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ORIGINAL ARTICLE

Diagnostic performance of prostate health index (PHI) in predicting prostate cancer on prostate biopsy

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Abstract

Introduction: Prostate health index (PHI) has been shown to have better diagnostic accuracy in predicting prostate cancer (PCa) in men with total prostate-specific antigen (PSA) levels between 4-10ng/ml. However, little is known of its value in men with elevated PSA beyond this range. This study aimed to evaluate the diagnostic performance of PHI in Malaysian men with elevated PSA values ≤ 20ng/ml. *Materials and Methods:* From March 2015 to August 2016, all men consecutively undergoing transrectal ultrasound (TRUS)-guided prostate biopsy with total PSA values ≤ 20ng/ml were recruited. Blood samples were taken immediately before undergoing prostate biopsy. The performance of total PSA, %fPSA, %p2PSA and PHI in determining the presence of PCa on prostate biopsy were compared. *Results:* PCa was diagnosed in 25 of 84 patients (29.7%). %p2PSA and PHI values were significantly higher ($p<0.05$) in patients with PCa than those without PCa. The areas under the receiver operating characteristic curves for total PSA, %fPSA, %p2PSA and PHI were 0.558, 0.560, 0.734 and 0.746, respectively. At 90% sensitivity, the specificity of PHI (42.4%) was five times better than total PSA (8.5%) and two times better than %fPSA (20.3%). By utilising PHI cut-off >22.52, 27 of 84 (32.1%) patients could have avoided undergoing biopsy. *Conclusion:* Findings of our study support the potential clinical effectiveness of PHI in predicting PCa in a wider concentration range of total PSA up to 20ng/ml.

Keywords: Prostate Health Index (PHI), prostate-specific antigen, prostate cancer, biopsy

INTRODUCTION

Prostate cancer (PCa) is the second most common cancer in men worldwide.[1] Although the incidence rate in Asian countries is much lower compared to the Western world, its incidence in Asian countries is increasing and also expected to be continuously rising.[1,2] This will pose a significant burden to the health care system; thus, early detection of PCa is imperative.

Prostate-specific antigen (PSA) is the most well-recognised prostate specific biomarker for PCa. However, it has limited sensitivity and specificity in diagnosing PCa. Besides PCa, a large number of cases of elevated total PSA (TPSA) is due to benign prostate conditions such as benign prostate hyperplasia and chronic prostatitis.[3] Other factors that also affect TPSA levels include biological variation, urinary tract infection, prostatic manipulation or ejaculation.[3] Because of these limiting factors, it is hard to find a universal appropriate TPSA cut-off for the diagnosis of prostate cancer.

Prostate biopsy remains the gold standard for confirmation of PCa. However, only about 25-30% of men who have had biopsies for elevated TPSA levels were found to have cancer,[3,4] while the majority had false-positive tests and underwent unnecessary biopsies. Furthermore, 15% of biopsies in men with lower levels of TPSA had detected cancer.[5]

Various efforts have been made to improve the ailing TPSA in detecting PCa accurately. Recently, serum p2PSA isoform was identified as the most specific marker of PCa.[6] A mathematical combination of TPSA, free PSA (fPSA) and p2PSA, also known as Prostate Health Index (PHI) has been shown to have better diagnostic accuracy than the commonly used serum TPSA and fPSA.[4,7,8]

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To date, there is lack of evidence on the clinical efficiency of PHI in Asians in which the incidence rate and cancer characteristics differ greatly compared to the western population.[1] In most studies, the diagnostic performance of PHI was evaluated at limited TPSA range of 2-10ng/ml.[9,10,11] A non-negligible proportion of patients with TPSA beyond this range may not have PCa. In view of this, our study aimed to further evaluate the diagnostic performance of PHI in Malaysian men with a wider concentration range of TPSA levels.

MATERIALS AND METHODS

Study design and population

This is a prospective observational study from March 2015 to August 2016 conducted at Universiti Kebangsaan Malaysia Medical Centre (UKMMC). The study included consecutive men undergoing transrectal ultrasound-guided (TRUS) prostate biopsy for suspected PCa with TPSA level of ≤ 20ng/ml. Men receiving 5-α-reductase inhibitors, evidence of acute prostatitis, urinary tract infection and those with previous history of prostatic surgery for any prostatic condition were excluded from this study.

Blood samples were drawn prior to TRUS biopsy. Patients then underwent TRUS biopsy according to standardised protocol; with a minimum of 12 biopsy cores taken. PCa was identified and graded according to the 2005 consensus conference of the International Society of Urological Pathology.[12]

The primary endpoint of this study was to directly compare the diagnostic accuracy of %p2PSA and PHI (index tests) in the detection of prostate cancer in comparison to the TPSA and %fPSA (standard tests). The number of potentially avoidable biopsies if these tests were used as a guide for prostate biopsy decision was calculated. Patients were stratified into two groups: cancer and no cancer.

Biochemical analysis

Serum samples for TPSA, fPSA and p2PSA were collected and centrifuged within two hours of collection, aliquoted and stored at -70ºC until analysis. Testing was performed on Access2 automated immunoassay analyser (Beckman Coulter, CA, USA), using Hybritech calibrators, controls, and reagents. In-house precision study was done prior to analysis according to the Clinical and Laboratory Standards Institute (CLSI) EP15-A2 protocol. The total CV of all analytes at all levels was acceptable at less than 3%, lower than the manufacturer's claim. Measurements of blood samples were done on two analytical batches to minimise the between-run imprecision using a single lot of calibrators, controls, and reagents. %fPSA (fPSA/TPSAx100), %p2PSA (p2PSA/fPSAx100) and PHI ([p2PSA/fPSA]x$\sqrt{}$TPSA) were then obtained via calculation.

Statistical analysis

Statistical analyses were performed using SPSS v.24 software. Continuous and categorical variables were summarised by the median and interquartile range (IQR) for skewed data and frequency measures, respectively. Mann-Whitney *U* test was used for comparisons of continuous variables and Chi-Square test was used for comparisons of categorical variables. Medcalc v.17.0.4 software was used to plot receiver operating characteristic (ROC). Predictive accuracy was quantified as the area under the receiver operating characteristic curve (AUC). The AUC between variables were compared using Delong's method. A two-sided *p*-value <0.05 was considered statistically significant in all analyses.

Ethics

This study was approved by the research ethics committee of Universiti Kebangsaan Malaysia (Approval number: UKM 1.5.3.5/244/FF-2015-012).

RESULTS

107 patients consented to the study. 23 patients were further excluded from analysis (12 patients were on 5-α reductase inhibitors, seven patients had a previous history of prostatic surgery and four patients had total PSA >20ng/ml post-analysis). The characteristics of the study population are shown in Table 1. Among the 84 patients studied, 25 (29.7%) patients were diagnosed PCa based on prostate biopsy and eight (32.0%) of these patients had Gleason score (GS) ≥7 (Table 1). Age, %p2PSA and PHI values were significantly higher in patients with PCa. Conversely, no statistically significant difference was noted in TPSA and fPSA values between patients with and without PCa.

In subgroup analysis of 63 patients with TPSA <10ng/ml, 18 (28.6%) patients had PCa and four (22.2%) patients had GS ≥7. In 21 patients with tPSA between 10-20ng/ml, seven (33.3%) patients had PCa and four (57.1%) patients had GS ≥7. In accuracy analysis, the AUCs of TPSA,

TABLE 1: Baseline characteristics of the study population

	Total (n=84)	Cancer (n=25)	No cancer (n=59)	*p*-value
Age, years	67.5 (38-84)	71.0 (52-79)	66.0 (38-84)	0.028*
Ethnicity, (%)				
Malay	31 (36.9)	9 (36.0)	22 (37.3)	0.796
Chinese	52 (61.9)	16 (64.0)	36 (61.0)	
Indian	1 (1.2)	0 (0.0)	1 (1.7)	
Suspicious DRE, (%)	17 (20.2)	6 (24.0)	11 (18.6)	0.567
Yes	67 (79.8)	19 (76.0)	48 (81.4)	
No				
TPSA, ng/ml	8.37 (1.61-19.49)	9.06 (1.61-18.57)	8.36 (1.74-19.49)	0.406
%fPSA	17.93 (3.56-38.30)	17.59 (7.50-26.26)	18.01 (3.56-38.30)	0.387
%p2PSA	1.12 (0.35-5.08)	1.49 (0.51-5.08)	0.95 (0.35-3.73)	0.001*
PHI	28.86 (11.81-101.31)	41.40 (16.17-101.33)	25.77 (11.81-85.93)	<0.001*
GS, (%)				
<7	N/A	17 (68.0)	N/A	
≥7	N/A	8 (32.0)	N/A	

DRE: digital rectal examination; TPSA: Total PSA; fPSA: free PSA; p2PSA: p2PSA isoform; PHI: prostate health index; GS: Gleason score

* statistical significant at *p*-value <0.05

%fPSA, %p2PSA and PHI were 0.558, 0.560, 0.734 and 0.746, respectively. Of the various parameters, PHI was the most accurate predictor of PCa in the study population (Fig.1A). In a subgroup men with TPSA <10ng/ml (Fig 1B), the AUCs of TPSA, %fPSA, %p2PSA and PHI were 0.540, 0.594, 0.759 and 0.753, respectively. The %p2PSA slightly outperformed PHI in this subgroup. There was a significant difference between the AUCs of PHI and TPSA in both the total study population (p=0.021) and the subgroup of TPSA <10ng/ml (p=0.037) although

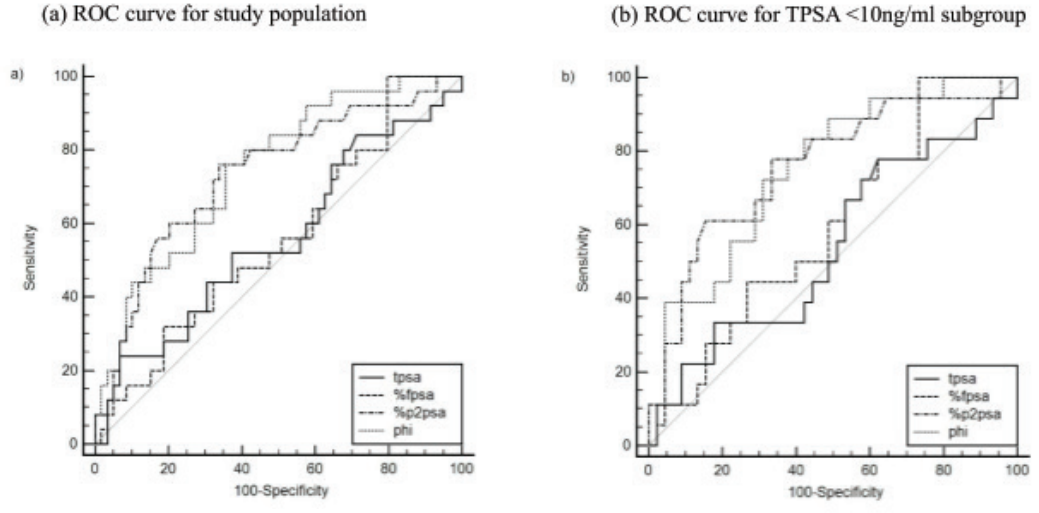

FIG. 1: Receiver Operating Characteristics (ROC) curves comparing the performance of various PSA-related parameters in predicting prostate cancer at biopsy (a) in the study population and (b) in TPSA <10ng/ml subgroup.

TABLE 2: Performance of PSA-related parameters in predicting biopsy outcomes

	Study population	TPSA <10ng/ml subgroup
	AUC (95% CI) at various TPSA levels	
TPSA	0.558 (0.445-0.666)	0.540 (0.410-0.666)
%fPSA	0.560 (0.447-0.668)	0.594 (0.463-0.716)
%p2PSA	0.734 (0.626-0.824)	0.759 (0.635-0.858)
PHI	0.746 (0.649-0.835)	0.753 (0.628-0.853)
	p-value for different AUC between TPSA and other PSA-related parameters	
%fPSA vs. TPSA	0.979	0.625
%p2PSA vs. TPSA	0.099	0.084
PHI vs. TPSA	0.021*	0.037*

AUC: area under the curve
* statistical significant at *p* value <0.05

%p2PSA showed better performance in the latter population (Table 2).

The optimal cut-off for PHI in the study population was 30.20 with sensitivity of 76.0% (95% CI: 54.8-90.6) and specificity of 64.1% (95% CI: 49.2-74.9). Whereas, in the TPSA <10ng/ml subgroup, the optimal cut-off for PHI was 25.77, with a sensitivity of 83.3% (95% CI: 58.6-96.4) and specificity of 55.6% (95% CI: 40.0-70.3), lower than the cut-off in the study population.

At 90% sensitivity (Table 3), in both the study population and TPSA <10ng/ml subgroup, PHI had the optimal specificity of 42.4% (cut-off ≥22.52) and 40.0% (cut-off ≥21.27), respectively. If we had applied the PHI value found in this study as the decision cut-off value for prostate biopsy in the study population and in men with TPSA <10ng/ml, biopsy could have been avoided for 27 (32.1%) and 20 (31.7%) patients, respectively. At_these PHI cut-offs of 90% sensitivity, none of the cancer cases missed had GS >7 and thus considered as low-risk cases.

We also tested the manufacturer's recommended PHI range (taken from the manufacturer's package insert) into our study population (Table 4). For PHI value below 21, chances for prostate biopsy will be negative is more than 90% as stated in the manufacturer insert. Our study findings were in agreement with the manufacturer for PHI below 21. In both total study population and subgroup TPSA <10ng/ml,

TABLE 3: The cut-off, specificity and number of potentially avoidable biopsies of various PSA-related parameters at fixed sensitivity of 90%

	Cut-off for biopsy	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	No avoidable biopsy (%)
a) Study population (n=84)					
TPSA	≥3.45	8.5 (2.8-18.7)	29.9 (27.0-32.9)	71.4 (34.2-92.3)	7 (8.3)
%fPSA	≤24.66	20.3 (11.0-32.8)	32.9 (29.2-36.8)	85.7 (59.1-96.1)	14 (16.7)
%p2PSA	≥0.78	30.5 (19.2-43.9)	35.9 (31.4-40.8)	90.0 (69.3-97.3)	20 (23.8)
PHI	≥22.52	42.4 (29.6-55.9)	40.4 (34.6-46.4)	92.6 (76.2-97.9)	27 (32.1)
b) TPSA <10ng/ml subgroup (n=63)					
TPSA	≥3.45	11.1 (3.7-24.1)	28.6 (24.8-32.7)	71.4 (34.8-92.2)	7 (11.1)
%fPSA	≤23.94	26.7 (14.6-41.9)	32.7 (27.6-38.1)	85.7 (59.8-96.0)	14 (22.2)
%p2PSA	≥0.88	37.8 (23.8-53.5)	36.4 (30.2-43.1)	89.5 (65.6-97.1)	19 (30.2)
PHI	≥21.27	40.0 (25.7-55.6)	37.2 (30.7-44.2)	90.0 (69.9-97.2)	20 (31.7)

PPV: positive predictive value; NPV: negative predictive value

91.3% and 90.0% of biopsies were negative, respectively, and no Pca with GS >7 were missed. As the PHI values increased, the percentage of PCa and GS >7 cases detected correspondingly increased. In high-risk group (PHI >40), 50% of cases underwent prostate biopsy were positive in both total study population and subgroup TPSA <10ng/ml with 38.5% and 37.5% of cases having GS >7, respectively.

DISCUSSION

It is generally accepted that TPSA is not an ideal marker for early detection of PCa. Despite evidence of reduction in PCa mortality by TPSA testing from European Randomized Study of Screening for Prostate Cancer (ERSPC) trial, there was also significant risk of overdiagnosis and overtreatment of indolent cancer and a large number of unnecessary biopsies.[13] This highlights the need for a clinically more useful biomarker for early detection of PCa.

A recent meta-analysis and systemic review consistently showed that p2PSA derivatives (%p2PSA and PHI) outperformed the traditionally used TPSA and %fPSA in predicting PCa.[7,8] However, most of these studies were done in Caucasian populations, which have a much higher incidence of PCa. The limited number of studies done in Asians[9,10,11] were somehow restricted to only looking at the TPSA range between 2-10ng/ml. This so-called diagnostic grey zone was originally derived from the Caucasian population and may not represent the actual diagnostic grey zone in Asian men.

Our study examined the wider range of TPSA up to ≤ 20ng/ml. Our results showed that PHI performs better than TPSA and %fPSA in discriminating biopsy outcome. The better performance of PHI over standard tests was observed in men with tPSA <10ng/ml and in men with TPSA values up to 20ng/ml. The AUC of PHI in the study population was significantly higher than TPSA (0.746 vs 0.558). Using PHI biopsy threshold of ≥22.52 in the study population, about one-third of the patients would have avoided biopsies with no risk of missing high-grade PCa (GS ≥7). At 90% sensitivity, the specificity of PHI (42.4%) was five times better than TPSA (8.5%) and two times better than %fPSA (20.3%). The extended application of PHI in the study population will considerably reduce the number of unnecessary biopsies while still maintaining the high sensitivity in detecting PCa and its aggressive counterpart.

Our findings are in agreement with a study by Na *et al*.[14] performed on a larger prospective cohort of 636 Chinese men with TPSA ranged from 0.04 to 2006ng/ml, which concurred that PHI was superior to TPSA at all TPSA levels. The AUC of PHI in the entire cohort was 0.88 compared to TPSA of 0.81. The AUC of PHI versus TPSA in subset analysis of patients with TPSA 2-10ng/ml, 10.1-20ng/ml and > 20ng/ml were 0.73, 0.81, 0.90 and 0.53, 0.58, 0.80, respectively. Thus, PHI showed the greatest advantage particularly in TPSA range of 2-20ng/ml. Unfortunately, we are unable to compare the cut-off value as Na *et al*. did not report the cut-off value used.

TABLE 4: Performance of PHI using manufacturer recommended range

Manufacturer		**a) Total Study population (n=84)**		
PHI range*	Risk (Probability of cancer; 95% CI)	Total	Cancer detected (%)	GS ≥7 (%)
0 – 20.9	Low (8.4%; 1.9–16.1)	23	2 (8.7)	0 (0.0)
21 – 39.9	Moderate (21.0%; 17.3–24.6)	36	10 (27.8)	3 (30.0)
40+	High (44.0%; 36.0–52.9)	25	13 (52.0)	5 (38.5)
Manufacturer		**b) Subgroup of TPSA <10ng/ml (n=63)**		
PHI range*	Risk (Probability of cancer; 95% CI)	Total	Cancer detected (%)	GS ≥7 (%)
0 – 20.9	Low (8.4%; 1.9–16.1)	20	2 (10.0)	0 (0.0)
21 – 39.9	Moderate (21.0%; 17.3 – 24.6)	27	8 (29.6)	1 (12.5)
40+	High (44.0%; 36.0 – 52.9)	16	8 (50.0)	3 (37.5)

*PHI result range using Hybritech calibration

In the subset analysis of patients with TPSA <10ng/ml, our findings were in agreement with other studies of Asian men that also looked into the performance of PHI in the almost similar TPSA range.[9,10,11] Ito *et al*.[9] who studied men with TPSA 2-10ng/ml including men with abnormal DRE found that at different sensitivity levels ranging from 70%-95%, PHI showed a higher specificity than TPSA and %fPSA in predicting PCa. Ng *et al*.[11] and Tan *et al*.[10] who studied men with TPSA range of 4-10ng/ml with normal DRE also reported that PHI was the best predictor of PCa with AUCs of 0.793 and 0.768, respectively. However, the cut-off reported for PHI at a sensitivity of 90% was different in each study. The PHI cut-off identified in our study was lower (PHI: 22.52; specificity: 42.2%) compared to other studies (PHI range: 24.9-26.7; specificity range: 33-55%).[9,10,11]

The discrepancies between the optimal cut-off and the specificity were most likely due to the differences in the sample size and methodologies adopted, as well as the difference in the incidence rates of PCa across different populations. Nevertheless, all studies[9-11,14] agreed that PHI was more superior than current standard biomarkers and may potentially reduce unnecessary prostate biopsies and biopsy-related morbidities.

The main limitation of this study was the relatively small sample size. However, our study served as a preliminary study that represents our own population. To conclusively prove that PHI is a superior marker, larger prospective studies are needed.

In conclusion, the findings of our study are in agreement with other Asian and Caucasian population studies and support the potential clinical usefulness of PHI in TPSA between 2-10ng/ml and a wider range up to 20ng/ml.

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Conflict of interest: The authors declare they have no conflict of interest.

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