Prostate Health Index outperforms other PSA derivatives in predicting a positive biopsy in men with tPSA <10 ng/mL: Largest prospective cohort in Taiwan

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Abstract

Background: Few prospective studies have focused on the performance of the Prostate Health Index (PHI) in Asian populations. Therefore, we aimed to evaluate the performance of the PHI in predicting prostate cancer (PCa) compared with standard prostate-specific antigen (PSA) tests.

Methods: We prospectively enrolled patients with suspected PCa with a total PSA (tPSA) level 4 to 10 ng/mL or tPSA <4 ng/mL and a suspicious digital rectal examination between February 2017 and September 2018. All of the patients underwent a 12-core transrectal ultrasound-guided prostate biopsy. Prebiopsy blood samples were analyzed for tPSA, free PSA (fPSA), percentage of fPSA (%fPSA), [-2]proPSA (p2PSA), and percentage of p2PSA (%p2PSA). The PHI was calculated as (p2PSA/fPSA) × √tPSA. The areas under the receiver operating characteristic curve (AUCs) were estimated for the PSA derivatives in addition to their specificities at a prespecified sensitivity of 90%.

Results: Of the 307 enrolled patients, 95 (30.9%) had PCa on biopsy. Excluding fPSA, all of the PSA derivatives were significantly different between the positive and negative biopsy groups. Of the various derivatives, the PHI (AUC: 0.783) showed the best performance in predicting the results of the initial biopsy compared with tPSA (AUC: 0.611). At a sensitivity of 90%, the PHI had the best specificity of 46.7% compared with 23.2% for tPSA. Using a PHI cutoff value of 35.15 for biopsy, 108 (35.2%) patients could have avoided undergoing a biopsy. To detect Gleason score ≥ 7 disease at 90% sensitivity, the threshold for PHI was 36.96 with a specificity of 52.1%.

Conclusion: PHI was the best biomarker among the PSA derivatives in predicting PCa at biopsy in men with tPSA < 10 ng/mL. The risk of a Gleason score ≥ 7 increased with increasing PHI.

Keywords: Prostate cancer; Prostate Health Index; Prostate-specific antigen

1. INTRODUCTION

Prostate cancer (PCa) has long been the most common cancer in men in Europe and North America.[1,2] Although the incidence of PCa in Asia is relatively low, it has rapidly increased over the last two decades, including in Taiwan.[1] PCa was the fifth most common cancer affecting men worldwide in 2014, with an age-standardized PCa incidence rate of 29.1 per 100 000 person-years.[3] Although the incidence of PCa in Taiwan is much lower than in Europe (59.3 per 100 000 person-years) and the United States (123.2 per 100 000 person-years),[4,5] approximately 44% of PCa cases are confirmed as being late stage at diagnosis.[6] In contrast, 80% to 92% of cases of PCa in the United States are diagnosed at an early stage.[5,7] These findings indicate that PCa is a critical and urgent public health challenge in Taiwan.

Prostate-specific antigen (PSA) has been widely used as a serum marker for PCa screening and monitoring disease progression, and it has dramatically increased the rate of early detection while significantly reducing PCa-specific mortality. However, the low specificity of PSA in determining the presence of PCa and the inability to discriminate between clinically significant and indolent cancer may lead to unnecessary prostate biopsies and overtreatment, especially in men presenting with a total PSA (tPSA) level of <10 ng/mL.[3,8]

Precursor of PSA (proPSA), a subform of free PSA (fPSA), includes four different isoforms in serum, [-2]proPSA (p2PSA), [-4]proPSA, [-5]proPSA, and [-7]proPSA, according to the length of the proleader peptide sequences, ie, two, four, five, or seven amino acids.[9] P2PSA is considered to be the most cancer-specific form, and elevated levels have been reported in the serum of men with PCa.[10] Two p2PSA-based derivatives, Prostate Health Index (PHI) and %p2PSA, defined as ([p2PSA/fPSA] × √tPSA)

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and ([p2PSA/fPSA] × 100), respectively, have been reported to be increased in patients with PCa and to be better able to distinguish PCa from benign prostatic disease than tPSA or fPSA.[11]

A systematic review by Abrate et al[12] and meta-analysis by Wang et al[13] reported that %p2PSA and PHI were consistently more accurate than standard PSA for the prediction of prostate biopsy outcomes, and that they could guide prostate biopsy decision making. Nevertheless, most of the currently available information on %p2PSA and PHI is based on studies in Caucasian populations, who have a higher incidence of PCa. Few prospective studies have focused on the performance of %P2PSA and PHI in Asian populations. Therefore, we aimed to evaluate the performance of %p2PSA and PHI for the prediction of PCa compared with standard PSA tests in a cohort of Taiwanese undergoing a first biopsy due to a gray-zone elevation of tPSA <10 ng/mL.

2. METHODS

2.1. Study design

This was a prospective observational study performed from February 2017 to September 2018 to determine whether %p2PSA and PHI testing can outperform other PSA derivatives in the detection of PCa at first biopsy in patients with serum tPSA <10 ng/mL.

The study was approved by Ethics Committee of Taipei Veterans General Hospital. All patients were thoroughly informed about the procedure and possible complications. Written consent was obtained from all of the patients.

2.2. Subjects

This study enrolled consecutive men with a tPSA level 4 to 10 ng/mL with or without a suspicious digital rectal examination (DRE) and those with a tPSA <4 ng/mL and a suspicious DRE. The exclusion criteria were acute prostatitis or urinary tract infections, a prior history of PCa, use of any dosage of 5-α reductase inhibitors within the previous 3 months, a previous prostate biopsy, and having undergone transurethral resection of the prostate.

2.3. Study endpoints

The primary endpoint was the performance of the PHI for the prediction of PCa compared with standard PSA tests, including the sensitivity, specificity, and diagnostic accuracy in determining the presence of PCa at prostate biopsy. Diagnostic yields were calculated, including the number of possible biopsies that could have been avoided and the number of potentially aggressive cancers (Gleason score ≥7) that would have been missed.

2.4. Methods

Prebiopsy blood samples were analyzed for tPSA, fPSA, and p2PSA levels using a Beckman Coulter DxI800 Unicel Immunoassay system (Beckman Coulter, Taiwan Inc., Taipei, Taiwan). The PHI was calculated using the formula: PHI = (p2PSA/fPSA) ×√PSA. The percentage of fPSA (%fPSA) was determined as fPSA to tPSA ratio, and the percentage of p2PSA (%p2PSA) was determined as p2PSA to fPSA ratio. PSA density (PSAD) was defined as tPSA/prostate volume, with prostate volume being determined by transrectal ultrasound (TRUS) as width (cm) × height (cm) × length (cm) × 0.52.

All of the patients underwent at least a 12-core TRUS biopsy, with a standard template and extra sampling of echogenic lesions, if identified. Biopsy specimens were analyzed histologically and graded according to the 2005 Consensus Conference of the International Society of Urological Pathology.[14]

2.5. Statistical analysis

Basic statistical analyses of the participants' characteristics were performed using the Mann-Whitney *U* test for continuous variables and χ^2 test for categorical variables. Areas under the receiver operating characteristic (ROC) curves (AUCs) were estimated for the various PSA derivatives, along with the specificity at a prespecified sensitivity of 90%. Logistic regression models were used to predict the detection of PCa. All statistical analyses were carried out using SPSS Statistics version 22 (IBM Corp, Armonk, NY, USA), assuming a two-sided test with a 5% level of significance.

3. RESULTS

The demographic and clinical characteristics of the 307 patients and values of the various PSA derivatives are shown in Table 1. The positive biopsy rate was 30.9% (95/307). Subgroup analysis revealed that the positive prostate biopsy rate was 13.7% (7/51) in the patients with tPSA <4 ng/mL and suspicious DRE. Among the 95 patients diagnosed with PCa, 43 (45.3%) had Gleason score 6 disease, 33 (34.7%) had Gleason score 7 disease, and 19 (20.0%) had Gleason 8-10 disease. Apart from fPSA, all of the other PSA derivatives were significantly different between the positive and negative biopsy groups.

Table 1

Demographic and clinical characteristics

	Total (n = 307)	No cancer (n = 212)	Cancer (n = 95)	*p*
Median (range) age, years	66.00 (57.67-74.33)	66.00 (57.61-74.39)	68.00 (59.88-76.12)	0.171
Abnormal DRE, n (%)	78 (25.4%)	15 (7.1%)	63 (66.3%)	<0.001
Median (range) prostate volume, mL	66.80 (28.02-105.58)	72.20 (33.2–111.20)	50.54 (15.08-86.00)	0.001
Median (range) PSAD, ng/mL^2	0.08 (0.01-0.15)	0.07 (0.01-0.13)	0.12 (0.05-0.19)	<0.001
Median (range) tPSA, ng/mL	5.90 (3.67-8.13)	5.71 (3.49-7.93)	6.69 (4.5-8.88)	0.001
Median (range) fPSA, ng/mL	1.01 (0.08-1.94)	1.01 (0.41-1.61)	1.03 (0.54-1.52)	0.611
Median (range) %fPSA	0.17 (0.09-0.25)	0.19 (0.11-0.27)	0.16 (0.09-0.23)	<0.001
Median (range) p2PSA, pg/mL	15.93 (6.48-25.38)	14.85 (5.75-23.95)	17.87 (8.33-27.41)	<0.001
Median (range) %p2PSA	1.63 (0.73-2.53)	1.47 (0.76-2.18)	1.90 (1.03-2.77)	<0.001
Median (range) PHI	38.59 (20.86-56.32)	35.70 (21.87-49.53)	48.79 (28.00-69.58)	<0.001
Gleason score, n (%)				
6	N/A	N/A	43 (45.3%)	
7	N/A	N/A	33 (34.7%)	
8–10	N/A	N/A	19 (20.0%)	

DRE = digital rectal examination; N/A = not available; PHI = Prostate Health Index; fPSA = free PSA; %fPSA = fPSA to tPSA ratio; PSA = prostate-specific antigen; PSAD = PSA density; tPSA = total PSA; p2PSA = [-2]pro PSA; %p2PSA = p2PSA to fPSA ratio.

Table 2

Comparison AUC of various PSA derivatives

	AUC (95% CI)	*p*
Prostate volume	0.546 (0.473-0.615)	<0.001
PSAD	0.714 (0.651-0.772)	<0.001
tPSA	0.611 (0.543-0.678)	0.002
fPSA	0.506 (0.433-0.577)	0.873
%fPSA	0.627 (0.559-0.694)	<0.001
p2PSA	0.666 (0.599-0.731)	<0.001
%p2PSA	0.706 (0.644-0.766)	<0.001
PHI	0.783 (0.728-0.836)	<0.001

AUC = area under curve; CI = confidence interval; fPSA = free PSA; %fPSA = fPSA to tPSA ratio; PHI = Prostate Health Index; PSA = prostate-specific antigen; PSAD = PSA density; tPSA = total PSA; p2PSA = [-2]pro PSA; %p2PSA = p2PSA to fPSA ratio.

The performance of each PSA derivative in discriminating biopsy outcomes, as determined by AUC, is presented in Table 2 and Fig. 1. Of the various derivatives, the PHI (AUC: 0.783; $p < 0.001$) showed the best performance in predicting the results of the initial biopsy compared with tPSA (AUC 0.611; $p = 0.002$).

To further assess the performance of the PSA derivatives, we performed an analysis at a preset sensitivity level of 90% (Table 3). The PHI had the best specificity of 46.7% compared with 23.2% for tPSA. Using a PHI cutoff value of 35.15 for biopsy, 108 (35.2%) patients could have avoided undergoing a biopsy. To detect Gleason score ≥ 7 disease at 90% sensitivity, the threshold for PHI was 36.96 with a specificity of 52.1%.

We then evaluated the performance of the PHI using the manufacturer's banding of PHI levels (Tables 4 and 5) and found that the percentage of GS ≥ 7 disease increased with increasing PHI level. When the PHI ranged from 36 to 54.9 and ≥55, 17.8% and 53.7% of GS ≥ 7 cancers were detected, respectively.

Using the cutoff values of distinct PSA derivatives and clinical characteristics tested by ROC curves at the preset sensitivity level of 90% to predict PCa, we performed logistic regression analysis. Univariate analysis showed that prostate volume, PSAD, %fPSA, and all of the p2PSA-related parameters were statistically significant predictors of PCa, especially PHI and %p2PSA (both $p < 0.001$) (Table 6). Age and prostate volume were analyzed in multivariate analyses as the base prediction model, and tPSA, fPSA, %fPSA, p2PSA, %p2PSA, and PHI were added to the base model and tested, respectively. PSAD was excluded from the multivariate model to avoid multicollinearity problems. In the multivariate analysis, only tPSA and p2PSA-related parameters were significant independent predictors of a positive biopsy. PHI ≥ 35.15 had the greatest odds ratio of 7.02 (95% CI: 6.63-7.40; $p < 0.001$).

4. DISCUSSION

The PHI test was approved by the Food and Drug Administration (FDA) in 2012 for use as an aid in discriminating PCa from benign prostatic conditions in men aged ≥50 years with a total serum PSA level of 2 to 10 ng/mL and nonsuspicious DRE. In the pivotal clinical trial submitted for FDA approval, 658 men were studied (324 with PCa and 334 without),[15] and the AUCs were 0.708 for the PHI and 0.516 for tPSA. Fixing the sensitivity at 90%, the specificity of the PHI was 31.1% compared with 10.8% for tPSA ($p < 0.001$), which represented a nearly 3-fold improvement in PCa detection compared with tPSA testing alone. A meta-analysis by Wang et al reported that the pooled AUCs of %p2PSA and PHI were 0.86 (95% CI: 0.84-0.87) and 0.70 (95% CI: 0.65-0.74), respectively, in predicting PCa.[13] Another meta-analysis by Filella et al showed a pooled clinical specificity of 31.6% at the 90% sensitivity threshold (95% CI: 29.2%-34.0%).[16]

Our results showed that the PHI was the best biomarker to predict PCa at biopsy in men with tPSA < 10 ng/mL. At 90% sensitivity, the specificity of the PHI (46.7%) was two times better than that of tPSA (23.2%), potentially avoiding unnecessary biopsies in 35.2% of the patients with a cutoff value of

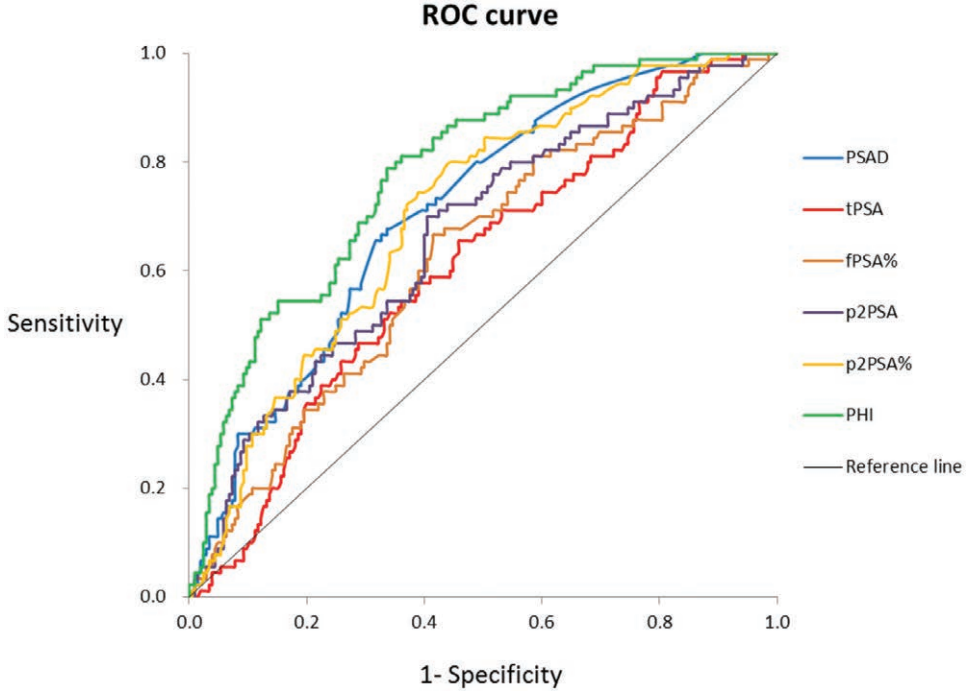

Fig. 1 Receiver operating characteristic (ROC) curves comparing various prostate-specific antigen (PSA) derivatives.

Table 3

Specificity of various PSA derivatives at prespecified sensitivity of 90%

	Cutoff	Specificity	Avoidable biopsies if biopsied at the cutoff (% of all biopsies, n = 307)
PSAD	≥0.06	36.9	73 (23.8%)
tPSA	≥4.21	23.2	62 (20.2%)
fPSA	≤0.49	11.1	34 (11.1%)
%fPSA	≤0.27	16.7	53 (17.3%)
p2PSA	≥10.79	25.1	63 (20.5%)
%p2PSA	≥1.32	35.0	88 (28.7%)
PHI	≥35.15	46.7	108 (35.2%)
PHI (for GS ≥ 7)	≥36.96	52.1	141 (45.9%)

GS = Gleason score; fPSA = free PSA; %fPSA = fPSA to tPSA ratio; PHI = Prostate Health Index; PSA = prostate-specific antigen; PSAD = PSA density; tPSA = total PSA; p2PSA = [-2]pro PSA; %p2PSA = p2PSA to fPSA ratio.

Table 4

Performance of PHI test according to manufacturer banding of PHI levels

PHI level	Total (n = 307)	GS > 7 cancer (n = 52) (%)	All cancer (n = 95) (%)	No cancer (n = 212) (%)
0-26.9	39	0 (0.0)	1 (2.6)	38 (97.4)
27.0-35.9	81	4 (4.9)	10 (12.3)	71 (87.7)
36.0-54.9	146	26 (17.8)	55 (37.7)	91 (62.3)
≥55.0	41	22 (53.7)	29 (70.7)	12 (29.3)

GS = Gleason score; PHI = Prostate Health Index.

≥35.15. The AUCs for PHI and tPSA were 0.783 and 0.611, respectively. Multivariate logistic regression analyses revealed that both tPSA and PHI were significant independent predictors of a positive biopsy. Furthermore, PHI ≥ 35.15 had the greatest odds ratio of 7.02.

4.1. Comparisons with other Asian prospective studies

In the first prospective cohort study focusing on the performance of %p2PSA and PHI in detecting PCa in Asia, Tan et al evaluated 157 men presenting with a tPSA level 4 to 10 ng/mL and normal DRE in Singapore.[17] They found that the PHI test had the best performance in predicting the results of the initial biopsy, with an AUC of 0.794 vs 0.479 for tPSA. At a sensitivity of 90%, the specificity of PHI was 58.3%, more than three times the specificity of tPSA at 17.3%, potentially avoiding unnecessary biopsies in 49% of the patients with a cutoff value of ≥26.75.

Chiu et al prospectively evaluated PHI in a large cohort of 569 men with a tPSA level 4 to 10 ng/mL and nonsuspicious DRE in Hong Kong,[18] and found AUCs for the PHI and tPSA of 0.76 and 0.54, respectively. At the 10% and 20% risk thresholds for PCa, 38.4% and 55.4% of the biopsies could have been avoided in the PHI-based model, respectively.

In a prospective, multicenter study in Shanghai, Na et al found that the PHI performed better than tPSA in discriminating biopsy outcomes,[19] with an AUC of 0.87 for PHI and 0.60 for tPSA in 660 patients with a tPSA level ranging from 2 to 10 ng/mL. At a sensitivity of 88.2%, a biopsy threshold at PHI ≥ 32 would have avoided 52.0% of the biopsies in this cohort.

Hsieh et al reported that the ability of the PHI to predict prostate biopsy outcomes was better than that of tPSA (AUC 0.77 vs 0.57) in an initial biopsy in Taiwanese men with a serum PSA level 4 to 10 ng/mL.[20] Using a PHI of 20.7 as the threshold, 26.6% of biopsies could have been avoided at a sensitivity of 90%.

Cheng et al demonstrated that the PHI was better than tPSA in predicting PCa at biopsy in Taiwanese men with a tPSA level ≤10 ng/mL (AUC 0.772 vs 0.544).[21] At 90% sensitivity, the specificity of the PHI for a positive biopsy was 27.27%, potentially avoiding unnecessary biopsies in 22.3% of the cases with a cutoff value of ≥21.62.

Table 5

Performance of PHI for prediction of GS ≥7 cancer according to manufacturer banding of PHI levels

PHI level	Sensitivity (%) (for GS ≥ 7 cancer)	Specificity (%) (for GS ≥ 7 cancer)	Avoidable biopsies, n (%)	GS ≥ 7 cancer missed, n (%)	GS 6 cancer reduced, n (%)
≥27.0	100	15.3	39 (12.7)	0 (0.0)	1 (2.3)
≥36.0	92.3	45.5	120 (39.1)	4 (7.7)	7 (16.3)
≥55.0	42.3	92.5	266 (86.6)	30 (57.7)	36 (83.7)

GS = Gleason score; PHI= Prostate Health Index.

Table 6

Logistic regression analyses to predict the detection of prostate cancer at biopsy

Variable	Cutoff	Crude OR (95% CI)	*p*	Adjusted OR[a] (95% CI)	*p*
Age		1.03 (1.01-1.04)	0.086		
Prostate volume		0.99 (0.98-0.99)	<0.001		
PSAD[b]	0.06	4.48 (4.09-4.85)	<0.001		
tPSA	4.21	1.90 (1.56-2.24)	0.060	3.13 (2.73-3.53)	0.004
fPSA	0.49	0.93 (0.54-1.32)	0.851	1.64 (1.19-2.08)	0.268
%fPSA	0.27	0.46 (0.09-0.84)	0.040	0.65 (0.26-1.04)	0.271
p2PSA	10.79	3.27 (2.88-3.65)	0.002	4.10 (3.70-4.51)	<0.001
%p2PSA	1.32	3.87 (3.53-4.21)	<0.001	3.82 (3.46-4.18)	<0.001
PHI	35.15	8.08 (7.70-8.46)	<0.001	7.02 (6.63-7.40)	<0.001

CI = confidence interval; OR = odds ratio; fPSA = free PSA; %fPSA = fPSA to tPSA ratio; PHI = Prostate Health Index; PSA = prostate-specific antigen; PSAD = PSA density; tPSA = total PSA; p2PSA = [-2]pro PSA; %p2PSA = p2PSA to fPSA ratio.

[a]Adjusted for age and prostate volume.

[b]Excluded in multivariate model to avoid multicollinearity problems.

Table 7

Prospective studies of PHI in Asian populations with total PSA < 10 ng/mL

	Case number	PSA range, ng/mL	Percentage of positive biopsy	AUC	Cutoff	PHI		
						Sensitivity, %	Specificity, %	% avoidable biopsies if biopsied at the cutoff
Present study	307	<10	30.9	0.783	35.15	90	46.7	35.2
Tan et al[17]	157	4-10	19.1	0.794	26.75	90	58.27	49
Chiu et al[18]	569	4-10	10.9	0.76	N/A	90	N/A	38.4
Na et al[19]	660	2-10	20.6	0.87	28	93.4	50.6	41.5
					32	88.2	62.4	52.0
Hsieh et al[20]	154	4-10	23.4	0.77	20.7	90	30.5	26.6
Cheng et al[21]	213	≤10	27.0	0.772	21.62	90	27.27	22.3

AUC = area under curve; N/A = not available; PHI = Prostate Health Index; PSA = prostate-specific antigen.

All previous Asian prospective studies have shown clear advantages in using the PHI to detect PCa compared with tPSA. Nonetheless, there have been large differences in the cutoff values of PHI to differentiate PCa from benign prostatic tissues and the specificities and percentages of avoidable biopsies among the studies. The cutoff value of PHI in the present study is higher than that in other Asian cohorts (Table 7), which may be due to the highest detection rate of PCa at 30.9% among all Asian series. To date, there is still no consensus regarding the optimal value of PHI, and the reference range of PHI may be specific to a particular ethnic group.

4.2. PHI for the detection of potentially aggressive cancers (GS ≥7 or more)

The use of the PHI has been included in the National Comprehensive Cancer Network (NCCN) guidelines for the early detection of PCa version 2.2015, which state that a PHI > 35 indicates a higher probability of high-grade PCa in patients who have never undergone a biopsy or after a negative biopsy. We found that the detection of GS ≥ 7 cancers increased as the PHI increased. In our cohort, at 90% sensitivity for high-grade PCa (GS ≥ 7), a PHI cutoff of 36.0 could have resulted in the avoidance of 120 biopsies (39.1%), with four GS ≥ 7 cancers (7.7%) being overlooked.

Tan et al reported that in a cohort of Singapore men with tPSA 4 to 10 ng/mL, a PHI cutoff of 27.0 could have avoided approximately 51% of the biopsies, while missing 2.5% of cases with GS ≥ 7 PCa.[17] In addition, Loeb et al investigated 658 U.S. men with tPSA 4 to 10 ng/mL and found that a PHI cutoff of 28.6 could have avoided approximately 30% of the biopsies, while missing 10% of cases with GS ≥ 7 PCa.[15]

4.3. Prostate volume for prediction of PCa

Prostate volume has been shown to be a predictor of PCa, and a lower prostate volume has been associated with a higher PCa detection rate in TRUS-guided prostate biopsies.[22] In the present study, prostate volume was significantly larger in the negative biopsy group than in the positive biopsy group (72.20 ± 39.00 mL vs 50.54 ± 35.46 mL; p = 0.001), and the AUC was 0.546 for prostate volume. Therefore, age and prostate volume were analyzed in multivariate logistic analysis as the base prediction model. Each PSA derivative was added to the base model, and the results showed that PHI ≥ 35.15 had the greatest adjusted odds ratio of 7.02 (95% CI: 6.63-7.40; p < 0.001).

4.4. Study strengths and weaknesses

The present study is the largest prospective cohort study to examine the performance of the PHI for the prediction of PCa compared with standard PSA tests in Taiwan. The relatively large sample size may have increased the statistical significance of our findings. In addition, we only enrolled men with suspected PCa who had never had a prior biopsy. The decision to perform an initial biopsy is distinctly different from the decision to select men for a repeat biopsy, and including men with a history of prostate biopsy in the pool of study subjects can cause selection bias.

The present study has several limitations. First, the study participants were all drawn from tertiary care clinics, limiting the generalizability of our findings with regards to primary care patients and the general population. Second, an abnormal DRE was not an exclusion criterion, and 25.4% of our cohort had a suspicious DRE. A meta-analysis by Naji et al reported that DRE had a poor performance for PCa screening,[23] with pooled sensitivity of DRE performed by primary care clinicians of 0.51 (95% CI: 0.36-0.67) and pooled specificity of 0.59 (95% CI: 0.41-0.76). Furthermore, Chiu et al reported that the PHI was equally effective in men with an abnormal DRE.[24] Including all of the patients who were clinically indicated for a TRUS biopsy means that the cutoff value of PHI for PCa detection in our cohort is more applicable to real-world practice. Third, we did not take into account false-negative prostate biopsies and upgrading and downgrading of PCa from biopsy to radical prostatectomy.

In conclusion, the PHI was preferable to conventional PSA tests in predicting PCa at biopsy in men with a tPSA level <10 ng/mL. At 90% sensitivity, the specificity of the PHI for a positive biopsy was 46.7%, potentially avoiding unnecessary biopsies in 35.2% of the patients with a cutoff value of ≥35.15.

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