Original Article

Comparisons of the diagnostic accuracy across prostate health index, prostate health index density, and percentage free prostate-specific antigen for clinically significant prostate cancer: a prospective diagnostic study

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Background: As the novel serum biomarkers, it has not been clearly clarified that the diagnostic accuracy of prostate health index (PHI) and prostate health index density (PHID) are superior to that of percentage free prostate-specific antigen (%fPSA) in detection of clinically significant prostate cancer (csPCa), especially in the gray zone. Therefore, this study aimed to compare the diagnostic value of PHI, PHID, and %fPSA for csPCa in the patients with prostate-specific antigen (PSA) >4 ng/mL and those with PSA within 4–10 ng/mL.

Methods: In this study, the serum samples and clinicopathological features were prospectively obtained from the patients who underwent prostate biopsy between September 2019 and December 2020. According to the inclusion criteria, the patients with total PSA (tPSA) >4 ng/mL, prostate magnetic resonance imaging or ultrasound clearly suggesting an occupying lesion were enrolled in this study. The patients with Gleason score ≥7 indicated csPCa. The receiver operating characteristic curves and the area under the curve (AUC) values were used to assess the diagnostic performance.

Results: Among the 296 patients (mean age 67.5 years, median tPSA 7.94 ng/mL) included in this study, there were 54 in the csPCa group (mean age 70.4 years, median tPSA 11.0 ng/mL) and 242 in the non-csPCa group (mean age 66.8 years, median tPSA 7.67 ng/mL). Based on the PSA level, there were 198 patients with PSA within the gray zone, which included 40 patients in the csPCa group and 158 in the non-csPCa group. In all patients, the sensitivity of PHID for detecting csPCa was 96.30%, and the specificity was 33.06% with the cut-off value of 0.51. Moreover, both PHID and PHI did better in the diagnosis of csPCa (AUC: 0.880 and 0.867, respectively) compared with other PSA derivative markers. Similarly, in the patients with PSA level in the gray zone, the diagnostic accuracy of PHID and PHI in predicting csPCa (AUC: 0.788 and 0.777, respectively) were better than other PSA derivative markers.

Conclusions: PHID presented the better diagnostic accuracy in predicting csPCa in patients with PSA in the gray zone than other PSA derivative markers, which could be a promising biomarker for making the biopsy strategy.

Keywords: Prostate cancer (PCa); prostate health index (PHI); prostate health index density (PHID); gray zone

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Introduction

The serum prostate-specific antigen (PSA) and its derivative, percentage free PSA (%fPSA), have been widely used as biochemical markers for prostate cancer (PCa) screening in the early stages (1,2). However, its application has been much debated due to its poor specificity, especially in patients with PSA in the gray zone (PSA 4–10 ng/mL) (3). In a multicenter study, a total of 1,362 patients from 4 different study sites who had total PSA (tPSA) values of 1.6–8.0 µg/L were enrolled to evaluate the diagnostic performance of tPSA and %fPSA for detecting prostate cancer (4). The results showed that the diagnostic accurancy of tPSA and %fPSA were not satisfactory [area under the curve (AUC): 0.56 and 0.61, respectively]. Moreover, the result of another prospective, multicenter study indicated that the positive predictive value of %fPSA was only 0.325 for men with high-grade PCa (Gleason Score ≥7) (5). As a result, a large number of patients have undergone unnecessary prostate biopsies or been diagnosed with a nonclinically significant PCa which would not have affected the patient during the natural course of his lifetime. Furthermore, about 2% of patients have post-biopsy complications, such as infection, bleeding, or voiding difficulty (6). Such overdiagnosis and overtreatment not only deplete medical resources, but also harm the patients. Therefore, it is urgent to develop a novel biomarker to help the patients to avoid unnecessary prostate biopsies.

Highlight box

Key findings

- We found prostate health index density was more accurate in predicting positive biopsies with clinically significant prostate cancer in patients who have a prostate-specific antigen (PSA) level of 4–10 ng/mL.

What is known and what is new?

- Early diagnosis of clinically significant prostate cancer (csPCa) is challenging, and biopsy decision determined by conventional PSA is inaccurate and leads to excessive unnecessary biopsies;
- Prostate health index (PHI) is more accurate in screening positive biopsies. However, studies on PHI density (PHID) for predicting positive biopsy with csPCa have produced mixed results.

What is the implication, and what should change now?

- PHI should be used as routine protocol instead of conventional PSA in screening potential positive biopsies with csPCa to avoid unnecessary biopsies. PHID potentially outperforms PHI in patients with PSA in the gray zone in this setting.

The isoform [-2]proPSA (p2PSA), which is a truncated variant of proPSA, is a relatively new serum marker for the early diagnosis of PCa (7). P2PSA derivatives, percentage of p2PSA (%p2PSA) and prostate health index (PHI), are calculated based on p2PSA and are superior to free PSA (fPSA) in diagnosing and predicting PCa (8,9). PHI was approved by the Chinese Food and Drug Administration, and its performance compared to conventional markers has not been fully studied in the Chinese population, which was the primary goal of this study. In addition, current guidelines recommend the use of PSA density (PSAD) to further improve the accuracy of PSA screening (10), and thus we hypothesized that PHI density (PHID), like PSAD, could also outperform PHI. However, the conclusions from published studies remain controversial (11-13). In a study including a large Caucasian group with 1,446 men from a single-center, PHID showed only a small advantage in comparison with PHI alone. And in smaller prostates, PHI even outperformed PHID (11). Moreover, Friedl *et al.* assessed the diagnostic performance of PHI and PHID in 112 males (12). And the results indicated that the AUC value of PHI (0.79) was higher than PHID (0.77). Similarly, in a prospective, observational multicenter study of two prostate biopsy cohorts from Asia, PHID did not improve the predictive ability of PHI for either PCa or clinically significant prostate cancer (csPCa) (13). Therefore, these controversial results promote us to investigate the diagnostic performance of PHID compared to PHI and %fPSA in predicting csPCa, especially in patients with PSA in the gray zone. We present the following article in accordance with the STARD reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-23-80/rc).

Methods

General information

This study was a prospective, observational single-center study in a prostate biopsy cohort at the First Hospital of Shanxi Medical University between September 2019 and December 2020. Serum samples and clinicopathological features were prospectively obtained from each patient who underwent prostate biopsy. The inclusion criteria were patients with indications for prostate biopsy [PSA >4 ng/mL, prostate magnetic resonance imaging (MRI) or ultrasound clearly suggesting an occupying lesion, etc.]. The exclusion criteria were: (I) patients with a history of other

malignancies, (II) patients with interfering factors affecting PSA levels (related medical operations, use of 5α-reductase inhibitors, and history of acute urinary tract infection within 3 months), and (III) patients with missing diagnostic data. Out of 434 specimens, a total of 296 patients were finally enrolled in this study. Further subgroup analysis was performed on patients whose rectal examinations were negative and PSA values were between 4 and 10 ng/mL. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The protocol for this study was approved by the Ethics Committee of the First Hospital of Shanxi Medical University (approval No. K040). And all the participants gave informed consent before taking part in this study.

Research methods

Specimen collection and testing

Venous blood samples were collected immediately before transperineal prostate biopsy, processed within 3 hours, and stored at –20 to –80 ℃ until further analyses. Blood samples were processed using the Access 2 immunoassay system (DxI 800; Beckman Coulter, Brea, CA, USA). tPSA, fPSA, and p2PSA were measured according to Hybritech standards. PHI was calculated according to the formula PHI = p2PSA/fPSA × √tPSA, and PHID was calculated according to the formula PHID = PHI/PV. Preoperative prostate volume (PV) was measured by multiparametric MRI (mpMRI) of the prostate.

Prostate biopsy and pathology

All patients underwent mpMRI cognitive fusion plus rectal ultrasound-guided transperineal prostate biopsy. Depending on the PV and the location of the lesions suggested by mpMRI [prostate imaging-reporting and data systems (PI-RADs) score >3], 12–14 needles of systematic biopsy and targeted biopsy were performed (1–2 needles for each area with PI-RADs score >3). Transperineal prostate biopsy specimens were analyzed by an experienced urologic pathologist who did not know the results of the blood sample testing. PCa was given a grade according to the Gleason score: a score of ≥7 indicated csPCa, and a score of <7 indicated non-csPCa or no PCa findings.

Statistical methods

All data were processed and analyzed using SPSS 26.0 statistical software. Quantitative data conforming to normal distribution are presented as mean ± standard deviation, and the differences between groups were compared using independent samples *t*-test. Quantitative data that were not normally distributed are presented as median and interquartile range (IQR), and the differences between groups were compared using the Mann-Whitney test. The receiver operating characteristic (ROC) curve was plotted, and the AUC value was measured to evaluate the diagnostic performance. Statistical differences between AUCs were evaluated using the DeLong method (14). The 25th percentile value of PHID was considered as the cut-off value to calculate the sensitivity and specificity. Furthermore, we also investigated the prevalence of csPCa between 25th and 75th percentile value of PHID and >75th percentile value of PHID. A two-tailed P<0.05 was defined as statistically significant.

Results

General information about the study population

Based on the inclusion and exclusion criteria, a total of 296 patients were finally enrolled in this study. The clinicopathological characteristics of the patients are presented in *Table 1*. Among the 76 patients (25.68%) with PCa, 54 patients with Gleason score ≥7 were diagnosed with csPCa. We classified a total of 242 patients, including 22 patients with Gleason score <7 and 220 patients (74.32%) without malignancy, as the non-csPCa group. The differences between the csPCa and the non-csPCa groups were statistically significant with respect to patient age, tPSA, p2PSA, PHI, and PHID (*Table 1*). Furthermore, in the subgroup analysis, a total of 198 patients exhibited PSA in the gray zone.

Diagnostic performance of PHI and PHID for csPCa in all patients

The results of the diagnostic analysis showed that, the AUC value for PHI (0.867) was higher than that for p2PSA (0.805) and the other parameters, including the value for tPSA (0.699) and %fPSA (0.602). PHID had a slightly higher (although not significantly different) AUC value than PHI, indicating that PHID had an ability to diagnose csPCa comparable to PHI (both P<0.05, see *Table 2* and *Figure 1*).

The median PHID value was 0.65 in all patients, and the 25th and 75th percentile values were 0.51 and 1.06. Fifty-two (96.30%) of the 54 csPCa patients who had a PHID

Table 1 Baseline characteristics of patients

Feature	Overall (n=296)	Non-csPCa (n=242) (BPH and Gleason <7)	csPCa (n=54) (Gleason ≥7)	P
Age (years), mean ± SD	67.5±7.9	66.8±7.8	70.4±8.0	0.030*
Prostate volume (mL), median (IQR)	44.76 (35.84–57.20)	44.96 (35.96–59.00)	43.92 (32.76–51.98)	0.357
tPSA (ng/mL), median (IQR)	7.94 (5.90–11.88)	7.67 (5.63–10.27)	11.00 (7.21–18.72)	0.001*
%fPSA (%), median (IQR)	16.89 (12.03–22.25)	18.21 (12.18–22.87)	13.66 (11.78–17.56)	0.099
p2PSA (ng/L), median (IQR)	15.70 (10.03–25.85)	13.74 (9.02–22.05)	30.21 (17.53–95.66)	<0.001*
PHI, median (IQR)	32.52 (23.81–52.75)	29.41 (21.30–42.78)	64.14 (40.52–136.23)	<0.001*
PHID, median (IQR)	0.65 (0.51–1.06)	0.59 (0.47–0.83)	1.62 (1.02–3.04)	<0.001*

*, P<0.05 was significant. csPCa, clinically significant prostate cancer; BPH, benign prostatic hyperplasia; IQR, interquartile range; tPSA, total prostate-specific antigen; %fPSA, percentage free prostate-specific antigen; p2PSA, isoform [-2]proPSA; PHI, prostate health index; PHID, prostate health index density; SD, standard deviation.

Table 2 Diagnostic efficacy of various parameters in diagnosing csPCa in all patients included in this study

Parameters	AUC	95% CI	P
tPSA	0.699	0.589–0.810	0.012*
%fPSA	0.602	0.491–0.713	<0.001*
p2PSA	0.805	0.720–0.890	0.270
PHI	0.867	0.796–0.938	–
PHID	0.880	0.803–0.957	0.807

*, P<0.05 was significant. csPCa, clinically significant prostate cancer; AUC, area under the curve; CI, confidence interval; tPSA, total prostate-specific antigen; %fPSA, percentage free prostate-specific antigen; p2PSA, isoform [-2]proPSA; PHI, prostate health index; PHID, prostate health index density.

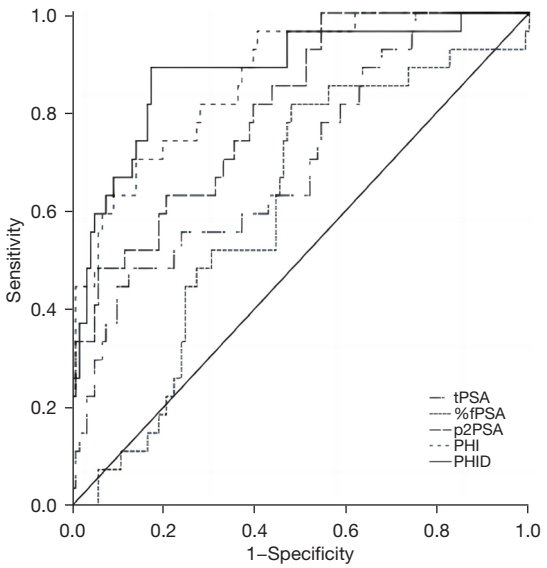

Figure 1 Receiver-operating characteristic curve analysis for each parameter and PSA level of 4–50 ng/mL. PSA, prostate-specific antigen; tPSA, total prostate-specific antigen; %fPSA, percentage free prostate-specific antigen; p2PSA, isoform [-2]proPSA; PHI, prostate health index; PHID, prostate health index density.

value >0.51. The sensitivity of PHID for detecting csPCa was 96.30%, and the specificity was 33.06% with the cut-off value of 0.51. Using the 25th percentile of PHID as the cut-off value, a negative predictive value of 97.56% was achieved; the diagnosis was missed in only 2 (3.70%) patients with csPCa. As shown in *Figure 2*, the prevalence of csPCa increased significantly with increasing PHID values, with 2.44% of patients with PHID <0.51 developing csPCa, and the prevalence of csPCa increased to 9.86% in the PHID range of 0.51–1.06. In patients with PHID >1.06, 52.78% were diagnosed with csPCa.

Diagnostic performance of PHI and PHID in patients with PSA within 4–10 ng/mL

A biopsy decision within this specific PSA range is mostly difficult. Therefore, we additionally analyzed those 198 men with PSA values within 4–10 ng/mL, which included 40 cases in the csPCa group and 158 cases of PCa with Gleason <7 in the non-csPCa group. The patients were significantly older in the csPCa group compared to the non-csPCa group, with significantly higher levels of PSA, %fPSA, p2PSA, PHI, and PHID. Further comparison of the performance of each marker in predicting PCa in

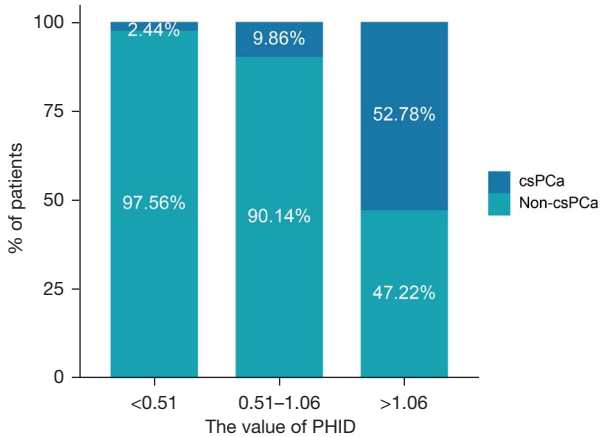

Figure 2 The diagnostic efficiency of PHID in the diagnosis of csPCa in < Q25, Q25–Q75 and > Q75. PHID, prostate health index density; csPCa, clinically significant prostate cancer.

Table 3 Diagnostic efficacy of various parameters in diagnosing PCa in patients with PSA level of 4–10 ng/mL

Parameters	AUC	95% CI	P
tPSA	0.508	0.391–0.625	0.001*
%fPSA	0.569	0.449–0.689	0.014*
p2PSA	0.691	0.579–0.802	0.029*
PHI	0.777	0.662–0.892	–
PHID	0.788	0.672–0.904	0.035*

*, P<0.05 was significant. PCa, prostate cancer; PSA, prostate-specific antigen; AUC, area under the curve; CI, confidence interval; tPSA, total prostate-specific antigen; %fPSA, percentage free prostate-specific antigen; p2PSA, isoform [-2] proPSA; PHI, prostate health index; PHID, prostate health index density.

patients with PSA 4–10 ng/mL revealed the following: PHID (AUC: 0.788) > PHI (AUC: 0.777) > p2PSA (AUC: 0.691) (differences were significant, P=0.035, P=0.029). Compared to PHI, tPSA and %fPSA, with an AUC of 0.508 and 0.569, respectively, had poorer diagnostic power, and the difference was statistically significant (both P<0.05, see *Table 3* and *Figure 3*). These results showed that PHID outperformed all the other PSA derivative markers in detecting csPCa in patients with PSA within the gray zone.

Discussion

The treatment strategy for patients with nonsignificant

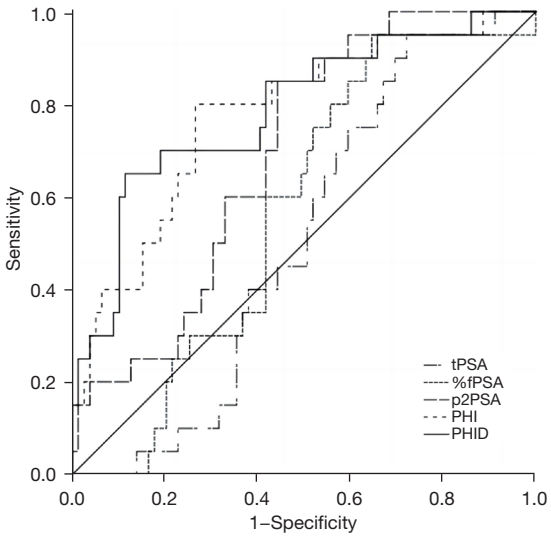

Figure 3 Receiver-operating characteristic curve analysis for each parameter and PSA level of 4–10 ng/mL. PSA, prostate-specific antigen; tPSA, total prostate-specific antigen; %fPSA, percentage free prostate-specific antigen; p2PSA, isoform [-2]proPSA; PHI, prostate health index; PHID, prostate health index density.

PCa includes watchful waiting and active surveillance, with only csPCa patients requiring curative treatment (10). Therefore, the screening of csPCa becomes an important part of the treatment strategy (15). Studies have shown that approximately 75% of patients undergo unnecessary prostate biopsies based on PSA values only (16,17). Excessive biopsies lead to serious complications, such as urinary tract infections, pain, and hematuria (18). In addition, 1.3% of these patients experience complicated infections, and 3.9% even require further hospitalization, seriously affecting quality of life (19). The PSA is now widely used for screening PCa patients. And the application of %fPSA could improve the detection rate of PCa. However, studies have shown that the diagnostic efficacy of %fPSA for PCa is still limited at the time of initial biopsy. A meta-analysis by Huang *et al.* demonstrated that the sensitivity of %fPSA for predicting positive biopsy patients ranged from 0.5 to 0.94 [pooled sensitivity 0.70, 95% confidence interval (CI): 0.67–0.72], while the specificity ranged from 0.31 to 0.93 (pooled specificity 0.55, 95% CI: 0.57–0.60) (20). Our study results showed that PHI and PHID significantly outperformed %fPSA in predicting positive biopsy in patients with PSA in the gray zone and in predicting csPCa in all patients with an increased PSA.

In this study, we observed that 2.44% of patients

with PHID <0.51 (< Q25) and 52.78% of patients with PHID >1.06 (> Q75) developed csPCa, which further demonstrated that as PHID increases, the detection rate of csPCa also increases. Subsequently, we further evaluated the predictive ability of PHI, PHID, and conventional indicators for csPCa. The sensitivity of PHID for detecting csPCa was 96.30%, and the specificity was 33.06% based on the 25th percentile (0.51) of PHID as the cutoff value, and only 2 (3.70%) patients with csPCa were missed. The AUC value of PHI and PHID for predicting csPCa were 0.867 and 0.880, respectively, which indicated the good diagnostic performance of PHI and PHID. In contrast, traditional tumor markers tPSA and %fPSA were both significantly inferior to PHI in predicting clinically significant PCa, with an AUC of 0.699 (P=0.012) and 0.602 (P<0.001), respectively. These outcomes were consistent with the findings of a study of 412 Taiwanese men conducted by Chiu *et al.* (21), whose results showed an AUC for tPSA, %fPSA, %p2PSA, PSAD, PHI, and PHID of 0.56, 0.63, 0.76, 0.74, 0.77, and 0.82, respectively, for csPCa detection in all patients with elevated PSA. Overall, the results of our study suggested that PHID and PHI had a high prediction rate for csPCa in all patients.

In terms of predicting PCa in patients with PSA in the gray zone, a European study in 2020 involving a large number of patients with PSA 1–8 ng/mL found that the diagnostic efficacy of PHID in predicting positive biopsy had an AUC of 0.819, which was superior to that of PHI, with an AUC of 0.789 (P=0.0219) (22). In this study, we found the same diagnostic performance in the gray zone of PSA 4–10 ng/mL, with the AUC of PHID higher than that for PHI in predicting biopsy with csPCa (AUC: 0.788 *vs.* 0.777, P=0.035). In contrast, conventional markers, including tPSA and %fPSA, had inferior diagnostic performance in patients with PSA in the gray zone (AUC: 0.508 and 0.569, respectively). In all, PHID had the best accuracy rate in predicting csPCa in patients whose PSA was within the gray zone. However, it is important to emphasize that, due to the small number of csPCa patients (n=40), the better performance of PHID compared wtih PHI in predicting csPCa in patients with PSA in the gray zone should be validated in the larger cohort. And it would be the goal and direction of our future research.

With their excellent performance, both PHI and PHID could serve as alternative markers for Gleason monitoring in PCa patients undergoing active surveillance as they can accurately predict the Gleason level of prostate biopsy results, thereby avoiding overdiagnosis and overtreatment. Furthermore, advances in diagnostic imaging technology have made it possible to identify lesions that are difficult to visualize using conventional methods (23). Therefore, it is expected that the combination of PHI and PHID and imaging investigation would allow patients to be free from undergoing painful prostate biopsies every year, leading to a significant improvement in their quality of life.

There were some limitations to this study. First, as a single-center study, the sample size was small, although all patients in this prospectively established patient pool decided to undergo prostate biopsy after preoperative analysis, enabling a more objective comparison of the diagnostic ability of PHI and PHID with traditional markers. Secondly, we used mpMRI cognitive fusion prostate biopsy instead of machine fusion, which might lead to some diagnostic limitations relating to technology. Therefore, further multicenter studies with large samples are needed to validate the results of this study.

Conclusions

Compared to %fPSA, PHI had higher accuracy in predicting csPCa in patients with elevated PSA. Compared to PHI, PHID resulted in comparable performance in these patients and did even better in patients with PSA in the gray zone and thus should form part of the treatment strategy for PCa patients.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-23-80/rc

Data Sharing Statement: Available at https://tau.amegroups.com/article/view/10.21037/tau-23-80/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.

com/article/view/10.21037/tau-23-80/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The protocol for this study was approved by the Ethics Committee of the First Hospital of Shanxi Medical University (approval No. K040). And all the participants gave informed consent before taking part in this study.

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