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ORIGINAL ARTICLE

The predictive value of the prostate health index vs. multiparametric magnetic resonance imaging for prostate cancer diagnosis in prostate biopsy

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Abstract

Purpose To compare the ability of Prostate Health Index (PHI) to diagnose csPCa, with that of total PSA, PSA density (PSAD) and the multiparametric magnetic resonance (mpMRI) of the prostate.

Methods We analysed a group of 395 men planned for a prostate biopsy who underwent a mpMRI of the prostate evaluated using the PIRADS v1 criteria. All patients had their PHI measured before prostate biopsy. In patients with an mpMRI suspicious lesions, an mpMRI/ultrasound software fusion-guided biopsy was performed first, with 12 core systematic biopsy performed in all patients. A ROC analysis was performed for PCa detection for total PSA, PSAD, PIRADS score and PHI; with an AUC curve calculated for all criteria and a combination of PIRADS score and PHI. Subsequent sub-analyses included patients undergoing first and repeat biopsy.

Results The AUC for predicting the presence of csPCa in all patients was 59.5 for total PSA, 69.7 for PHI, 64.9 for PSAD and 62.5 for PIRADS. In biopsy naive patients it was 61.6 for total PSA, 68.9 for PHI, 64.6 for PSAD and 63.1 for PIRADS. In patients with previous negative biopsy the AUC for total PSA, PHI, PSAD and PIRADS was 55.4, 71.2, 64.4 and 69.3, respectively. Adding of PHI to PIRADS increased significantly ($p = 0.007$) the accuracy for prediction of csPCa.

Conclusion Prostate Health Index could serve as a tool in predicting csPCa. When compared to the mpMRI, it shows comparable results. The PHI cannot, however, help us guide prostate biopsies in any way, and its main use may, therefore, be in pre-MRI or pre-biopsy triage.

Keywords Prostate cancer · Prostate health index · Prostate MRI · MRI · TRUS fusion biopsy · PSA density · PIRADS

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Introduction

Despite its high incidence, prostate cancer (PCa) often occurs as a low risk disease which would not endanger patients' lives and wellbeing for years to come after primary diagnosis [1]. Selective diagnosis of clinically significant disease (csPCa) only is therefore a key step in general prostate cancer management.

After 30 years of being the standard diagnostic tool for PCa, transrectal ultrasound-guided (TRUS) systematic 12 core biopsy following elevated prostate-specific antigen (PSA), has proven to have a rather low detection rate (30–50% in first biopsy) [2], and can miss foci of csPCa [3]. This means that using PSA (in patients with negative digital rectal examination) as the only triage tool, over 50% of patients are needlessly subjected to the discomfort and potential complications of prostate biopsy.

Recently, there has been an emphasis on incorporating magnetic resonance imaging (MRI) into PCa diagnostic algorithm as it is a very useful tool in PCa diagnosis and pre-treatment visualization [4, 5]. The use of prostate MRI in every patient with elevated PSA levels, might, however, cause longer waiting periods or more expenses. It would therefore be useful to have cheaper, simpler tests to select high risk patients in which to perform prostate MRI and an eventual prostate biopsy.

New biochemical markers or a novel use of existing ones or their combinations promise to do just that. One of the most promising new biomarkers of PCa seems to be the free PSA isoform [-2] proPSA and the Prostate Health Index (PHI) which is a numerical score calculated using the levels of total PSA, free PSA and [-2] proPSA [6].

In this study we aimed to compare the ability of PHI to diagnose PCa, particularly its clinically significant variant, with that of total PSA, PSAD and the multiparametric magnetic resonance of the prostate (mpMRI). After the head to head comparison, we evaluated the combined diagnostic efficacy of PHI and mpMRI.

Methods

This multicentre study comprises a group of 395 men planned for a prostate biopsy for elevated total PSA levels with negative digital rectal examination at four different hospitals. Clinical and pathological data consisting of age, PSA, PSA, PSAD, Prostate Imaging Reporting and Data System (PIRADS) score, PHI, number of previous biopsies and prostate biopsy result were collected.

Biopsies were performed in four hospitals with 51 biopsies done in hospital 1, 215 in hospital 2, 8 in hospital 3 and 121 in hospital 4. Clinicopathological characteristics in our cohort are presented in (Table 1). The distribution of highest PIRADS score per patient is shown in (Table 2).

We enrolled 249 biopsy naive patients and 144 patients with previous negative biopsies. In two patients the number of previous biopsies was not available. The average number

Table 1 Clinicopathological characteristics of all patients undergoing prostate biopsy

Number of patients	395
Average	
Age (years)	63.407 (SD 6.966)
PSA (ng/ml)	8.995 (SD 7.824)
PHI	57.931 (SD 42.807)
PSAD (ng/ml^2)	0.201 (SD 0.201)

PSA prostate-specific antigen, *PHI* prostate health index, *PSAD* PSA density, *SD* standard deviation

Table 2 Distribution of highest PIRADS score per patient

Highest PIRADS score	Number of patients
1	18
2	42
3	120
4	111
5	104

PIRADS prostate imaging reporting and data system

of previous biopsies in the repeat biopsy subgroup was 1.82 [standard deviation (SD) 1.30].

All patients first underwent an mpMRI of the prostate using a 1.5 T machine with an endorectal coil or a 3 T machine without an endorectal coil. T1-weighted, T2-weighted, dynamic contrast, and diffusion-weighted sequences were performed, with ADC maps calculated. The MR images were then evaluated using the PIRADS V1 system [7]. Version 1 of the PIRADS system was used because the onset of the project was before the implementation of PIRADS version 2 at all participating sites.

All patients had their PHI calculated from plasmatic levels of three kallikreins using the Beckman and Coulter PHI formula ([-2]proPSA/free PSA) $\times \sqrt{\text{PSA}}$ [6]. PSA density was calculated using total PSA and prostate volume measured by transrectal ultrasound.

Patients then underwent transrectal prostate biopsy in antibiotic prophylaxis. In patients with an mpMRI suspicious lesions (PIRADS 3–5), an mpMRI/ultrasound software fusion-guided biopsy from each lesion was performed first, with 12 core systematic biopsy performed in all patients.

Biopsy cores were then analysed by certified pathologists and reported using the Gleason grading system. Clinically significant PCa was defined as the presence of at least one sample with a Gleason four or five grade lesion, or ISUP (International Society of Urological Pathologists) Grade Group > 1.

Statistical analysis

Logistic regression models (both univariable and multivariable) were calculated to determine the ability of total PSA, PSAD, mpMRI PIRADS score and PHI to predict any PCa and csPCa in prostate biopsy. Predictive accuracy of each variable was quantified as the area under the receiver operating characteristics (ROC) curve (AUC). A multivariable logistic model assessed their predictive independency. The significance of the difference between areas under ROC curves for different predictive models was assessed by the DeLong test. Subsequent sub analyses included patients undergoing first and repeat biopsy. Clinically significant

PCa was evaluated separately in all patient subgroups. All statistical analyses were conducted with R statistical package version 3.5.1. (R Core Team, Vienna, Austria, 2018).

Results

We performed biopsies in 395 patients with 296 positive and 99 negative results for PCa. The calculated predictive powers in the form of AUCs for individual parameters for any PCa in all patients, as well as in both subgroups are presented in (Table 3), with separate analyses for csPCa presented in (Table 4). Both (Tables 3, 4) also include the calculated thresholds, sensitivity, and specificity for each parameter to better characterize their predictive values.

In the whole cohort, PHI was most accurate in predicting csPCa on prostate biopsy (AUC 69.720), while PSAD was the most accurate variable in predicting PCa in general (AUC 83.207). Figure 1 shows the ROC curves for PIRADS, PSA, PHI, PSAD, PIRADS + PHI and PIRADS + PHI + PSAD for csPCa in the whole cohort.

In biopsy naive patients, PSAD was the most accurate predicting factor for any PCa (AUC 92.714), outperforming both PIRADS score and PHI. For the prediction of csPCa, PHI is superior to PSAD (AUC 68.879), although the difference is not statically significant. In patients with previous negative biopsies PSAD stands as the most accurate predictor for any PCa. Again, in the csPCa subgroup, PHI is the most accurate predictor of csPCa (AUC 71.235).

The combination of PHI, PIRADS and PSAD provides the most accurate prediction for any PCa in all patients (AUC 85.914). This combination yields an AUC of 94.003 for any PCa, in the first biopsy subgroup, and an AUC of 83.717 in the repeat biopsy subgroup. When considering only csPCa the combined use of PHI and PIRADS outperforms all other parameters with AUCs of 69.452 in the whole cohort and 66.746 and 75.088 for first and repeated biopsies, respectively. Adding PSAD to the combination of PIRADS and PHI does not increase the predictive accuracy for csPCa in any group.

Table 5 shows the results of the DeLong analysis of statistical significance of the differences between the calculated AUCs.

Discussion

In this study, we analysed the predictive value of PHI versus total PSA, PSAD and PIRADS score for PCa (csPCa) in prostate biopsy. We found the following articles to compare our results with.

Table 3 Predictive accuracy of each variable for any PCa quantified as the area under the receiver operating characteristics curve (AUC), with threshold, sensitivity, and specificity for each variable

	AUC	Threshold	Specificity	Sensitivity
All patients, any PCa, N = 395				
PIRADS	76.230 (71.606–80.855)	3.500	0.659	0.808
PSA	72.110 (65.597–78.262)	4.650	0.889	0.475
PHI	75.468 (69.827–81.109)	40.775	0.763	0.657
PSAD	83.207 (78.462–87.952)	0.101	0.842	0.697
PIRADS + PHI	80.065 (75.284–84.846)	− 1.056	0.708	0.778
PIRADS + PHI + PSAD	85.914 (81.814–90.014)	− 0.887	0.767	0.818
First biopsy, any PCa, N = 249				
PIRADS	76.885 (70.414–83.355)	3.500	0.714	0.783
PSA	89.570 (84.922–94.218)	4.650	0.872	0.783
PHI	85.339 (79.739–90.940)	35.040	0.857	0.739
PSAD	92.714 (89.48–95.944)	0.099	0.869	0.870
PIRADS + PHI	87.042 (81.670–92.415)	− 1.147	0.823	0.804
PIRADS + PHI + PSAD	94.003 (91.086–96.919)	− 1.912	0.809	0.978
Repeat biopsy, any PCa, N = 144				
PIRADS	73.098 (65.554–80.642)	3.500	0.543	0.827
PSA	61.570 (52.010–71.129)	6.980	0.717	0.481
PHI	67.910 (58.605–77.215)	41.005	0.791	0.558
PSAD	74.634 (66.315–82.953)	0.135	0.696	0.692
PIRADS + PHI	75.634 (67.841–83.427)	− 1.088	0.516	0.923
PIRADS + PHI + PSAD	83.717 (77.099–90.335)	− 0.516	0.761	0.769

PIRADS prostate imaging reporting and data system, *PSA* prostate-specific antigen, *PHI* prostate health index, *PSAD* PSA density, *AUC* the area under curve (with upper and lower control limits)

Table 4 Predictive accuracy of each variable for csPCa quantified as the area under the receiver operating characteristics curve (AUC), with threshold, sensitivity, and specificity for each variable

	AUC	Threshold	Specificity	Sensitivity
All patients, GS > 6, N = 364				
PIRADS	65.171 (59.409–70.935)	3.500	0.730	0.525
PSA	59.528 (53.309–65.747)	7.425	0.582	0.587
PHI	69.720 (64.061–75.378)	49.470	0.730	0.595
PSAD	64.933 (59.009–70.856)	0.139	0.736	0.533
PIRADS + PHI	69.452 (63.672–75.232)	0.818	0.697	0.595
PIRADS + PHI + PSAD	67.820 (62.040–73.600)	0.742	0.645	0.642
First biopsy, GS > 6, N = 237				
PIRADS	63.086 (55.944–70.227)	0.801	0.778	0.455
PSA	61.602 (54.1–69.114)	8.485	0.481	0.705
PHI	68.879 (61.889–75.868)	41.055	0.864	0.462
PSAD	64.635 (57.238–72.031)	0.183	0.575	0.682
PIRADS + PHI	66.746 (59.398–74.094)	0.773	0.716	0.551
PIRADS + PHI + PSAD	66.104 (58.856–73.352)	0.831	0.688	0.558
Repeat biopsy, GS > 6, N = 125				
PIRADS	69.338 (59.619–79.058)	3.500	0.650	0.647
PSA	55.441 (44.328–66.554)	7.415	0.625	0.518
PHI	71.235 (61.310–81.161)	49.470	0.775	0.600
PSAD	64.485 (54.262–74.708)	0.139	0.750	0.588
PIRADS + PHI	75.088 (65.598–84.579)	0.316	0.550	0.847
PIRADS + PHI + PSAD	73.029 (63.390–82.669)	0.423	0.575	0.824

PIRADS Prostate Imaging Reporting and Data System, *PSA* prostate-specific antigen, *PHI* prostate health index, *PSAD* PSA density, *AUC* the area under curve (with upper and lower control limits)
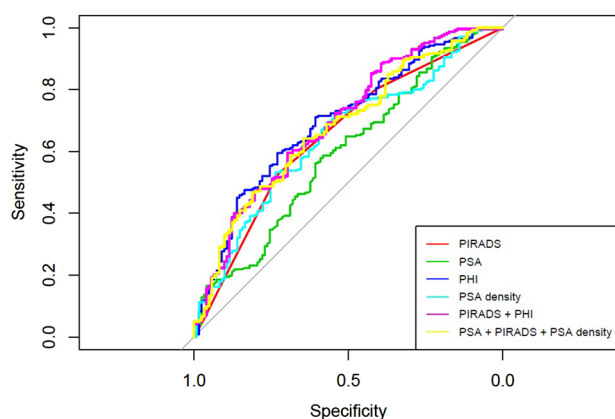

Fig. 1 ROC curves for PIRADS, PSA, PHI, a PIRADS + PHI for csPCa in the whole cohort. *PIRADS* Prostate Imaging Reporting and Data System, *PSA* prostate-specific antigen, *PHI* prostate health index, *PSAD* PSA density

In 2010 Le analysed the ability of [-2] proPSA and PHI to predict PCa on a group of over 2000 patients [-2] proPSA (AUC 0.76) and PHI (AUC 0.77) both outperformed total PSA (AUC 0.50) in PCa detection [8]. In a multicentre study in 2011, Catalona reached similar results of PHI outperforming total PSA in PCa diagnosis (PHI AUC 0.703) including csPCa (PHI AUC 0.724) [9]. A 2013 meta-analysis

comprising eight studies and a total of 2919 patients shows the superiority of PHI over both PSA and free to total PSA ratio (sensitivity for the detection of PCa for PHI was 90%, with a specificity of 31.6%) [10].

In a 2014 article reviewing published evidence of PHI efficacy, Stacy Loeb describes PHI as a simple and inexpensive blood test, that outperforms total PSA in prostate cancer prediction and should be a part of a multivariable approach to screening [6]. A later paper by the same author states that adding PHI to current predictive models [PCPT (Prostate Cancer Prevention Trial) and ERSCP (European Randomized study of Screening for Prostate Cancer)] increases their predictive accuracy [11].

A 2018 study describes the clinical utility of PHI in decision making in urology practice setting. The use of PHI resulted in significant reduction of the number of performed biopsies (60.3% vs. 36.4%) and there was a decrease in the overall percentage of Gleason score six tumours detected in the PHI group (9.9% vs. 18.4%) [12].

These and other papers published since the first use of PHI show the superiority of PHI when compared with total or free PSA. Our results concur with these statements, particularly when focusing on csPCa, where PHI outperformed total PSA in all patient groups. In the whole cohort and the repeat biopsy subgroup the difference between AUC for PHI and PSA was statistically significant; there

Table 5 The statistical significance of the differences between areas under ROC curves (from Tables 3 and 4) for different predictive models as assessed by the DeLong test

	p value		p value
All patients		All patients, GS > 6	
PSA vs. PHI	0.307	PSA vs. PHI	0.002
PSA vs. PIRADS	0.288	PSA vs. PIRADS	0.127
PSA vs. PIRADS + PHI	0.026	PSA vs. PIRADS + PHI	0.003
PHI vs. PIRADS + PHI	0.034	PHI vs. PIRADS + PHI	0.904
PIRADS vs. PIRADS + PHI	0.038	PIRADS vs. PIRADS + PHI	0.007
PSAD vs. PHI	0.007	PSAD vs. PHI	0.102
PSAD vs. PIRADS	0.036	PSAD vs. PIRADS	0.978
PSAD vs. PIRADS + PHI	0.266	PSAD vs. PIRADS + PHI	0.159
First biopsy		First biopsy, GS > 6	
PSA vs. PHI	0.242	PSA vs. PHI	0.078
PSA vs. PIRADS	0.001	PSA vs. PIRADS	0.726
PSA vs. PIRADS + PHI	0.450	PSA vs. PIRADS + PHI	0.198
PHI vs. PIRADS + PHI	0.245	PHI vs. PIRADS + PHI	0.443
PIRADS vs. PIRADS + PHI	0.000	PIRADS vs. PIRADS + PHI	0.028
PSAD vs. PHI	0.023	PSAD vs. PHI	0.247
PSAD vs. PIRADS	0.000	PSAD vs. PIRADS	0.925
PSAD vs. PIRADS + PHI	0.068	PSAD vs. PIRADS + PHI	0.581
Repeat biopsy		Repeat biopsy, GS > 6	
PSA vs. PHI	0.248	PSA vs. PHI	0.002
PSA vs. PIRADS	0.059	PSA vs. PIRADS	0.034
PSA vs. PIRADS + PHI	0.015	PSA vs. PIRADS + PHI	0.000
PHI vs. PIRADS + PHI	0.080	PHI vs. PIRADS + PHI	0.300
PIRADS vs. PIRADS + PHI	0.213	PIRADS vs. PIRADS + PHI	0.080
PSAD vs. PHI	0.137	PSAD vs. PHI	0.173
PSAD vs. PIRADS	0.799	PSAD vs. PIRADS	0.490
PSAD vs. PIRADS + PHI	0.863	PSAD vs. PIRADS + PHI	0.072

PIRADS Prostate Imaging Reporting and Data System, *PSA* prostate-specific antigen, *PHI* prostate health index *PSAD* PSA density

was no statistically significant difference in the first biopsy subgroup.

Furthermore, our study offers a direct head to head comparison with mpMRI of prostate, which is currently considered a golden standard in PCa visualisation and prediction and is a part of European Association of Urology guidelines [1]. Compared to this more expensive and more complicated technology which can be difficult to interpret [13, 14], PHI offers a similar and even superior predictive ability for csPCa. Combining these two methods yields even more accurate prediction in patients undergoing repeat biopsy, especially for csPCa. We were unable to find any direct comparisons in a literature search to compare our results with, except a 2018 article by Druskin et al., describing the superior diagnostic accuracy of PHI density when compared to PSA and PHI while being complementary to PIRADS score [15]. Further prospective studies are therefore needed.

The repeat biopsy group analysis yields very promising (and statistically significant) results for both PHI and the combination of PHI and PIRADS in csPCa prediction. This cannot, however, be said about the biopsy naïve patient group. Similar results have been shown in recent meta analyses evaluating mpMRI in PCa diagnostics [16, 17]. In our cohort PHI yields more accurate prediction in the first biopsy csPCa subgroup, but, despite a visible trend, the difference between AUC for PSA and PHI in this subgroup is not statistically significant.

PSAD shows superior predictive accuracy when analysing patients with any PCa in all patient subgroups, with even greater accuracy when combined with PHI and PIRADS. This, however, is not true for csPCa as in all patient subgroups PHI is superior to PSAD in predicting csPCa involvement. Despite this trend being present in all csPCa subgroups, the difference between AUCs is not statistically significant. Adding PSAD to PHI and PIRADS also does not improve the predictive accuracy for csPCa of PHI and

PIRADS combined. PSAD might thus increase the diagnosis of PCA, although not only its clinically significant variant, which might lead to overdiagnosis of clinically insignificant PCa.

The generally high number of positive biopsies in our analysis may stem form a higher average PSA in our cohort, when compared to other published studies. Despite higher average, PSA was still lagging after PHI in csPCa prediction. This is also true for a rather higher percentage of patients with positive mpMRI (PIRADS > 2), where, as with PSA, despite higher general values, PIRADS score is still inferior to PHI in csPCa prediction.

When considering the cost of PHI, it is important to note that while PHI is more expensive than both PSA and PSAD, it surpasses both in diagnostic accuracy of csPCa, so the additional expenses might be worth it, especially in cases where the use of PHI allows the omission of MRI or prostate biopsy and thus saves considerable expenses.

Study limitations

The definition of csPCa has been evolving during recent years and a global consensus has not yet been reached. Overall, Gleason score of > 6 (ISUP > 1) seems to be prevalent in most recent criteria [18, 19], and we therefore used it to define csPCa in our study. Maximum core length is also often used in the definition pf csPCa, it was however not available for all patients, so we did not include it in the final analysis. As needle widths and core length may differ between hospitals, we think, that Gleason score remains the most important factor.

Both 1, 5 T with an endorectal coil and 3 T without endorectal coil MRI machines were used in this study. This may present a limitation; however, studies have shown that both are of similar accuracy and image quality from the reader's point of view [20–22].

Similarly, using the PIRADS version one mpMRI reporting system might come as a limitation. This was due to this study being a part of an ongoing larger study which started before the implementation of the PIRADS version two. The superiority of the PIRADS version two over version one has not yet been established [23–25] however, and different in-house reporting systems are still being used [26–28]. It is therefore unclear, whether the results would have been different with the use of PIRADS version one.

As it is not yet generally recommended to routinely perform only targeted biopsies (especially in biopsy naïve patients, with only weak recommendation strength rating for repeat biopsies) [1], we performed systematic biopsy in all patients in this study regardless to the results of MRI. It was therefore not possible to analyse targeted and systematic biopsies separately.

Conclusion

Prostate Health Index could serve as a reliable tool in predicting clinically significant PCa. When compared to current highest diagnostic standard – the mpMRI, it shows comparable results without the added costs of obtaining and interpreting MRI of the prostate. The PHI cannot, however, help us guide prostate biopsies in any way, and its main use may therefore be in pre-MRI or pre-biopsy triage, where it could further decrease the number of needlessly performed prostate biopsies.

Compliance with ethical standards

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