50	21	18	3	10	19
Na et al. 2017 [44]	32	0.9754	0.479	1,538	488	476	12	503	547
Dolejsova et al. 2018 [41]	34.36	0.9511	0.2105	320	225	214	11	20	75
Barisiene et al. 2020 [31]	44.47	0.691	0.814	210	81	56	25	105	24
Hsieh et al. 2020 [36]	30	0.917	0.436	102	24	22	2	34	44
Stojadinovic et al. 2020 [34]	30.7	0.971	0.376	200	35	34	1	62	103
Chiu et al. 2021 [24]	31	0.9	0.453	412	94	85	9	144	174
Ferro et al. 2021 [25]	61.68	0.533	0.885	196	90	48	42	94	12
Garrido et al. 2021 [26]	37.96	0.78	0.781	237	100	78	22	107	30
Kim et al. 2021 [28]	33.4	0.9	0.4	140	48	43	5	37	55
Stejskal et al. 2021 [27]	49.47	0.595	0.73	395	364	217	147	23	8

Se, sensitivity; Sp, specificity; N, number; csPCa, clinically significant prostate cancer; TP, true positive; FN, false negative; TN, true negative; FP, false positive; NA, not available information.

The HSROC plots in Figures 7 and 8 report the points representing the sensitivity-specificity pairs of the single PCa and csPCA studies, the summary operating point (summary values for sensitivity and specificity) and the summary ROC curve, together with the 95% confidence region around the summary operating point and the 95% prediction region.

Discussion

In this systematic review and meta-analysis, we evaluated the accuracy of PHI as a biomarker of PCa and csPCa by analysing results from 60 studies, including a total of 14,255 individuals. The main findings of our meta-analysis can be summarised as follows: (i) the pooled sensitivity and specificity of PHI for PCa detection were 0.791 (95%CI 0.739–0.834) and 0.625 (95%CI 0.560–0.686), respectively; (ii) the pooled sensitivity and specificity of PHI for csPCa detection were 0.874 (95%CI 0.803–0.923) and 0.569 (95% CI 0.458–0.674), respectively; (iii) DOR was 6.302 and 9.206, respectively for PCa and csPCa detection, suggesting moderate to good effectiveness of PHI as a diagnostic test. Overall, our findings suggest that PHI has a high accuracy for detecting PCa and discriminating between aggressive and non-aggressive PCa. Thus, it could be useful as a biomarker in predicting patients harbouring more aggressive cancer and guiding biopsy decisions.

The early detection of PCa and the discrimination between benign and malignant forms is fundamental for the appropriate intervention. The gold standard for PCa diagnosis remains the biopsy. However, the laboratory has a key role in early identifying patients at high risk of PCa, eligible for biopsy. The most widely used screening biomarker worldwide is PSA. In the past, a one-size-fits-all approach based on PSA was used for early identifying PCa and consequently determining the need for prostate biopsy in all men. However, PSA is characterised by a low specificity for PCa and it is not associated with the aggressiveness of cancer. In the last decades, multiparametric magnetic resonance imaging (mpMRI) of the prostate has emerged as the gold standard for predicting positive biopsy [73]. The Prostate Imaging Reporting and Data System (PI-RADS) score released by an international collaboration of the American College of Radiology (ACR) and European Society of Uroradiology (ESUR) in 2015 is a structured reporting schema that helps to determine the risk of csPCa on prostate mpMRI. The PI-RADS score ranges from 1 to 5 and it should be interpreted as follows: 1–2=low risk of PCa; 3=intermediate risk of PCa; and 4–5=high risk of PCa.

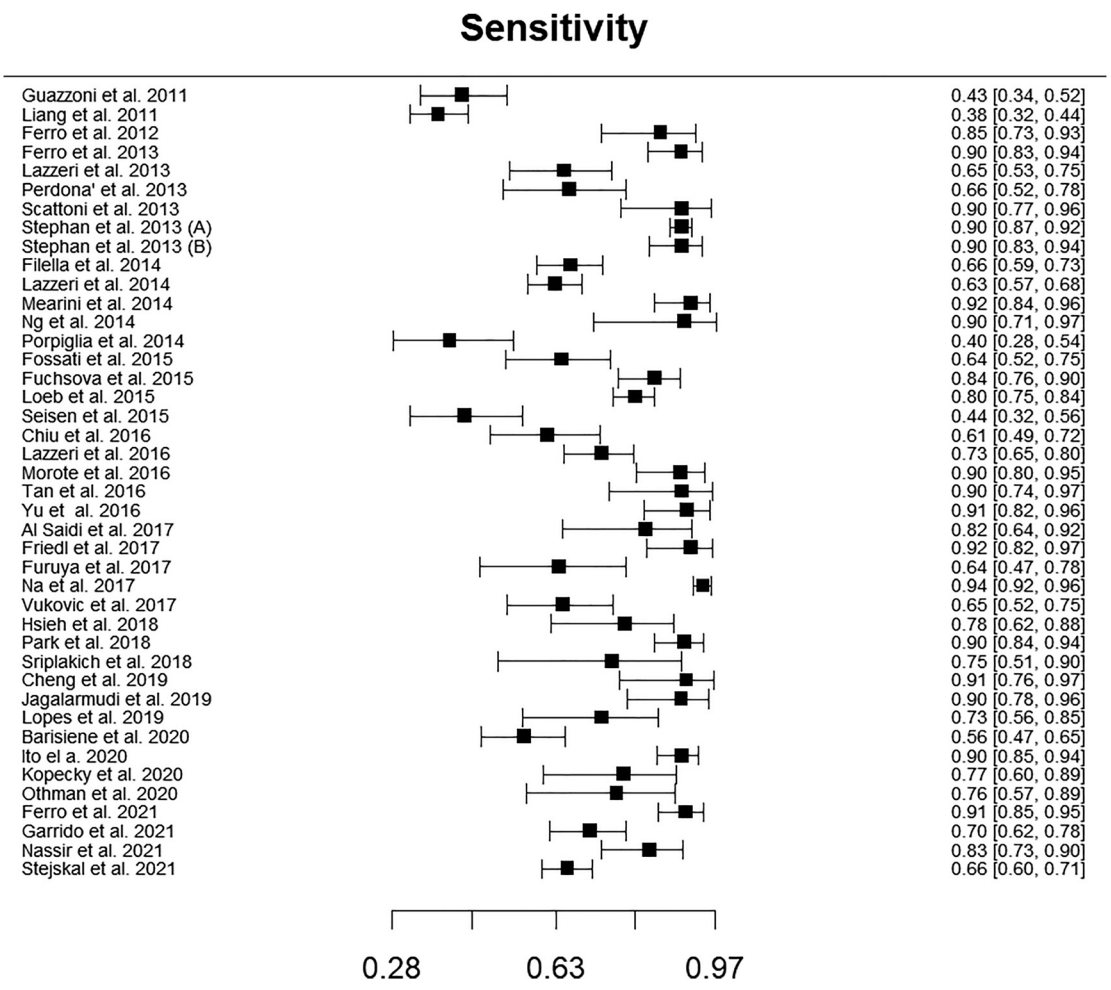

Figure 2: Forest plot of sensitivity of PHI for detecting PCa.
Studies were ordered following date of publication.

PI-RADS 3 represents a "gray zone", with only 15% of patients having PCa. Additionally, PPV has been reported to be 0.49 for csPCa, and a few patients with a negative mpMRI have high-grade PCa [74]. Thus, mrMRI presents some limitations in selecting patients to undergo biopsy [75–77]. It should also be considered that mpMRI is an expensive tool and requires an experienced radiologist.

The drawbacks of PSA and mpMRI could be overcome by the most recent developed index PHI.

The latter should be used in clinical practice as a complementary test to PSA and mpMRI. Indeed, PHI should be evaluated when PSA has a value within the "gray zone", between 2 and 10 μg/L, allowing to spare unnecessary biopsies and to select patients for active surveillance. Similarly, it could be used when a PI-RADS 3 is obtained. Some Authors also tested if PHI could be used as an alternative test to mpMRI, but less evidence is available to date [25, 27, 61].

Interestingly, our data show that PHI could reliably detect patients with more aggressive PCa. The association between PHI and PCa aggressiveness is supported by literature evidence. Several Authors reported a significant correlation between PHI levels and histological features of tumor malignancy, such as grade, stage, and volume, evaluated after radical prostatectomy [78, 79]. Additionally, some Authors showed that PHI could predict the biochemical recurrence (BCR) of the PCa [80, 81]. The performance of PHI for predicting csPCa has been evaluated alone or in combination with other tools. Hsieh et al. showed that the combination of mpMRI and PHI has a

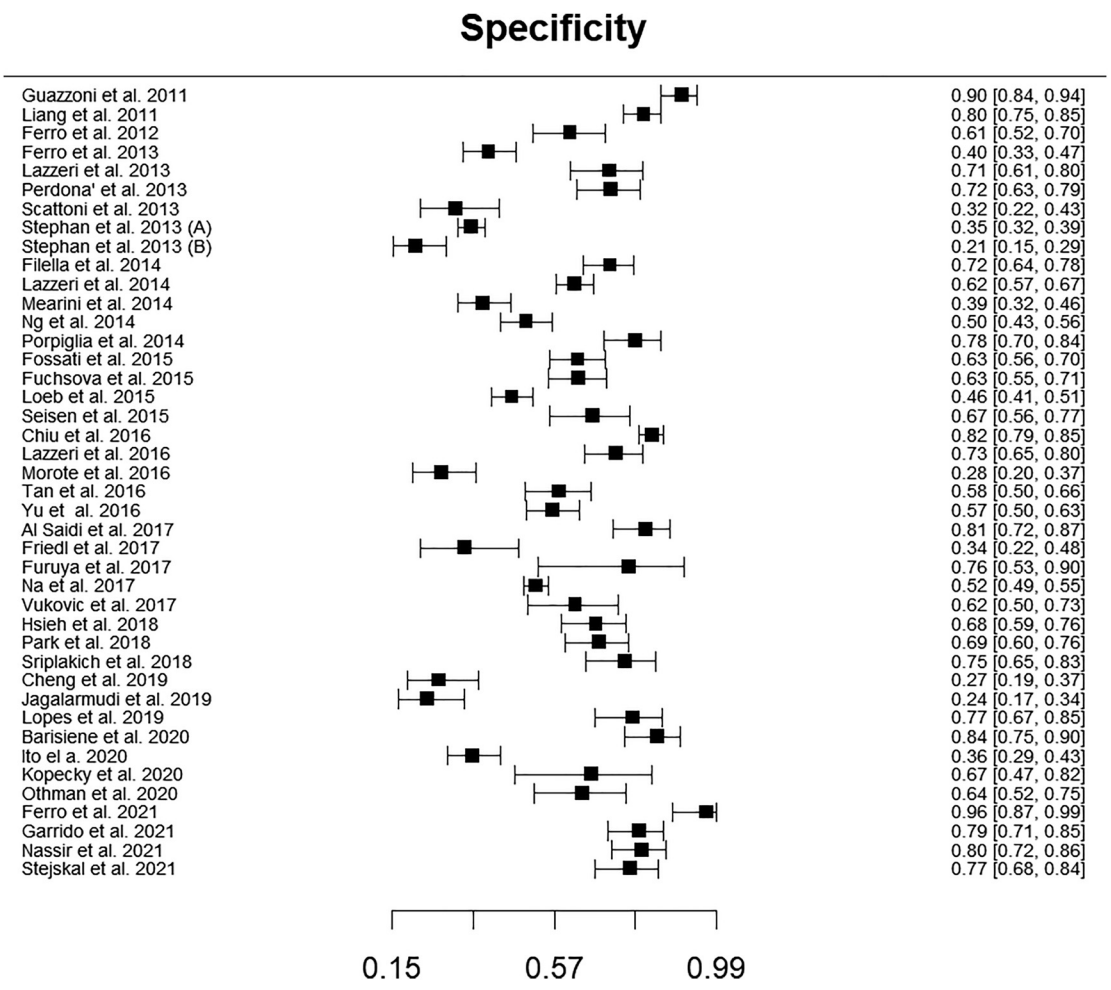

Figure 3: Forest plot of specificity of PHI for detecting PCa.
Studies were ordered following date of publication.

better predictive power for csPCa than PHI and mpMRI alone and would have avoided up to 50% of biopsies while missing only one csPCa patient [35]. Kim et al. proposed a strategy based on the use of PHI as a triage test for identifying patients eligible for mpMRI and/or biopsy [28]. Such a strategy could be effective, efficient, and cheap, allowing the selection of only high-risk patients for more laborious and expensive investigations. Foj et al. recently developed a nomogram also incorporating PHI to address the individual probability of aggressive PCa in patients at biopsy [82]. Similarly, Loeb et al. developed a nomogram including PHI [56], showing that adding PHI to currently available risk prediction tools significantly improved the prediction of aggressive prostate cancer.

Some observations should be made because some issues hamper the introduction of PHI in clinical practice. First, there is no consensus on the optimal decisional cut-off for both detecting PCa and csPCa, with a high variability of proposed PHI values, ranging from 21.33 to 63.9 for PCa and from 26.7 to 67.6 for csPCa. This could be related to the high heterogeneity among studies in terms of sample size, inclusion criteria adopted, and the use of different calibrations (Table 1). Specifically, the Beckman Coulter gives the possibility to calibrate the PSA according to the Hybritech method or the WHO standard. However, there is a discrepancy of 16–20% between the PHI values obtained using the two calibrations, with WHO calibration turning out lower PHI values than Hybritech ones [83]. Thus, different cut-offs should be adopted according to the calibration method chosen. Additionally, some Authors established the best cut-off PHI according to the Youden Index, others according to the best sensitivity and others

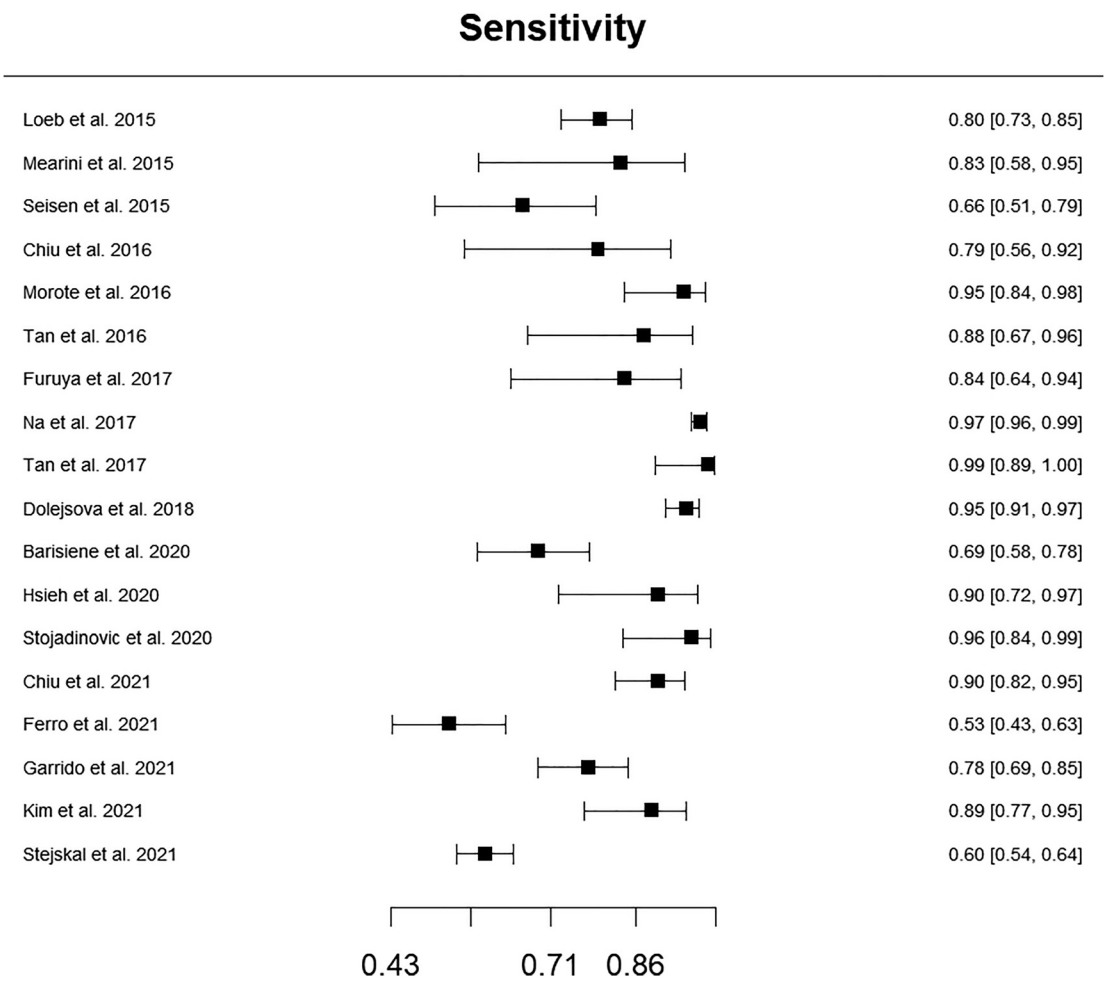

Figure 4: Forest plot of sensitivity of PHI for detecting csPCa.
Studies were ordered following date of publication.

according to the best specificity. When selecting a test cut-off, which maximises sensitivity or specificity or a trade-off between them, several elements should be taken into consideration, among them the prevalence of the disease in the population or in a particular subgroup, combination with the result of other biomarkers or procedures (i.e. DRE, PSA), risk of unnecessary further procedures (i.e. biopsy) and potential post-procedure complications, missed diagnoses and economic impact. Although some cost-consequence analysis studies have been performed to assess the impact of different PHI cut-offs, it is not entirely clear if these results are applicable to different populations, at what stage of the diagnostic process or with other biomarkers PHI should be used, or if missed diagnoses are true missed or instead delayed diagnoses [84]. It is reasonable to argue that different cut-offs could be applied to different subgroups of patients based on disease prevalence or a specific diagnostic strategy (rule-in vs. rule-out, single vs. multiple biomarkers, population vs. high-risk patients). Many other studies are needed to evaluate and define specific PHI cut-offs.

Finally, prostate volume (PV) could influence the heterogeneity of PHI results among studies. Interestingly, Filella et al. showed that the diagnostic performance of PHI changes according to PV, with the highest accuracy in patients with small prostate volume [85]. Moreover, several Authors described an association between PV and PCa as well as tPSA. Accordingly, the PHI density (PHID), calculated as PHI/PV, has been introduced. Mearini et al. first assessed the value of PHID in PCa detection showing a good diagnostic accuracy but comparable to those of PHI [86]. Tosoian et al. found that PHID outperformed PHI for detecting csPCa [79]. Conversely, Friedl et al. reported a higher AUC of PHI than PHID [87]. Stephan et al., in a

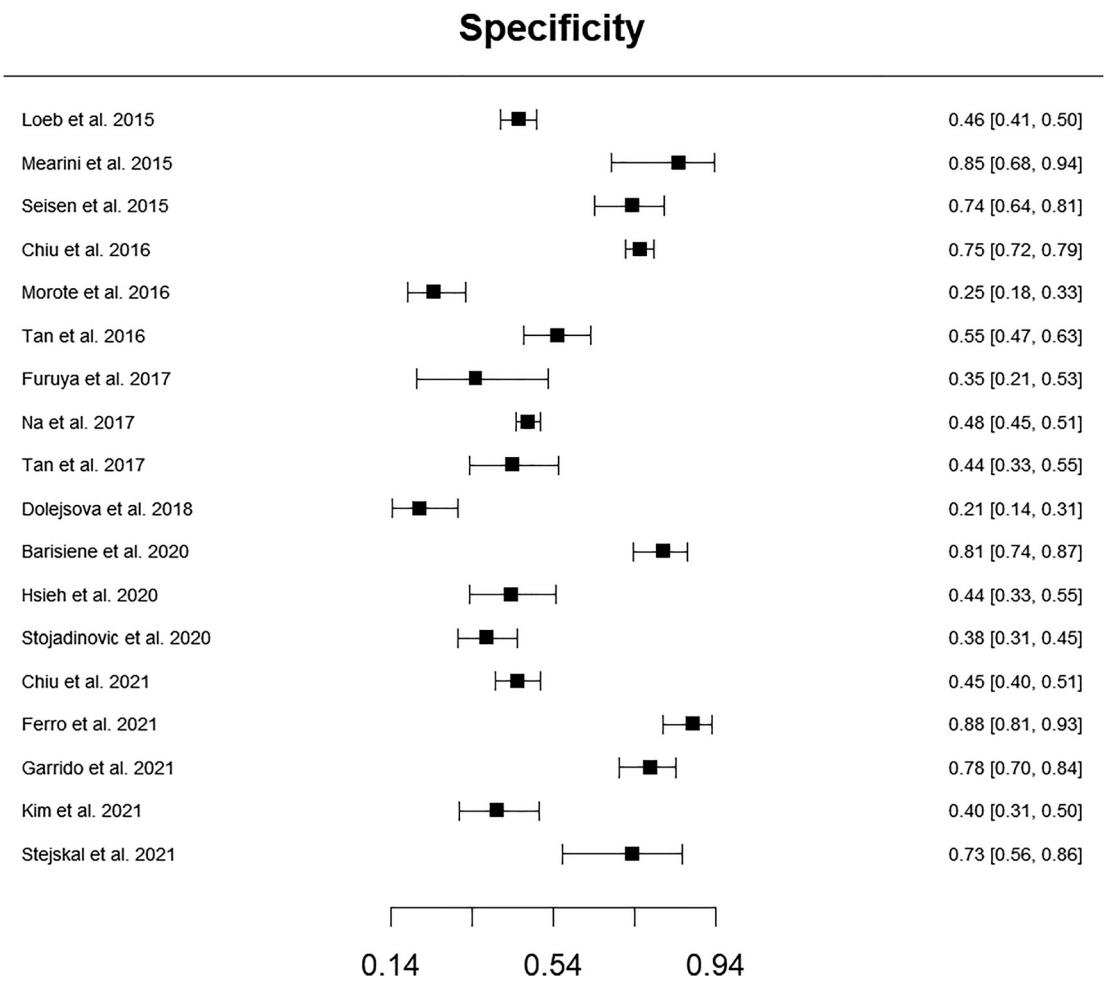

Figure 5: Forest plot of specificity of PHI for detecting csPCa.
Studies were ordered following date of publication.

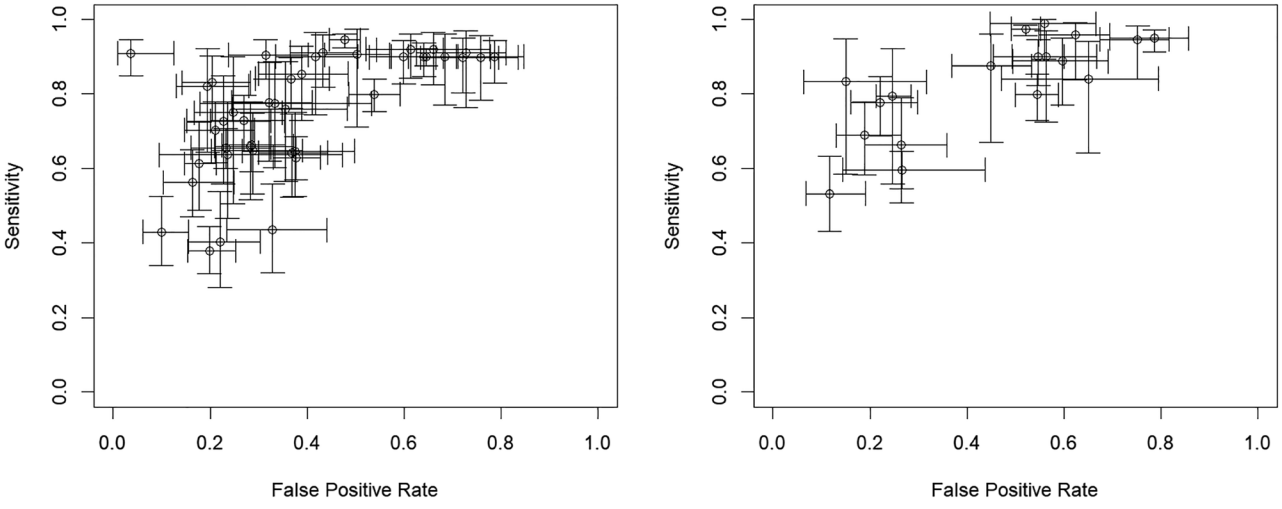

Figure 6: Crosshair plots of the sensitivity and specificity across the studies investigated for PCa (left) or csPCa-3 (right).

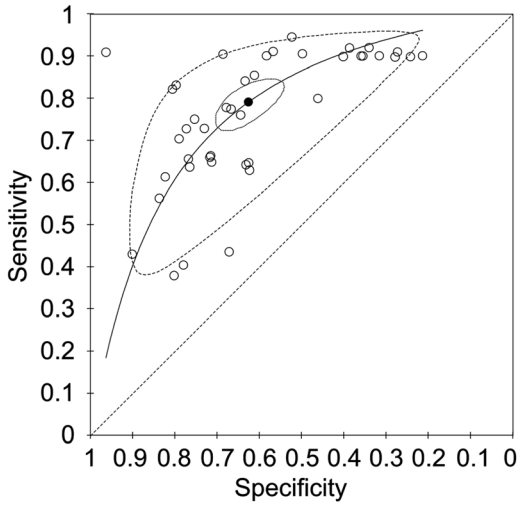

Figure 7: Hierarchical summary receiver operating characteristic (HSROC) plots for diagnostic accuracy of PHI in detecting PCa. Open circles represent sensitivity-specificity pairs of the 42 included studies. Black circle indicates the summary operating point (summary values for sensitivity and specificity). The curve solid line represents the summary ROC curve, whereas the solid and dashed closed curves indicate, respectively, the 95% confidence region around the summary operating point and the 95% prediction region. The range of the summary ROC curve was limited from the min to the max specificity of the included studies.

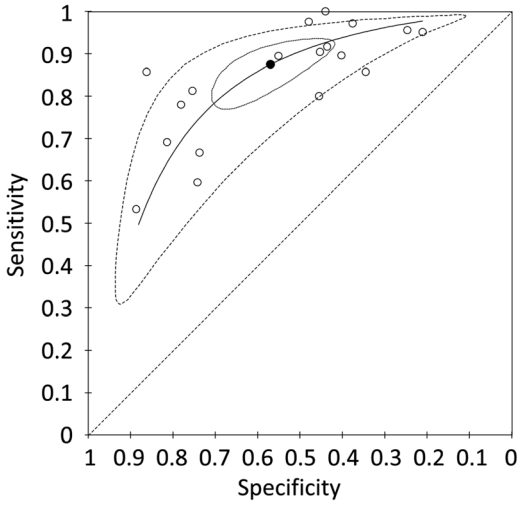

Figure 8: Hierarchical summary receiver operating characteristic (HSROC) plots for diagnostic accuracy of PHI in detecting csPCa. Open circles represent sensitivity-specificity pairs of the 18 included studies. Black circle indicates the summary operating point (summary values for sensitivity and specificity). The curve solid line represents the summary ROC curve, whereas the solid and dashed closed curves indicate, respectively, the 95% confidence region around the summary operating point and the 95% prediction region. The range of the summary ROC curve was limited from the min to the max specificity of the included studies.

prospective large cohort study showed that PHID had better accuracy than PHI for detecting PCa but not csPCa [88]. Overall, the contrasting literature evidence achieved to date cannot to draw conclusions whether PV could improve the predictive ability of PHI. Thus, more studies are required to evaluate the usefulness of PHID for PCa and csPCa detection.

A cost-effectiveness strategy based on the best combination of PSA, PHI and mpMRI for detecting patients at high risk of PCa eligible for biopsy and with more aggressive forms should be developed, validated, and integrated into the guidelines. For this purpose, large-multicentre randomized-controlled studies are mandatory.

In conclusion, our data show that PHI is a reliable biomarker of PCa and csPCa. Nowadays, Clinicians have valuable tools for triaging patients at risk of PCa. Thus, the clinical paradigm should be shifted toward a more personalized approach to prostate biopsy decisions based on a multiparameter approach integrating biomarkers, including PSA and PHI, and clinical findings from mpMRI.

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Informed consent: Not applicable.
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