Development and Internal Validation of a Prostate Health Index Based Nomogram for Predicting Prostate Cancer at Extended Biopsy

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Abbreviations and Acronyms

DCA = decision curve analysis
DRE = digital rectal examination
fPSA = free PSA
f/tPSA = free-to-total PSA
p2PSA = [–2]proPSA
PCa = prostate cancer
PCA3 = prostate cancer antigen 3
PHI = Prostate Health Index
PSA = prostate specific antigen
tPSA = total PSA
TRUS = transrectal ultrasound

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Purpose: We developed and validated a Prostate Health Index (Beckman Coulter, Brea, California) based nomogram to predict prostate cancer at extended prostate biopsy.

Materials and Methods: The study population consisted of 729 patients who were scheduled for prostate biopsy following suspicious digital rectal examination and/or increased prostate specific antigen. Total and free prostate specific antigen, percent free-to-total prostate specific antigen, [–2]proPSA and the prostate health index [([–2]proPSA/free prostate specific antigen) × √total prostate specific antigen)] were determined. Logistic regression models were fitted to test prostate cancer predictors. Predictive accuracy estimates of biopsy outcome predictions were quantified. Regression coefficients were used to create a decision making tool to predict prostate cancer. A calibration plot was used to evaluate the extent of overestimating or underestimating the observed prostate cancer rate. Decision curve analysis provided an estimate of the net benefit obtained using the prostate health index based nomogram.

Results: Overall 280 of 729 patients (38.4%) were diagnosed with prostate cancer at extended prostate biopsy. On accuracy analyses prostate health index emerged as the most informative predictor of prostate cancer (AUC 0.70) compared to established predictors, such as total prostate specific antigen (0.51) and percent free-to-total prostate specific antigen (0.62). Including the prostate health index in a multivariable logistic regression model based on patient age, prostate volume, digital rectal examination and biopsy history significantly increased predictive accuracy by 7% from 0.73 to 0.80 ($p < 0.001$). Nomogram calibration was good. Decision curve analysis showed that using the prostate health index based nomogram resulted in the highest net benefit.

Conclusions: The prostate health index based nomogram can assist clinicians in the decision to perform biopsy by providing an accurate estimation of an individual risk of prostate cancer.

Key Words: prostate, prostate-specific antigen, nomograms, prostatic neoplasms, biopsy

Due to the widespread use of PSA, the number of patients who undergo prostate biopsy is constantly increasing. Although PSA can be considered a reliable and useful marker for PCa diagnosis, it lacks specificity because it

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is organ specific but not cancer specific. In consequence, only a minority of patients who undergo prostate biopsy is currently diagnosed with PCa.[1] The high rate of negative results may be referred to the inability of clinicians to accurately predict the presence of PCa. Since the use of single established PCa risk factors fails to accurately predict PCa at biopsy, several groups have advocated multivariable prediction tools to individually predict the risk of harboring PCa at initial biopsy.[2,3] However, the models remain imperfect in their predictive ability and new biomarkers are required to decrease the error margin of existing models.[4,5]

Recent studies demonstrated that PHI, a mathematical combination of tPSA, fPSA and p2PSA, is more increased in patients with PCa relative to their counterparts without PCa and it improves the accuracy of established predictors in determining PCa at prostate biopsy.[6–10] Furthermore, PHI appears to be related to pathological outcomes, such as pathological stage and Gleason sum.[11]

Based on these findings, we developed a PHI based nomogram to individually estimate the patient risk of PCa at extended biopsy. To validate this prediction tool, we evaluated the discrimination ability and calibration of the model.[12,13] Finally, we performed DCA to assess the clinical usefulness of the model.[14]

MATERIALS AND METHODS

Study Population

The study population consisted of 729 white patients with tPSA between 0.5 and 20 ng/ml who were prospectively referred to our tertiary care department of urology for initial or repeat prostate biopsies between July 2010 and July 2011. The decision to perform initial biopsy was based on certain criteria, including increased tPSA and/or suspicious DRE or suspicious TRUS. Repeat biopsies were performed in patients with 1 or 2 previous negative prostate biopsies with persistent suspicion of PCa based on abnormal DRE, increased tPSA and/or low percent f/tPSA. Patients with bacterial acute or chronic prostatitis, those treated with previous endoscopic surgery of the prostate for benign prostatic hyperplasia and those under treatment with drugs that may alter serum PSA were excluded from study. In addition, patients with marked blood protein alterations (normal plasma range 6 to 8 gm/100 ml), those with hemophilia and those who had been previously poly-transfused were also excluded from study since these conditions may alter the p2PSA concentration. The study was approved by the hospital ethics committee (Protocol 2PROPSA/13.03.2010) and all patients provided informed consent before being enrolled.

METHODS

A blood sample was drawn before any prostatic manipulations such as DRE, TRUS and prostate biopsy, which might cause a transient increase in biomarkers. Blood samples were processed by the UniCel® Dxl 800 Immunoassay System analyzer and managed according to Semjonow et al.[15] tPSA, fPSA, percent f/tPSA, p2PSA and PHI [(p2PSA/fPSA) $\times \sqrt{}$tPSA)] were determined using the Hybritech® calibration in all patients. TRUS determined prostate size was assessed before biopsy. Patients underwent ambulatory TRUS guided prostate biopsies, performed by the attending urologists according to a standardized institutional saturation scheme consisting of at least 18 biopsy cores taken from the prostate gland to achieve a higher detection rate.[16] Specimens were processed and evaluated by a single experienced genitourinary pathologist blinded to test results. PCa was identified and graded according to the 2005 International Society of Urological Pathology consensus conference definitions.[17] Patients diagnosed with high grade prostatic intraepithelial neoplasia or atypical small acinar proliferation of the prostate were not considered to have the outcome of interest (PCa) and were included in the control group.

Statistical Analysis

The Kolmogorov-Smirnov test was used to assess the normal distribution of variables. The Student and Mann-Whitney U tests were used to compare normally and non-normally distributed continuous variables, respectively. The chi-square test was used to compare categorical variables. Patients were stratified according to the presence or absence of PCa at biopsy.

Univariable and multivariable logistic regression models were fitted for the prediction of PCa at biopsy and complemented by predictive accuracy tests. Tested variables included in the models consisted of patient age, prostate volume, DRE, biopsy history, tPSA, percent f/tPSA, p2PSA and PHI. Predictive accuracy was quantified as the ROC AUC with a value of 100% indicating perfect prediction and 50% equivalent to the toss of a coin. Spearman ρ coefficient analysis was used to test the correlation between different continuous variables. To test the added value of PHI in determining the presence of PCa at biopsy, this variable was included in the base multivariable model. This model was subsequently compared to logistic regression models with tPSA, percent fPSA and p2PSA as covariables. The gain in predictive accuracy was quantified and AUCs were compared using the method of DeLong et al.[18] In addition, specificity was determined at 90% sensitivity of the different PCa predictors.

Multivariable regression coefficients were used to develop a PHI based nomogram. To decrease the overfit bias and internally validate our results, all univariable and multivariable predictive accuracy tests were subjected to 200 bootstrap resamples. Calibration plots were used to graphically explore the extent of underestimation or overestimation of the observed PCa rate. Finally, DCA was performed to determine the net benefit derived from using the newly developed nomogram, as described by Vickers and Elkin.[14]

All statistical analyses were performed using SPSS®, version 16.0 or S-Plus® Professional. On all analyses 2-sided $p < 0.05$ was considered significant.

RESULTS

Table 1 lists demographic and clinical characteristics of the overall study population. Prostate cancer at biopsy was diagnosed in 280 of 729 patients (38.4%). Gleason score was less than 7 in 149 patients (53.4%) and 7 or greater in 131 (46.6%). High grade prostatic intraepithelial neoplasia and atypical small acinar proliferation were detected in 36 (4.9%) and 15 patients (2.1%), respectively. Overall 485 patients (66.5%) underwent initial biopsy and 244 (33.5%) underwent repeat biopsy. DRE was suspicious in 129 individuals (17.7%).

When comparing patients with and without PCa at biopsy, patients with PCa were significantly older (mean age 66.6 vs 63.2 years) and had significantly smaller prostate glands (median prostate volume 49 vs 66 ml, each $p < 0.001$). Median tPSA did not differ significantly between men without vs with PCa (6.0 vs 6.1 ng/ml, $p = 0.576$). Conversely, percent fPSA was significantly lower (0.14 vs 0.17, $p = 0.001$) and p2PSA was significantly higher (17.1 vs 15.9, $p = 0.040$) in patients with PCa relative to their counterparts without PCa. PHI was also significantly higher in patients diagnosed with PCa relative to those without PCa (48.5 vs 37.4, $p < 0.001$).

In univariable logistic regression models, patient age, DRE, biopsy history and prostate volume were statistically significant predictors of PCa at biopsy (each $p < 0.001$, table 2). In addition, percent fPSA, p2PSA and PHI were significantly associated with PCa at biopsy (each $p \leq 0.008$, table 2 and fig. 1). In contrast, tPSA was not significantly associated with the presence of PCa ($p = 0.460$). On bivariate accuracy analyses, PHI was the most accurate predictor of PCa (AUC 0.70), followed by prostate volume (0.68) and percent fPSA (0.62).

In multivariable logistic regression models testing the predictors of PCa at biopsy, patient age ($p < 0.001$), prostate volume ($p < 0.001$), DRE ($p = 0.007$) and biopsy history ($p = 0.038$) achieved independent predictor status (table 2). The accuracy of the multivariable model based on these clinical variables was 0.73. Including PHI in this model significantly increased its accuracy by 0.07 from 0.73 to 0.80 ($p < 0.001$). Notably the multivariable model including PHI was significantly more accurate than the multivariable model including tPSA (AUC 0.73, $p < 0.001$), percent fPSA (AUC 0.75, $p = 0.002$) and p2PSA (AUC 0.75, $p = 0.001$). Similarly, at 90% sensitivity the specificity of the multivariable model including PHI (41.6%) was higher than that of the models including tPSA (34.6%), percent fPSA (35.1%) and p2PSA (35.6%) (table 3).

Logistic regression coefficients were used to develop a nomogram based on the independent predictors of PCa at biopsy, namely age, prostate volume, DRE, biopsy history and PHI. Figure 2, *A* shows the nomogram developed using these variables. The calibration plot of the nomogram was good (close to the 45-degree line) within the whole range of predicted probabilities (fig. 2, *B*).

Finally, DCA showed that the model including PHI resulted in the highest net benefit (fig. 3). For example, at a threshold probability of 30%, which means that one would choose to perform biopsy when risk of PCa was 30% or greater, using the PHI based nomogram would result in 21 fewer patients per 100 undergoing unnecessary prostate biopsies.

Table 1. *Study population descriptive characteristics*

	Overall	No PCa	PCa	p Value
No. pts (%)	729	449 (61.6)	280 (38.4)	—
Mean ± SD age	64.3 ± 7.8	63.2 ± 7.6	66.6 ± 7.6	<0.001 (Student t test)
No. previous biopsy (%):				
No	485 (66.5)	277 (61.7)	208 (74.3)	0.001 (chi-square test)
Yes	244 (33.5)	172 (38.3)	72 (25.7)	
No. DRE (%):				
Unsuspicious	600 (82.3)	397 (88.4)	203 (72.5)	<0.001 (chi-square test)
Suspicious	129 (17.7)	52 (11.6)	77 (27.5)	
No. Gleason score category (%):				
Less than 7	Not available	Not available	149 (53.4)	—
7 or Greater	Not available	Not available	131 (46.6)	—
Median ml vol (range):				
Prostate	58 (9–230)	66 (9–230)	49 (9–140)	<0.001 (Mann-Whitney test)
Transition zone	31 (1–178)	35 (1–178)	23 (1–103)	<0.001 (Mann-Whitney test)
Median ng/ml tPSA (range)	6.1 (0.5–19.9)	6.0 (0.5–19.9)	6.1 (1.0–19.9)	0.576 (Mann-Whitney test)
Median fPSA (range):				
Ng/ml	1.0 (0.1–6.3)	1.1 (0.1–6.3)	1.0 (0.1–5.6)	<0.001 (Mann-Whitney test)
%	0.16 (0.02–0.43)	0.17 (0.05–0.41)	0.14 (0.02–0.43)	<0.001 (Mann-Whitney test)
Median pg/ml p2PSA (range)	16.4 (0.1–137.0)	15.9 (0.1–72.6)	17.1 (0.1–137.0)	0.040 (Mann-Whitney test)
Median PHI (range)	41.2 (6.5–192.8)	37.4 (6.5–192.8)	48.5 (11.4–185.5)	<0.001 (Mann-Whitney test)

Table 2. *Logistic regression analysis predicting PCa probability at biopsy in overall population*

	Age	Prostate Vol	DRE Suspicious vs Unsuspicious	Biopsy History Yes vs No	tPSA	% f/tPSA*	p2PSA*	PHI	Multivariable Model AUC (95% CI)	Predictive Accuracy Gain (95% CI)
Individual predictor variable AUC (95% CI)†	0.60 (0.56–0.64)	0.68 (0.64–0.72)	0.58 (0.53–0.61)	0.56 (0.53–0.60)	0.51 (0.48–0.55)	0.62 (0.58–0.65)	0.55 (0.52–0.58)	0.70 (0.66–0.73)		
Bivariate analysis OR (95% CI)	1.049 (1.028–1.071)	0.977 (0.971–0.984)	2.896 (1.960–4.279)	0.557 (0.401–0.774)	0.985 (0.946–1.026)	0.007 (0.000–0.024)	1.015 (1.004–1.026)	1.034 (1.025–1.045)		
p Value	<0.001	<0.001	<0.001	<0.001	0.460	0.008	0.006	<0.001		
Multivariate analysis base model OR (95% CI):	1.075 (1.050–1.101)	0.975 (0.968–0.982)	1.830 (1.178–2.842)	0.663 (0.449–0.977)	—	—	—	—	0.73 (0.70–0.77)	—
p Value	<0.001	<0.001	0.007	0.038						
+ tPSA	1.075 (1.050–1.101)	0.973 (0.966–0.980)	1.827 (1.174–2.842)	0.645 (0.437–0.954)	1.042 (0.990–1.096)	—	—	—	0.73 (0.70–0.77)	0.00
p Value	<0.001	<0.001	0.008	0.074	0.112					
+ % fPSA	1.088 (1.061–1.115)	0.980 (0.973–0.987)	1.812 (1.157–2.836)	0.599 (0.402–0.891)	—	0.007 (0.001–0.027)	—	—	0.75 (0.72–0.79)	0.02
p Value	<0.001	<0.001	0.009	0.011		0.003				
+ p2PSA	1.068 (1.042–1.094)	0.970 (0.962–0.977)	1.842 (1.177–2.881)	0.688 (0.465–1.019)	—	—	1.034 (1.016–1.052)	—	0.75 (0.72–0.79)	0.02
p Value	<0.001	<0.001	0.007	0.062			<0.001			
+ PHI	1.077 (1.050–1.1105)	0.976 (0.969–0.983)	1.713 (1.078–2.720)	0.685 (0.457–1.028)	—	—	—	1.037 (1.026–1.049)	0.80 (0.76–0.83)	0.07‡
p Value	<0.001	<0.001	0.023	0.068				<0.001		

* Not included in base multivariable model due to strong correlation with PHI (PSA free and p2PSA Spearman $\rho = 0.139$ and 0.634, respectively, $p < 0.001$).

† Predictive value of individual variables and multivariable models in predicting PCa probability.

‡ Relative to other multivariable models using DeLong et al method[18] $p \leq 0.002$.

Figure 1. ROC AUC shows accuracy of total PSA, percent f/tPSA and PHI for predicting PCa at biopsy.

DISCUSSION

The results of our study confirm the superior accuracy of PHI in determining the presence of PCa at initial or repeat biopsy. Specifically, PHI was significantly more accurate than the currently used biomarkers (tPSA and percent fPSA). In addition, PHI significantly increased the predictive accuracy of established predictors of PCa by 7%. The nomogram developed using the bootstrap corrected regression coefficients showed good predictive accuracy (0.80) and optimal calibration at internal validation. These findings were further corroborated by DCA, which revealed that the PHI based nomogram resulted in the highest net benefit across a wide range of threshold probabilities, confirming the clinical usefulness of our prediction tool.

To our knowledge, only 2 studies have been done to develop prediction tools to determine PCa at initial or repeat biopsy. Stephan et al developed an artificial neural network based on age, tPSA, percent fPSA, prostate volume and DRE.[19] While their tool showed 0.74 accuracy at internal validation, its calibration was suboptimal. In addition, the low number of biopsy cores taken (8 to 12) represents an important study limitation.

Table 3. *Specificity at 90% sensitivity of variables predicting PCa at biopsy*

Predictors	% Specificity at 90% Sensitivity (95% CI)
tPSA	9.3 (6.8–12.4)
% fPSA	17.8 (14.4–21.7)
p2PSA	15.6 (12.4–19.3)
PHI	27.0 (22.1–30.4)
Base multivariable model:*	33.8 (29.1–38.8)
+ tPSA	34.6 (29.9–39.6)
+ % fPSA	35.1 (30.4–40.1)
+ p2PSA	35.6 (30.9–40.7)
+ PHI	41.6 (36.6–46.7)

* Including age, prostate volume, DRE and biopsy history.

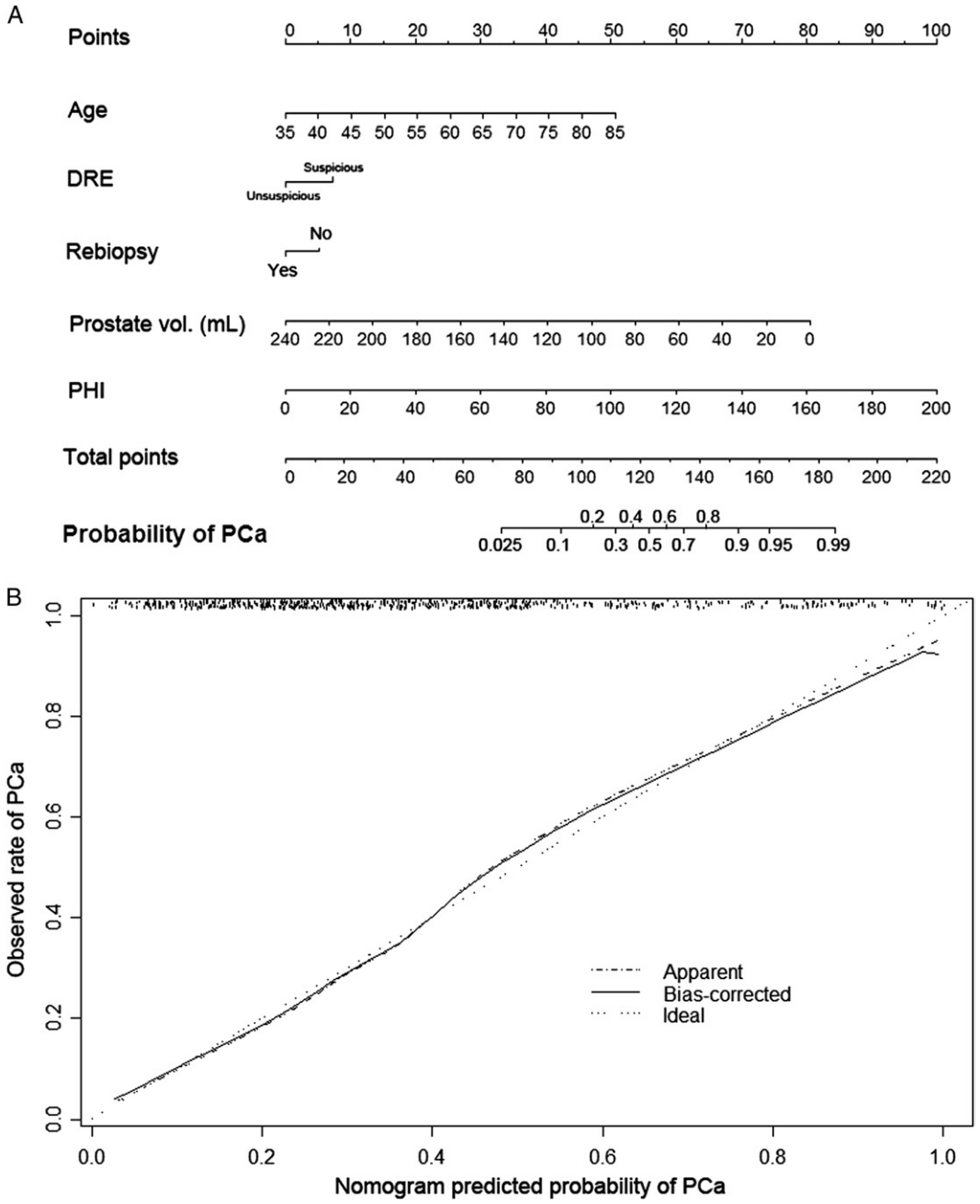

Figure 2. *A*, PHI based nomogram predicting probability of PCa at biopsy. Instructions for physicians: to obtain nomogram predicted probability of PCa, locate patient values at each axis. Draw vertical line to Points axis to determine how many points are attributed for each variable value. Sum points for all variables. Locate sum on Total Points line to assess individual probability of cancer on prostate biopsy on Probability of PCa line. *B*, local regression nonparametric smoothing plot shows PHI based nomogram calibration.

Similarly, Chun et al investigated the ability of PCA3 to determining the presence of PCa in patients who underwent initial or repeat prostate biopsy.[4] They confirmed the independent predictor status of PCA3 and developed a PCA3 based nomogram based on patient age, total PSA, DRE, prostate volume, biopsy history and PCA3 score, which showed 0.73 accuracy and good calibration properties. These findings were externally validated in a multi-institutional setting.[20] However, while discrimination and calibration properties are necessary to validate a prediction tool, it is now understood that these parameters should be complemented by DCA, which represents the benchmark to determine whether a tool could be useful in clinical practice. Nevertheless, the PCA3 test is not yet incorporated into clinical practice and since an appropriate cutoff level with acceptable performance characteris-

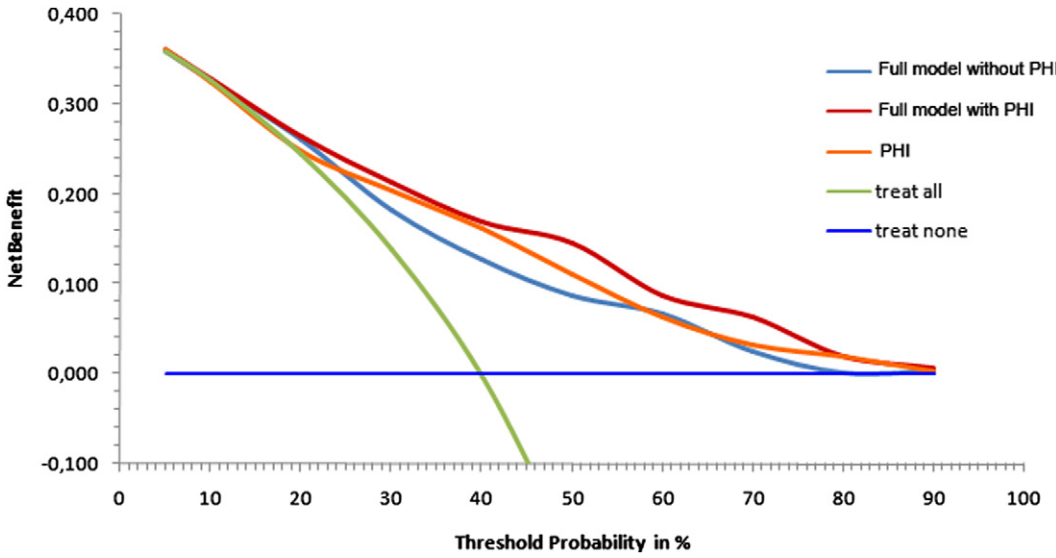

Figure 3. DCA shows net benefit derived from using multivariable model with PHI vs multivariable model without PHI vs PHI alone

tics has not been defined, this requires future study.[21]

Taken together, our findings demonstrate that PHI represents an informative marker to determine PCa at biopsy since it significantly increased the predictive accuracy of several commonly used PCa risk factors (age, DRE, prostate volume and biopsy history). Notably, the PHI based multivariable model was also significantly more accurate and showed higher specificity than models including tPSA, percent fPSA and p2PSA as covariables.

The newly developed PHI based nomogram fulfilled all of the criteria used to evaluate the effectiveness of a prediction tool.[13] Specifically, besides showing good predictive accuracy and optimal calibration, it also resulted in the highest benefit at DCA. In addition, the characteristics of the PHI based nomogram compare favorably to those of previously developed prediction tools. These findings confirm that the newly developed prediction tool could be used to obtain accurate predictions of the individual risk of PCa at biopsy.

Besides its strengths, which are represented by its prospective nature and the use of a standardized extended biopsy scheme, our study has some limitations. Only white patients were included in analysis, which may limit the applicability of our findings to other ethnicities.[10] Also, lack of external validation may limit the generalizability of our findings to populations different from that used to develop the model. However, in the absence of an external population, the bootstrap technique is considered the most reliable technique to validate a prediction tool.[22] In addition, because PHI groups tPSA, fPSA and p2PSA together in a single variable, we did not include other biomarkers in the final model. The decision to exclude additional biomarkers was based on 2 observations. 1) To avoid multicollinearity problems, predictors in strong correlation with other explanatory variables, such as PHI, tPSA and percent f/tPSA, were dropped from the final model. 2) The inclusion of other biomarkers, such as tPSA or percent fPSA, in the base multivariable logistic regression model would not have resulted in a statistically significant increase in the predictive accuracy of the model. Lack of external pathological review may also limit the significance of our results. 3) The tertiary care setting of the study may also be considered a limitation since our findings may not apply to a community based setting.

CONCLUSIONS

Our study confirmed that PHI represents an accurate marker to determine the presence of PCa at biopsy. To further assist clinicians in the decision to perform biopsy, we developed a PHI based nomogram that can provide individual estimates of the PCa risk. Our tool showed good discrimination and calibration properties at internal validation and DCA provided further evidence supporting its clinical usefulness. External validation in other populations and integration in Internet based risk calculators remain mandatory for the widespread use of PHI and our nomogram in clinical practice.

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EDITORIAL COMMENT

Since its dissemination 20 years ago, the PSA blood test has revolutionized the landscape of PCa, creating a robust increase in the number of men undergoing prostate biopsy.[1,2] These authors built a new nomogram based on a newly introduced marker, PHI. The nomogram achieved up to 80% accuracy. PHI has emerged as the most informative predictor of PCa compared to established predictors such as tPSA.

Despite this, the use of the marker in a wider spectrum of individuals, including those with higher tPSA and/or positive DRE, the potentially false-negative biopsy results in those in whom cancer may subsequently be identified and the limitation to 1 institution create the potential that this model may not work as well in a different setting. This raises the need for groups at other centers to confirm and externally validate the results.

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