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.