

The prostate health index (PHI) density: Are there advantages over PHI or over the prostate-specific antigen density?

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ABSTRACT

Background and aims: Overdiagnosis of prostate cancer (PCa) should be minimized. We wanted to evaluate the diagnostic performance of the prostate health index density (PHID) and compare it with that of the prostate health index (PHI) alone and of the prostate-specific antigen density (PSAD).

Materials and methods: 232 men scheduled for a prostate biopsy (prostate-specific antigen level: 2–10 µg/L), were enrolled. PHI, PHID and PSAD were evaluated considering PCa and clinically significant PCa (csPCa) as the outcomes.

Results: For PCa, the area under the curve (AUC) was higher for PHID (0.823) than for PHI (0.779) and PSAD (0.776). For csPCa, the AUC was also higher for PHID (0.851) but closer to that of PSAD (0.819) and PHI (0.813). For equal sensitivities (90%) for PCa, PHID and PSAD offered the highest specificities (37%), missing the same number of cancers (n = 11). Considering csPCa, PHI and PHID had similar specificities. PSAD reached the highest specificity (50.0%), sparing 32.8% of biopsies, while missing 9 cases of csPCa.

Conclusions: PHID has a better diagnostic performance than PHI for overall PCa detection, but very close to the PSAD performance. Considering csPCa, PHI and PHID perform almost equally, but PSAD has a better diagnostic performance.

1. Introduction

Prostate cancer (PCa) screening based on prostate-specific antigen (PSA) has been the subject of great debate and controversy, as it has been the cause of overdiagnosis and overtreatment of cancers that would not have clinical impact during the patient's lifetime [1]. These issues are largely due to the low specificity of PSA for cancer [2]. That is why there has been great effort to find new strategies and biomarkers that could improve PSA specificity for PCa. One of these strategies is PSA density (PSAD), which consists of the quotient of serum PSA divided by the volume of the prostate gland. The mechanism that explains that

PSAD is higher in PCa is that malignant cells are expected to produce elevations in serum PSA levels beyond what is expected from an equal volume of hyperplasia [2–3]. The results from several studies have shown some benefits of PSAD over PSA in detecting PCa, especially the most aggressive forms [4–5].

More recently, a form of free PSA (fPSA) that has consistently been reported to contribute to enhance PSA specificity for PCa, was identified: [-2]proPSA [6–7]. Its clinical utility has been mostly evaluated by its incorporation in a mathematical derivative of [-2]proPSA: the prostate health index (PHI) [8]. There is a large unanimity of several studies in corroborating that PHI improves not only overall PCa detection, but also

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the detection of clinically significant PCa (csPCa) [9–13].

In a similar way to what happens with PSAD, and certainly based on the same logical mechanism that explains its utility [14], a few authors have recently explored the hypothesis that PHI density (PHID) – the PHI value divided by the volume of the prostate – could improve even further the diagnostic performance of PHI. Their results have been promising so far [15–16]. It has also been reported that, in patients with a PSA level below 10 µg/L, PHI has an improved performance in smaller prostate glands (≤ 35 cc), meaning that the prostate volume has an impact on PHI performance [17].

Given the recent, and still not sufficiently explored, evidence about the possible advantages of PHID, and since it is necessary to find new diagnostic tools that can lower unnecessary biopsies and reduce PCa overdiagnosis, our main objective was to evaluate the clinical performance of PHID in overall PCa and csPCa detection, and compare it with PHI and PSAD.

2. Materials and methods

2.1. Study design

In this observational study, PSAD, PHI, and PHID were calculated in men with no previous history of PCa and PSA levels between 2 µg/L and 10 µg/L, irrespective of the digital rectal examination findings. The diagnostic accuracy of PSAD, PHI, and PHID was evaluated, with PCa and csPCa as the outcomes.

All participants provided written informed consent. The study protocol was approved by the institutional review board and complied with the Helsinki Declaration.

In all men included in the study, an initial or repeated prostate biopsy was performed with at least 12 cores. Pathological assessment of biopsy specimens was performed by the same expert genitourinary pathologist. Biopsy results were reported according to the definitions of the 2014 consensus conference of the International Society of Urological Pathology [18].

Blood collection to assess tumor markers was performed on the same day as the biopsy, but prior to the procedure.

The total prostate volume (TPV) was measured, using the usual ellipsoid formula, on transrectal prostate ultrasound (TRUS) or, whenever available, on multiparametric prostate magnetic resonance imaging (mpMRI). PHI was calculated using the formula $([-2]proPSA/fPSA) \times \sqrt{PSA}$, PHID density was estimated as $PHI/[TPV \text{ in cc}]$ and PSAD as $PSA/[TPV \text{ in cc}]$.

csPCa was defined according to the criteria established in the Prostate Cancer Research International Active Surveillance (PRIAS) study, for patients with a PSA value below 10 µg/L [19], with the exception of the criteria of a PSAD ≥ 0.2 µg/L/cc. Therefore, we have defined csPCa by the presence of at least one of the following characteristics: regional lymph node metastasis (N1), distant metastasis (M1), extracapsular disease ($T \geq 3$), total Gleason score (GS) ≥ 7 , number of positive biopsy cores > 2 or, whenever saturation biopsies were made (≥ 20 cores), $> 15\%$ of positive cores (or > 4 positive cores, if 15% of positive cores exceeded this number) [20].

2.2. Study subjects

232 consecutive patients from the Urology Department of the Central Lisbon University Hospital Center with a prostate biopsy scheduled for suspicion of PCa, were enrolled between December of 2017 and October of 2019. The inclusion criteria were as follows: no previous history of PCa, PSA level between 2 and 10 µg/L (Beckman Coulter Hybritech®), no previous transurethral resection of the prostate, no therapy with drugs that may affect PSA concentration (5- α -reductase inhibitors and androgens), no urinary infection contemporary to blood collection, or acute bacterial prostatitis in the three months prior to the biopsy, without hemophilia or history of multiple blood transfusions or chronic

renal failure, serum total protein concentration below 80 g/L. Patients with heavy hemolyzed serum samples were not included.

2.3. Blood samples processing and laboratory assays

Blood was collected into tubes without anticoagulants. For the pre-analytical in vitro stability of [-2]proPSA, the criteria described by Semjonow et al. were followed [21]. Samples were centrifuged and refrigerated (2–8°C) within 3 h of the blood draw. From each sample, an aliquot of serum was separated and frozen at -80 °C within 8 h after the blood draw. Samples were thawed only once to perform Beckman Coulter Hybritech® PSA, fPSA, and [-2]proPSA on the Access 2 immunoassay analyzer (Beckman Coulter, Brea, CA, USA), using the Hybritech calibration.

2.4. Statistical analysis

Non-normally distributed continuous variables were described by the median and interquartile range (IQR). The Mann–Whitney *U* test or Kruskal–Wallis test was used for comparison. Normally distributed variables were reported as mean and standard deviation (SD), and Student's *t*-test or ANOVA was used to compare values. Univariate and multivariate logistic regression analyses were applied to predict outcomes. Odds ratios (ORs) with 95% confidence intervals were also calculated. The predictive accuracy of the evaluated parameters was quantified using the area under the receiver operating characteristic curve (AUC). Statistical significance was defined as a two-sided *p* value < 0.05 . Statistical analysis was performed using IBM® SPSS® Statistics 26.0 (IBM Corp., Armonk, NY, USA, 2019). Positive (PPV) and negative (NPV) predictive values were calculated using MedCalc® Software version 14.8.1 (MedCalc Software Ltd., Ostend, Belgium).

3. Results

Of the 232 men enrolled, 50% had PCa and 50% had no cancer on biopsy. Of the 116 cancer patients, 98 (89% of cancer patients and 42% of all participants) had csPCa. The median age of all participants was 67.5 (IQR = 61–73) years. The median age of patients with PCa was slightly higher (69.5; IQR = 62–73 years) than the age of those without cancer (65; IQR = 60–71 years). Of the enrolled patients, 98.7% were Caucasian. TPV was obtained through TRUS in 85.8% of the patients, and it was derived from mpMRI in 14.2% of the participants.

The distribution of TPV, PSA, PSAD, PHI, and PHID values is shown in Table 1. For all these parameters, there was a significant difference ($p < 0.05$) between men with and without PCa, as well as between men with csPCa and those with insignificant PCa or without evidence of malignancy.

Considering the detection of PCa, the highest AUC was obtained with PHID (AUC = 0.823), followed by PHI (AUC = 0.779) and PSAD (AUC = 0.776). PSA had the lowest AUC (AUC = 0.609) (Fig. 1). The differences between the AUCs were significant between PSA and all the other tests ($p < 0.001$), but there were no significant differences between the AUCs of PHI and PHID ($p = 0.059$), PHID and PSAD ($p = 0.054$), and between those of PHI and PSAD ($p = 0.937$). Considering csPCa as the outcome, PHID also had the highest AUC (AUC = 0.851) and PSA had the lowest (AUC = 0.661) (Fig. 1). PHI and PSAD had similar AUCs (0.813 and 0.819, respectively). Similar to what was verified with PCa detection, the differences between the AUC values were significant only between PSA and all the other parameters ($p < 0.001$).

On univariate analysis, all the evaluated tests were predictors of PCa (Table 2) and csPCa (Table 3).

On multivariate analysis, both PSAD and PHID were independent predictors of PCa and csPCa ($p < 0.001$) when added to a base model consisting of PSA and PHI (Tables 2 and 3). Considering overall PCa detection, there was a gain of approximately 7% in diagnostic accuracy when PSAD (AUC = 0.838) or PHID (AUC = 0.833) were added to the

Table 1
Distribution of the measured parameters in the different groups of studied patients.

	PCa	No cancer	p value	csPCa	No cancer or insignificant PCa	p value
TPV, cc, median (IQR)	40.0 (31.3–54.5)	59.0 (46.3–80.0)	<0.001 ^a	39.0 (31.8–51.0)	59.0 (45.0–77.3)	<0.001 ^a
PSA, µg/L, mean (±SD)	6.6 (±2.0)	5.6 (±2.0)	0.004 ^b	6.9 (±1.9)	5.8 (±2.0)	<0.001 ^b
PSAD, µg/L/cc, median (IQR)	0.16 (0.11–0.21)	0.09 (0.07–0.12)	<0.001 ^a	0.17 (0.12–0.22)	0.09 (0.07–0.12)	<0.001 ^a
PHI, median (IQR)	45.6 (34.3–61.0)	29.8 (24.0–37.5)	<0.001 ^a	50.4 (39.0–63.0)	30.3 (24.0–37.5)	<0.001 ^a
PHID, median, per cc (IQR)	1.14 (0.77–1.60)	0.52 (0.35–0.68)	<0.001 ^a	1.31 (0.89–1.68)	0.53 (0.37–0.70)	<0.001 ^a

PCa prostate cancer, csPCa clinically significant prostate cancer, TPV total prostate volume, PSA prostate-specific antigen, PSAD prostate-specific antigen density, PHI prostate health index, PHID prostate health index density, SD standard deviation, IQR interquartile range.

^a Mann-Whitney test.

^b Student's *t* test.

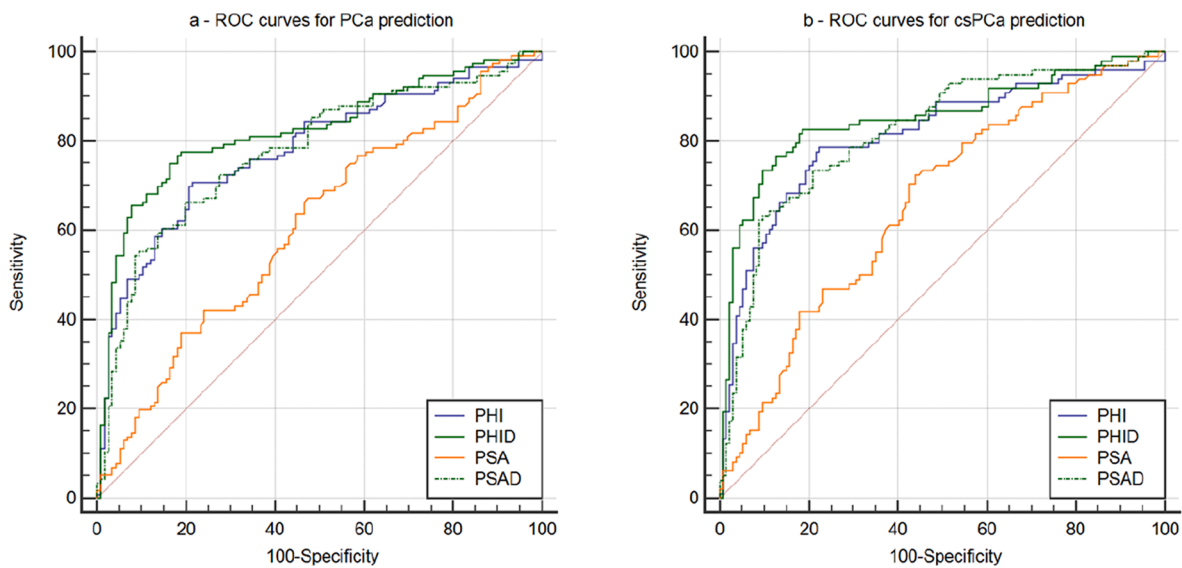


Fig. 1. Receiver-operating characteristic (ROC) curves for: (a) the prediction of overall prostate cancer (PCa); (b) the prediction of clinically significant prostate cancer (csPCa).

Table 2
Univariate and multivariate analysis for the prediction of prostate cancer.

Predictor	Univariate analysis			Multivariate analysis					
	AUC (95% CI)	OR (95% CI)	p value	Base model OR (95% CI)	p value	Base model and PSAD OR (95% CI)	p value	Base model and PHID OR (95% CI)	p value
PSA	0.609 (0.537–0.681)	1.22 (1.06–1.39)	0.004	0.99 (0.84–1.15)	0.824	0.80 (0.66–0.96)	0.018	1.07 (0.90–1.26)	0.464
PHI	0.779 (0.718–0.839)	1.07 (1.04–1.09)	<0.001	1.07 (1.04–1.15)	<0.001	1.06 (1.03–1.08)	<0.001	1.02 (0.98–1.05)	0.336
PSAD	0.776 (0.715–0.836)	5.39* (3.10–9.36)	<0.001			5.10* (2.61–9.95)	<0.001		
PHID	0.823 (0.768–0.879)	10.84 (5.09–23.12)	<0.001					7.44 (2.73–20.24)	<0.001
				AUC (95% CI)		AUC (95% CI)		AUC (95% CI)	
				0.781 (0.720–0.841)		0.838 (0.786–0.891)		0.833 (0.779–0.888)	

PSA prostate-specific antigen, PHI prostate health index, PSAD prostate-specific antigen density, PHID prostate health index density, AUC area under the receiver-operating characteristic curve, CI confidence interval, OR odds ratio.

*OR per unit change of 0.1.

base model (AUC = 0.781) (Table 2). When taking csPCa as the outcome, the gain in diagnostic accuracy was approximately 7% when PSAD (AUC = 0.870) or PHID (AUC = 0.869) were added to the base

model (AUC = 0.810) (Table 3).

When choosing the appropriate cutoffs that allowed a diagnostic sensitivity of approximately 90% for all tests, both PSAD and PHID had

Table 3
Univariate and multivariate analysis for the prediction of clinically significant prostate cancer.

Predictor	Univariate analysis			Multivariate analysis					
	AUC (95% CI)	OR (95% CI)	p value	Base model OR (95% CI)	p value	Base model and PSAD OR (95% CI)	p value	Base model and PHID OR (95% CI)	p value
PSA	0.661 (0.591–0.731)	1.33 (1.16–1.54)	<0.001	1.08 (0.91–1.27)	0.398	0.86 (0.71–1.05)	0.144	1.20 (1.00–1.45)	0.050
PHI	0.813 (0.753–0.872)	1.07 (1.05–1.10)	<0.001	1.07 (1.05–1.10)	<0.001	1.06 (1.04–1.09)	<0.001	1.01 (0.98–1.04)	0.494
PSAD	0.819 (0.762–0.875)	7.25* (4.02–13.06)	<0.001			6.04* (3.04–12.01)	<0.001		
PHID	0.851 (0.796–0.906)	14.19 (6.52–30.87)	<0.001					10.67 (3.81–29.82)	<0.001
				AUC (95% CI)		AUC (95% CI)		AUC (95% CI)	
				0.810 (0.752–0.869)		0.870 (0.819–0.920)		0.869 (0.816–0.921)	

PSA prostate-specific antigen, PHI prostate health index, PSAD prostate-specific antigen density, PHID prostate health index density, AUC area under the receiver-operating characteristic curve, CI confidence interval, OR odds ratio.

*OR per unit change of 0.1.

higher diagnostic specificities for PCa than PSA (13.8%) or PHI (26.7%). However, there were no differences between the diagnostic specificities of PSAD (36.2%) and PHID (37.1%), and the same was true for PPV (PSAD, 58.7%; PHID, 59.0%) and NPV (PSAD, 79.2%; PHID, 79.6%). There was also no difference between the number of spared biopsies between PSAD (n = 52) and PHID (n = 53), and the number of missed PCa cases was exactly the same (n = 11) (Table 4).

When applying to all tests the cutoffs that allowed approximately 90% of diagnostic sensitivity for csPCa, the diagnostic specificity of PHID (39.6%) was only slightly higher than that of PHI (35.8%). The same was true for the number of spared biopsies (PHID: n = 61; PHI: n = 58) and the number of missed csPCa would have been slightly lower with PHID (n = 8), when compared to PHI (n = 10). However, PSAD had higher specificity (50.0%), PPV (56.8%), and NPV (88.3%) than PHID. PSAD could spare more biopsies (n = 76) than PHI (n = 58) and PHID (n = 61) (Table 4).

4. Discussion

Both PHID and PSAD were predictors of PCa and csPCa (p < 0.001 on

univariate analysis), and both were independent predictors of the two outcomes when added to a base model with PSA and PHI (p < 0.001 on multivariate analysis), allowing a gain of 7% in predictive accuracy. The predictive accuracy, as evaluated by the AUC, was higher for PHID when considering both outcomes.

When analyzing their diagnostic performance in more detail, there were almost no differences between the performance of PSAD and PHID in overall PCa detection. With 90% diagnostic sensitivity, both tests reach similar specificities (close to 37%), and the number of spared biopsies and missed PCa cases was almost the same. However, both PHID and PSAD allow the spare of more biopsies than PHI alone, keeping the same amount of missed cancers (n = 11). This means that PHID can have some diagnostic advantage over PHI, but not over PSAD. Mearini et al. found that the AUC for PHID was significantly higher than the AUC for PSAD (0.77 versus 0.68), while we have found a smaller difference between the AUCs for PHID and PSAD (0.82 versus 0.78). However, the value of diagnostic specificity, at 90% sensitivity, found by these authors for PHID (40.7%) was only slightly higher than the specificity of PHID in our study (37.1%) [22]. For the same PSA range used in our study, between 2 and 10 µg/L, Stephan et al. calculated AUCs for PSAD (0.726)

Table 4
Diagnostic performance indicators of prostate-specific antigen, prostate health index, prostate-specific antigen density and prostate health index density, considering the detection of both prostate cancer and clinically significant prostate cancer.

Overall prostate cancer (PCa)								
Predictor	Cutoff	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	Missed PCa, n (%)	Missed csPCa, n (%)	Spared biopsies, n (%)
PSA	≥ 3.8 µg/L	90.5 (83.7–95.2)	13.8 (8.1–21.4)	51.2 (44.2–58.2)	59.3 (38.8–77.6)	10 (8.6)	5 (5.1)	26 (11.2)
PHI	≥ 24.0	90.5 (83.7–95.2)	26.7 (18.9–35.7)	55.3 (47.9–62.5)	73.8 (58.0–86.1)	11 (9.5)	7 (7.1)	40 (17.2)
PSAD	≥ 0.077 µg/L/cc	90.5 (83.7–95.2)	36.2 (27.5–45.6)	58.7 (51.1–66.0)	79.2 (65.9–89.2)	11 (9.5)	5 (5.1)	52 (22.4)
PHID	≥ 0.44 /cc	90.5 (83.7–95.2)	37.1 (28.3–46.5)	59.0 (51.4–66.3)	79.6 (66.5–89.4)	11 (9.5)	8 (8.2)	53 (22.8)
Clinically significant PCa (csPCa)								
Predictor	Cutoff	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	Missed PCa, n (%)	Missed csPCa, n (%)	Spared biopsies, n (%)
PSA	≥ 4.3 µg/L	90.8 (83.3–95.7)	22.4 (15.6–30.4)	45.9 (38.7–53.2)	77.1 (60.9–89.0)	17 (14.7)	9 (9.2)	39 (12.5)
PHI	≥ 27.0	90.8 (83.3–95.7)	35.8 (27.7–44.6)	50.6 (43.0–58.2)	84.3 (72.3–92.6)	15 (12.9)	10 (10.2)	58 (25)
PSAD	≥ 0.093 µg/L/cc	90.8 (83.3–95.7)	50.0 (41.2–58.8)	56.8 (48.6–64.7)	88.3 (78.8–94.5)	17 (14.7)	9 (9.2)	76 (32.8)
PHID	≥ 0.49 /cc	89.8 (82.0–95.0)	39.6 (31.2–48.4)	51.8 (44.0–59.6)	84.3 (72.9–92.2)	13 (11.2)	8 (8.2)	61 (26.3)

PSA prostate-specific antigen, PHI prostate health index, PSAD prostate-specific antigen density, PHID prostate health index density, CI confidence interval, PPV positive predictive value, NPV negative predictive value, PCa prostate cancer, csPCa clinically significant prostate cancer.

and PHID (0.835) quite similar to those we have found in our study cohort (PSAD: 0.776; PHID: 0.823) [16].

On the other hand, when comparing the diagnostic performance of PHI, PHID, and PSAD for csPCa detection, it is the PSAD that allows to spare more biopsies ($n = 76$), when compared to PHID ($n = 61$) or PHI ($n = 58$), while the number of missed csPCa was almost the same (between 8 and 10). For the same diagnostic sensitivity of approximately 90%, PHID can provide only a small gain in specificity when compared to PHI alone (39.6% versus 35.8%). Stephan et al. performed a similar study, however considering only the GS to define csPCa ($GS \geq 7$), and concluded that PHI and PHID performed equally in detecting csPCa, based only on the values of the AUCs [16]. Our results also show almost the same performance between PHI and PHID for csPCa detection. However, Tosoian et al. reached a different conclusion, based mostly on the values of the AUCs, considering that PHID had a higher discriminative ability for csPCa, when compared to PHI and PSAD [15]. On the contrary, our results showed that PSAD performed better than PHI and PHID in csPCa detection, allowing a diagnostic specificity of 50.0% at 90% specificity, compared to only 35.8% and 39.6% for PHI and PHID, respectively. PSAD spared more biopsies ($n = 76$) than PHI ($n = 58$) or PHID ($n = 61$), while maintaining approximately the same number of missed csPCa cases (PSAD, $n = 9$; PHI, $n = 10$; PHID, $n = 8$). However, if we had looked only at the values of the AUCs, we would probably have come to a similar conclusion to that of Tosoian et al., since the AUC for PHID was slightly higher (0.851) than the AUCs for PSAD (0.819) and PHID (0.813). Nevertheless, the differences between the AUCs were not significant ($p > 0.05$). In a study where similar criteria were used to define csPCa, and where PSA and [-2]proPSA were performed using the same methodology that we have used, Barisiene et al. also concluded that PHI and PHID had a slightly inferior specificity at 90% sensitivity compared to PSAD in predicting csPCa [23].

Nonetheless, the TPV measurement has some drawbacks, namely, intra- and inter-observer variability and reliability. Usually, the TPV is estimated by TRUS, using the ellipsoid formula, as was the case in the vast majority of the patients enrolled in this study. This implies that the observer has to measure the height, width, and length of the prostate by selecting two orthogonal views. However, the selection of the lines to make these three measurements from a set of selected images is not unambiguous and is highly dependent on the observer's preference. This can lead to a high inter-observer variability in the TPV estimation. In addition, there can be intra-observer variability, because the selection of images and views to be used is not clear-cut. Tong et al. reported an intra-observer variability of 15.5% and 93% reliability, and an inter-observer 21.9% variability and 87% reliability on TRUS estimation of TPV [24]. Of course, the variability and reliability of the TPV estimation can have impact both on PSAD and on PHID. Therefore, we can argue that, in csPCa detection, it may be preferable to rely on PHI, rather than on PHID, since the diagnostic performance of both is almost the same when considering csPCa as the outcome.

5. Conclusions

Our results support that PHI, PSAD, and PHID outperform PSA not only in overall PCA, but also in csPCa detection, in the 2–10 $\mu\text{g/L}$ PSA range. In overall PCA diagnosis, PHID offers a better diagnostic specificity over PHI, allowing more biopsies to be spared, while maintaining the same cancer detection rate. However, the diagnostic performance of PHID is very similar to that of PSAD. In csPCa detection, PHI and PHID performed almost equally, with similar specificities and predictive values, although PSAD had a better performance than PHID. This means that, both in overall and in csPCa detection, PHID does not offer advantages over PSAD. We believe that more studies should be undertaken not only to compare PHID with PSAD, but also to evaluate the possible clinical impact of TPV reliability and variability on PSAD and PHID values.

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CRedit authorship contribution statement

Manuel M. Garrido: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Ruy M. Ribeiro:** Writing - review & editing. **Luís C. Pinheiro:** Writing - review & editing. **Stefan Holdenrieder:** Writing - review & editing. **João T. Guimarães:** Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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