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Comparison of PHI and PHI Density for Prostate Cancer Detection in a Large Retrospective Caucasian Cohort

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Adenocarcinoma · Decision curve analysis · Prostate cancer · Prostate Health Index · Prostate Health Index density · Prostate-specific antigen

Abstract
Background: Beyond prostate-specific antigen (PSA), other biomarkers for prostate cancer (PCa) detection are available and need to be evaluated for clinical routine. ***Objective:*** The aim of the study was to evaluate the Prostate Health Index (PHI) density (PHID) in comparison with PHI in a large Caucasian group >1,000 men. ***Methods:*** PHID values were used from available patient data with PSA, free PSA, and [−2]proPSA and prostate volume from 3 former surveys from 2002 to 2014. Those 1,446 patients from a single-center cohort included 701 men with PCa and 745 with no PCa. All patients received initial or repeat biopsies. The diagnostic accuracy was evaluated by receiver operating characteristic (ROC) curves comparing area under the ROC curves (AUCs), precision-recall approach, and decision curve analysis (DCA). ***Results:*** PHID medians differed almost 2-fold between PCa (1.12) and no PCa (0.62) in comparison to PHI (48.6 vs. 33; p always <0.0001). However, PHID and PHI were equal regarding the AUC (0.737 vs. 0.749; $p = 0.226$), and the curves of the precision-recall analysis also overlapped in the sensitivity range between 70 and 100%. DCA had a maximum net benefit of only ~5% for PHID versus PHI between 45 and 55% threshold probability. Contrary, in the 689 men with a prostate volume ≤40 cm^3, PHI (AUC 0.732) showed a significant larger AUC than PHID (AUC 0.69, $p = 0.014$). ***Conclusions:*** Based on DCA, PHID had only a small advantage in comparison with PHI alone, while ROC analysis and precision-recall analysis showed similar results. In smaller prostates, PHI even outperformed PHID. The increment for PHID in this large Caucasian cohort is too small to justify a routine clinical use.

Introduction

During 3 decades, prostate-specific antigen (PSA) has been the landmark for prostate cancer (PCa) detection [1, 2]. But the low specificity of PSA is a high burden. After the detection of [−2]proPSA [3], the use of the Prostate Health Index PHI ([−2]proPSA/freePSA × √PSA) significantly enhanced the specificity of PSA in the last decade [4–6]. Analogous to the PSA density (PSA/prostate volume), the term PHI density (PHID: PHI/prostate vol-

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ume) has been proposed to further improve early diagnosis of PCa [7]. The results until the year 2019 were mostly favorable for PHID [7–10]. Only Friedl et al. [11] could not find a further improvement using PHID in comparison with PHI alone. The area under the receiver operating characteristic (ROC) curve (AUC) was higher for PHI (0.79) than for PHID (0.77) [11]. In 2020, Schulze et al. [12] found a small but significant advantage for PHID (AUC: 0.74) in comparison with PHI (AUC: 0.72). Similar favorable results were seen in another study in 210 men [13]. All studies have in common that the number of patients varied from 112 to 275 men and that all have been investigated mostly Caucasian men [7–13]. In contrast, a recent study in 2 large cohorts of Asian men (n = 595 and n = 1,025) concluded, that there is no additional value for PHID in comparison with PHI [14].

Therefore, the aim of this study was first to test the additional value of PHID versus PHI in a large cohort with >1,000 men and second to evaluate this relationship in a Caucasian cohort. Furthermore, different subgroup analysis (PSA <8 µg/L and use of different volume cutoffs) were performed in order to investigate if the value of PHID also detects clinically significant PCa with a Gleason score ≥7.

Materials and Methods

To obtain a large number of PHID values, we used available patient data from 2002 to 2014 with PSA, free PSA and [−2]proPSA, and prostate volume from 3 former surveys [15–17]. A number of n = 587 patients (PSA range 0–30 µg/L) were extracted from a data set published in 2009 [15]. We also included n = 391 patients (PSA 1.6–8 µg/L) from a Berlin multicenter cohort [16] and n = 468 patients (PSA 0–20 µg/L) from a comparison study of PHI and vitamin D [17]. Thus, 1,446 patients from existing data with consecutive sample collection were analyzed retrospectively.

All patients were consecutive biopsied (8–22 cores) within the Charité Hospital Berlin. The patients with suspicion for PCa underwent initial (n = 557) or repeat (n = 302) systematic biopsies and 166 patients from 2012 to 2014 underwent magnetic resonance imaging (MRI)/ultrasound fusion-guided biopsies. There was an almost equal distribution between PCa (n = 701, 48.5%) and no PCa (n = 745).

Prostate volume was determined by transrectal ultrasound and calculated using the prostate ellipse formula. Blood samples were strictly taken before biopsy or any other prostate manipulation. After allowing the blood to clot for a maximum of 1 h at room temperature, the samples were centrifuged at 1,600 g for 10 min at 4°C and the supernatants (serum) were stored at −80°C until analyzed according to recommendations [18–20] and as described before [16, 17]. The PSA ranged from 0.26 to 28.4 µg/L with most samples between 1.8 and 8 µg/L. The PSA and free PSA calibration were performed based on the WHO PSA reference material 96/670 and on the WHO free PSA reference material 96/668. The fully automated immunoassay device Access® (Beckman Coulter, Brea, CA, USA) was used for all measurements of PSA, free PSA, and [−2]proPSA in Berlin, as described [16, 17].

MedCalc version 19.6.1 (MedCalc Software Ltd., Ostend, Belgium) was used for statistical analysis. Correlations were analyzed by using the Spearman rank correlation coefficient (r_s), and group differences were assessed by the nonparametric Mann-Whitney U test. ROC curves and AUCs were estimated according to DeLong et al. [21]. The precision-recall curve is an alternative for ROC analysis and this curve plots the positive predictive value (named precision; y-axis) against the diagnostic sensitivity (named recall; x-axis) for different thresholds [22]. P values <0.05 were considered statistically significant. Decision curve analysis (DCA) was performed with the MATLAB Neural Network Toolbox (Mathworks, Natick, MA, USA), as already described [23]. In brief, a possible benefit of a marker is plotted against threshold probabilities, which then yields the decision curve. The DCA can identify the magnitude of benefit and the range of threshold probabilities, where the marker or model is of value [24].

Results

Table 1 provides the patient characteristic of the cohort with 1,446 patients. All parameters differed significantly between PCa and patients with no PCa, respectively. Due to the large number of patients, also age (65 vs. 66 years) and PSA (4.9 vs. 4.4 µg/L) differed significantly between PCa and no PCa. The medians for PHI (48.6 vs. 33, $p < 0.0001$) differed <1.5-fold but for PHID (1.12 vs. 0.62, $p \leq 0.0001$) the difference was 1.8-fold.

The AUCs for all PSA derivatives including percent free PSA (%fPSA) and PSA density (PSAD) are indicated in Table 2. PHID (0.749) impressed somewhat higher than PHI (0.737, $p = 0.226$), but no statistically relevant difference could be observed (Fig. 1a). Despite this negligible absolute AUC difference of 0.01 between PHID and PHI, DCA showed an advantage of a maximum of 5% net benefit for PHID for the range between 45 and 55% threshold probability (Fig. 1b). At 95% sensitivity, PHID had a marginal better specificity (21.9%, confidence interval CI: 19–25%) than PHI (18.3%, CI: 15.5–21.2%) but at 90% sensitivity, PHID (32.6%) and PHI (31.1%) had equal specificities. The precision-recall curves for PHI (green) and PHID (red) (Fig. 1c) showed almost similar positive predictive values for both parameters between 70 and 100% sensitivity with an overlap of their curves.

The Hybritech-calibrated PSA gray zone of 2–10 µg/L corresponds to WHO-calibrated values up to 8 µg/L. We additionally analyzed those 1,253 men with PSA values 1–8 µg/L. There were no changes as compared with the overall cohort with again significant differences between no PCa and PCa for all parameters (PSA 4.0 vs. 4.4 µg/L;

Table 1. Clinical characteristics of the cohort

Parameter	All patients (n = 1,446)	PCa (n = 701)	No PCa (n = 745)	p value
Age, years	65 (60–70)	65 (60–69)	66 (61–71)	0.0015
Prostate volume, cm^3	42 (30–60)	38 (28–50)	49 (34–68)	<0.0001
PSA, µg/L	4.64 (3.11–6.45)	4.9 (3.45–6.62)	4.38 (2.69–6.26)	<0.0001
%fPSA, %	11.7 (6.7–18.1)	10.3 (5.6–15.4)	13.9 (8.3–21.3)	<0.0001
PSAD	0.102 (0.07–0.16)	0.125 (0.09–0.19)	0.085 (0.06–0.13)	<0.0001
PHI	39.4 (28.9–55.4)	48.6 (35.3–68.4)	33.0 (24.9–43.5)	<0.0001
PHID	0.81 (0.53–1.28)	1.12 (0.73–1.64)	0.62 (0.43–0.89)	<0.0001

Data are given as medians with interquartile ranges in parentheses. p values refer to the differences between PCa and NEM patients. PSA, prostate-specific antigen; PCa, prostate cancer.

PHID 0.62 vs. 1.09). The AUCs for PHI (0.73) and PHID (0.74, p = 0.379) were again not different (Table 3). At 95% sensitivity, PHID had a significant better specificity (22.5%, CI: 19.3–25.9%) than PHI (15.7%, CI: 13–18.7%), but at 90% sensitivity, PHID (32.6%) and PHI (31.1%) had again equal specificities.

The use of different prostate volume cutoffs did not improve the performance of PHID. In contrary, PHI (AUC 0.732) showed a significant larger AUC than PHID (AUC 0.69, p = 0.014) in those 689 men with a volume ≤40 cm^3. PHI (0.726) also had a somewhat larger AUC than PHID (0.717, p = 0.49) for volumes <60 cm^3 (n = 1,079). In those 757 patients with a larger prostate size >40 cm^3, the AUC comparisons between PHI (0.72) and PHID (0.73, p = 0.17) provided again no differences. The 367 men with the largest glands (≥60 cm^3) similarly had also no AUC difference between PHI and PHID (0.736 vs. 0.73, p = 0.56).

PHI (r_s = 0.325, CI: 0.25–0.39) and PHID (r_s = 0.254, CI: 0.18–0.32) correlated significantly (p < 0.0001) with the Gleason score, but the Spearman Rank correlation coefficient was not different between PHID and PHI (p = 0.163). The distribution of no PCa and low-risk patients (Gleason score <7) combined versus all other PCa (Gleason score ≥7) provided no further improvement for PHID (AUC 0.751) in comparison with PHI (AUC 0.753, p = 0.88).

Table 2. AUC comparison of the overall cohort with n = 1,446 patients

Parameter	AUC	95% confidence interval	p value versus PHI
PSA	0.56	0.53–0.59	<0.0001
%fPSA	0.603	0.58–0.63	<0.0001
PSAD	0.68	0.65–0.70	<0.0001
PHI	0.737	0.71–0.76	–
PHID	0.749	0.73–0.77	0.226

PSA, prostate-specific antigen; AUC, area under the ROC curve.

Discussion

After the first implementation of PHID in 2014, 6 different studies with 118 to 275 men described a diagnostic advantage for PHID in comparison with PHI regarding the AUC [7–10, 12, 13]. These studies reported AUCs for PHID between 0.74 and 0.84 and lower AUCs for PHI between 0.72 and 0.79 [7–10, 12, 13]. Only Friedl et al. [11] found a larger AUC for PHI (0.79) than for PHID (0.77) in 112 men. In contrast to these data obtained from mostly Caucasian men [7–13], a recent study from 2020 in Asian men reported no benefit of prostate volume derivatives in addition with PHI in 2 different cohorts from a multicenter study [14]. Huang et al. [14] reported PHID not to be able to outperform PHI for predicting any or clinically significant PCa in either cohort of 595 or 1,025 Asian men. This is in agreement with our data from the present study in a similar large number of Caucasian patients. With no AUC difference between PHID (0.749) and PHI (0.737, p = 0.226), only the DCA showed an advantage of 5% net benefit for PHID for a small range of 45–55% threshold probability (Fig. 1b). Also, in those 1,253 men with PSA values 1–8 µg/L, the AUCs between PHID (0.74) and PHI (0.73, p = 0.379) were not different (Table 3). The small advantage for PHID versus PHI at 95% sensitivity (overall and PSA 1–8 µg/L cohort) with a

Table 3. AUC comparison of cohort with PSA values 1–8 µg/L in n = 1,253 patients

Parameter	AUC	95% confidence interval	p value versus PHI
PSA	0.571	0.54–0.60	<0.0001
%fPSA	0.614	0.59–0.64	<0.0001
PSAD	0.683	0.66–0.71	0.0041
PHI	0.731	0.71–0.76	–
PHID	0.741	0.72–0.765	0.3794

PSA, prostate-specific antigen.

3.5% and ~7% better specificity disappeared at 90% sensitivity. The precision-recall curves for PHI and PHID in Figure 1c further confirmed similar positive predictive values for all sensitivities >70%. Thus, using all these 3 approaches for determining overall diagnostic accuracy could not verify a clinically relevant difference in the diagnostic accuracy of PHI and PHID.

More importantly, the detection of clinically significant PCa including a Gleason score ≥7 in comparison with all other patients (low risk PCa with Gleason ≤6 and no PCa) showed also no benefit in using PHID (AUC 0.751) over PHI (AUC 0.753, p = 0.88). This clearly indicates that PHI alone is currently the strongest biomarker for PCa detection.

According to the literature Mearini et al. [7] published the first description of the term PHID in 2014, while Filella et al. [25] proposed in the same year an impact of prostate volume on PHI with an improved PHI performance in smaller glands. PHI (AUC: 0.82) and PHID (AUC: 0.84) similarly performed better in patients with small prostates ≤36 cm^3 than those men with the largest glands (≥50 cm^3) where PHI (0.65) and PHID (0.64) had lower AUC values [25] (personal information). The present data confirm Filella et al. [25] initial hypothesis that the diagnostic power of PHI is improved in smaller glands. In those 689 patients with small prostates ≤40 cm^3, PHI had a significant larger AUC (0.732) than PHID (0.69). As we already speculated in recent more positive prospective data on PHID [26], subgroup analyses with either selected small or relatively large glands might be the reason for lower AUCs for PHID in comparison with PHI because PHID already includes prostate volume. In addition, the higher number of repeat biopsies in this study (up to 35%) as compared with the prospective study (high number of initial and fusion biopsies) might be a further possible reason for differences.

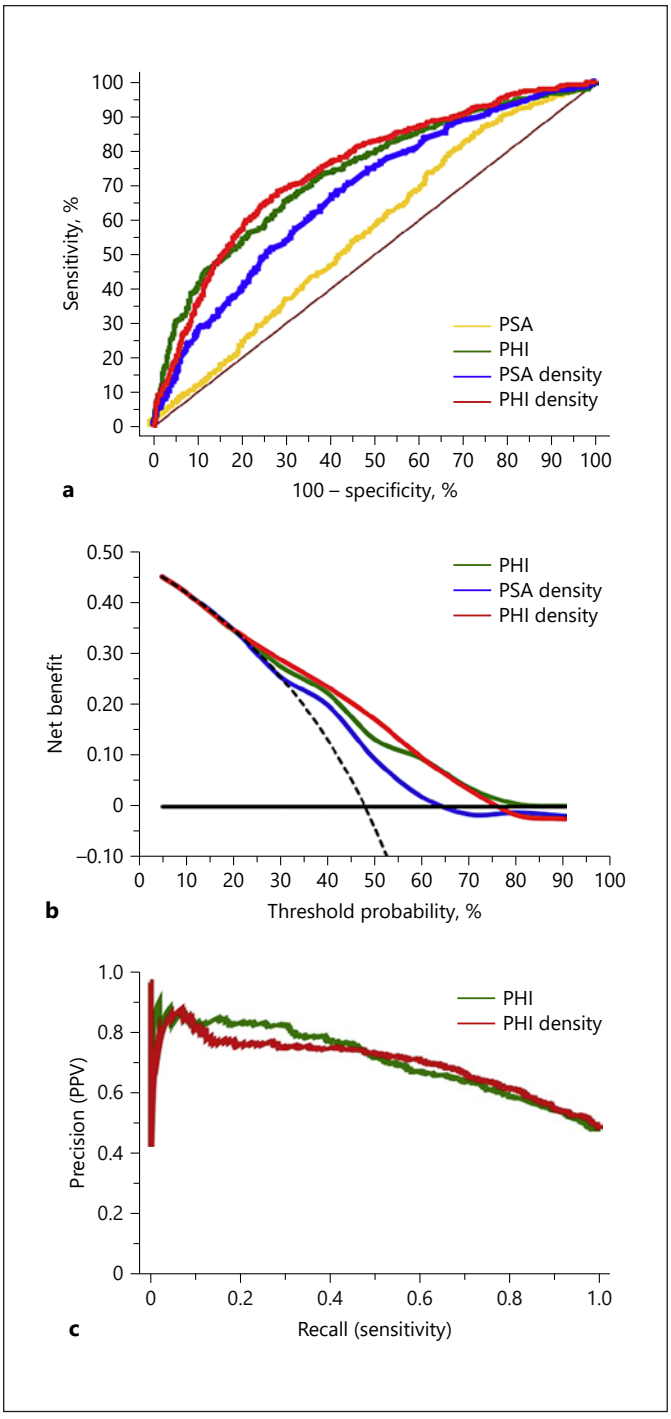

Fig. 1. Overall cohort with 1,446 patients with (**a**) ROC analysis for PSA (AUC: 0.56), PSAD (0.68), PHI (0.74), and PHID (0.75) and with (**b**) DCA comparing model 1 using PHI with model 2 using PSAD with model 3 using PHID, to biopsy-all and biopsy-none strategies as well as (**c**) precision-recall curves, which plot the positive predictive value (named precision) against the diagnostic sensitivity (named recall) for PHI and PHID. PSA, prostate-specific antigen; DCA, decision curve analysis; ROC, receiver operating characteristic; AUC, area under the ROC curve.

However, the literature showed that PHI currently seems to be the best biomarker for PCa detection. Furthermore, PHI improves the specificity over PSA and %fPSA [27, 28]. Regarding absolute PHI values and usable cutoffs, there might be racial differences, as already postulated [29] and discussed [28]. It remains unclear why the 6 positive PHID studies with an average of <200 patients are in contrast of the present study and the recent Asian multicenter study [14]. The smaller number of patients might be only 1 possible explanation. However, the data of the present study together with the ~1,600 Asian patients [14] represent >3,000 patients.

A weakness of the present study is that mostly systematic biopsies were performed and only 166 patients (from 2012 to 2014) underwent MRI/ultrasound fusion-guided biopsies. Furthermore, the subdivision in the first and repeat biopsy could not be evaluated from the first dataset until 2006, resulting in only 859 (59.4%) available biopsy history, whereas 302 (35%) underwent repeated biopsy and 557 (65%) primary biopsy, respectively. However, a possible difference for PHI and PHID due to the biopsy type (systematic or MRI/ultrasound fusion-guided) is not very likely. Druskin et al. [8] combined PHID with MRI and prior negative biopsy status in 241 patients. Their PHID medians were 1.18 and 0.55 in men with and without clinically significant PCa [8]. These absolute PHID medians are almost similar to our 1,253 patients with PSA values <8 μg/L with 1.09 for PCa and 0.62 for no PCa, respectively. The retrospective approach of this study is a further limitation. However, all pre-analytical factors including sample storage conditions and measurements have been performed identical to our elsewhere published prospective data on PHID [26].

Conclusions

This study proved a marginal benefit for PHID in comparison with PHI alone. While the DCA had a 5% advantage in a limited range, all other calculations including ROC analysis, subgroup analysis, and precision-recall curves showed no advantage for PHID. PHID was also not able to improve the detection of clinically significant PCa with a Gleason score ≥7 in comparison with PHI. Thus, PHI as marker combination of [−2]proPSA, free-PSA, and PSA remains as best biomarker for PCa detection. The advantage of PHID is too small for a routine clinical use recommendation.

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Statement of Ethics

The Ethics Committee of the Charité-University Medicine Berlin approved the study (EA1/134/12). Informed consent was obtained from all patients. The study was performed in accordance with the Declaration of Helsinki.

Conflict of Interest Statement

The authors declare that they have no conflict of interest. No competing interests related to the subject matter of the article.

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Author Contributions

Peters, Stephan, and Maxeiner designed the research study. Peters, Stephan, and Jung acquired the data. Peters, Stephan, Lein, Jung, and Maxeiner analyzed the data. Peters, Stephan, and Maxeiner wrote the paper. Stephan, Jung, Lein, Friedersdorff, and Maxeiner critically revised the manuscript. Stephan, Jung, and Maxeiner supervised the study.

Availability of Data and Material

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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