DECISION TREE ANALYSIS FOR PROSTATE CANCER PREDICTION IN PATIENTS WITH SERUM PSA 10 NG/ML OR LESS

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ANALIZA STABLA ODLUČIVANJA U PREDVIĐANJU KARCINOMA PROSTATE KOD BOLESNIKA SA SERUMSKIM NIVOOM PSA 10 NG/ML ILI MANJIM

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ABSTRACT

Serum prostate-specific antigen (PSA) testing increases the number of persons who undergo prostate biopsy. However, the best possible strategy for selecting patients for prostate biopsy has not yet been defined. The aim of this study was to develop a classification and regression tree (CART) decision model that can be used to predict significant prostate cancer (PCa) in the course of prostate biopsy for patients with serum PSA levels of 10 ng/ml or less.

The following clinicopathological characteristics of patients who had undergone ultrasound-guided transrectal prostate biopsy were collected: age, PSA, digital rectal examination, volume of the prostate, and PSA density (PSAD). CART analysis was carried out by using all predictors. Different aspects of the predictive performances of the prediction model were assessed.

In this retrospective study, significant PCa values were detected in 26 (26.8%) of a total of 97 patients. The CART model had three branching levels based on PSAD as the most decisive variable and age. The model sensitivity was 73.1%, the specificity was 80.3% and the accuracy was 78.3%. Our model showed an area under the receiver operating characteristic curve of 82.6%. The model was well calibrated.

In conclusion, CART analysis determined that PSAD was the key parameter for the identification of patients with a minimal risk for positive biopsies. The model showed a good discrimination capacity that surpassed individual predictors. However, before recommending its use in clinical practice, an evaluation of a larger and more complete database is necessary for the prediction of significant PCa.

Keywords: *Prostatic neoplasms; prostate-specific antigen density; decision tree.*

SAŽETAK

Testiranje na prostata specifični antigen (PSA) povisilo je broj osoba kod kojih se izvodi biopsija prostate. Međutim, najoptimalnija strategija selekcije bolesnika za biopsiju prostate još nije definisana. Cilj ove studije je kreiranje modela klasifikacionog i regresionog stabla odlučivanja (CART) koji bi se mogao koristiti u predviđanju signifikantnih karcinoma prostate (PCa) tokom biopsije prostate, kod bolesnika sa serumskim nivoom PSA od 10 ng/ml ili manjim.

Prikupljane su sledeće kliničkopatološke karakteristike bolesnika kod kojih je učinjena ultrazvukom vođena transrektalna biopsija prostate: starost, PSA, digitrektalni pregled, volumen prostate i gustina PSA (PSAD). CART analiza je izvedena korišćenjem svih prediktora. Procenjeni su različiti aspekti prediktivnih performansi predikcionog modela.

U ovoj retrospektivnoj studiji signifikantni PCa su utvrđeni kod 26 (26.8%) od ukupno 97 bolesnika. CART model ima tri nivoa grananja, na osnovu vrednosti PSAD, kao najpresudnije varijable i starosti. Senzitivnost modela je 73.1%, specifičnost 80.3% a tačnost 78.3%. Naš model je pokazao površinu ispod krive od 82.6%. Model ima dobru kalibraciju.

U zaključku, CART analiza utvrdila je PSAD kao parametar identifikacije bolesnika sa minimalnim rizikom pozitivne biopsije. Model je pokazao dobru diskriminacionu sposobnost koja prevazilazi pojedinačne prediktore. Međutim, pre preporuke kliničke primene, neophodna je evaluacija veće i kompletnije baze podataka radi predviđanja signifikantnih PCa.

Ključne reči: *neoplazme prostate; gustina prostata specifičnog antigena; stablo odlučivanja*

ABBREVIATIONS

AUC - area under the receiver operating characteristic curve;
CART - classification and regression tree analysis;
DRE - digital rectal examination;
IQR - interquartile range;
NPV - negative predictive value;
PCa - prostate cancer;
PCA3 - prostate cancer gene 3;
PHI - Prostate Health Index;
PPV - positive predictive value;
PSA - prostate-specific antigen;
PSAD - PSA density;
SD - standard deviation;
TRUS - transrectal ultrasound;
TZ - transition-zone

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INTRODUCTION

Prostate cancer (PCa) is estimated to be the most common cancer among men in Europe (1). Prostate biopsy is the gold standard for diagnosing PCa in men with elevated total serum prostate-specific antigen (PSA) levels or abnormal digital rectal examination (DRE) findings. Usage of the PSA test has dramatically increased the number of men who have undergone prostate biopsy over the last decades. However, serum PSA level alone, in the intermediate range (4.1–10.0 ng/ml), lacks specificity, potentially causing unnecessary treatment complications with prostate biopsy. In addition, overdiagnosis and overtreatment of indolent PCa is a serious health issue in most developed countries (2).

Efforts have been made to decrease the number of unnecessary biopsies. Multiple PSA derivatives have been advanced as early detection biomarkers, including age-specific PSA reference ranges, percentage of free PSA (3), PSA velocity (4), PSA density (PSAD) (5), transition-zone (TZ) PSAD (6), or presence of hypoechoic lesions on transrectal ultrasound (TRUS) (7). The most advanced PCa biomarkers include (-2) proPSA, %p2PSA, Prostate Health Index (PHI) (8), 4-kallikrein panel (9) or urine-based biomarkers, such as prostate cancer gene 3 (PCA3) (10).

In the last two decades, there has been extensive development of predictive tools to aid clinicians in predicting PCa diagnosis. Numerous multivariate models based on the combination of various clinical and demographic variables expressed by nomograms (7, 11-13), artificial neural networks (6), and risk calculators (14-16) provide better clinical performance than the results obtained with individual predictors (6, 7, 15). Despite these major efforts, there is no agreement as to whether these predictive PCa models improve the predictive accuracy of PSA testing and whether one model performs better than another. Furthermore, only limited reductions in the rate of unnecessary biopsies are possible. Thus, the best possible strategies for selecting appropriate patients for prostate biopsy have yet to be defined.

Classification and regression tree analysis (CART) has been applied in urology, especially for prostate cancer in the prediction of aggressive prostate cancer on biopsy (17, 18) or bone scan positivity (19). The procedure is a graphic representation of a series of decision rules and selects a useful subset of predictors or classifies subjects into high- and low-risk groups. Furthermore, the results of CART analysis are presented as a decision tree, which is intuitive and easier to understand than the results of many other statistical methods.

Based on these considerations, the aim of this study was to develop and compare the predictive accuracy of classification trees with those of the most important individual predictors for predicting clinically significant PCa on biopsy in patients with serum PSA levels of 10 ng/ml or less.

PATIENTS AND METHOD

This is a retrospective study carried out using a database of 239 patients who had undergone ultrasound-guided prostate biopsies over a 1-year study period from September 2016 through September 2017. Patient referrals were obtained in the course of routine clinical care and not as part of a population-based screening trial. After obtaining institutional review board approval, the data were collected regarding clinicopathological characteristics for each patient regarding prebiopsy assessment and included the following: age, PSA, DRE, volume of prostate, PSAD, total number of cores taken, Gleason score, and number of positive core biopsies. Exclusion criteria were patients with incomplete data and medical therapy known to affect PSA levels. The study included only patients with serum PSA levels of 10 ng/ml or less. The primary outcome was the detection of clinically significant prostate cancer on biopsy. Clinically insignificant prostate cancer was defined histopathologically according to the PRIAS inclusion criteria for low-risk PCa: T1C/T2, PSA ≤10 ng/ml, PSAD<0.2 ng/ml/ml, one or two positive biopsy cores, and Gleason score (GS)≤6 (2).

A member of the urology team performed a DRE on all patients. The DRE was classified as normal or suspicious/positive. At presentation, the serum PSA measurement (UniCel DxI 600 Access Immunoassay System, Beckman Coulter, USA) was performed. Before the biopsy procedure, all patients received a cleansing enema and prophylactic broad-spectrum antibiotics. A Toshiba (Aplio 300) ultrasound device with a 5-10-MHz probe was used to obtain ultrasound data and prostate biopsy samples. All patients underwent ultrasound-guided prostate biopsies performed using an 18-gauge biopsy instrument (Md-Tech, Pro-Mag I 2.5, USA). A median of ten biopsy cores was obtained, which were evaluated per each hospital's standard procedure and by local pathologists. Prostate volumes were obtained by measuring the gland in three dimensions, and volume was estimated using the following formula: 0.52 (length (cm) × width (cm) × height (cm)). The PSAD was calculated by dividing the serum PSA by the calculated prostate volume.

Statistical Analyses

Descriptive statistics were used for demographic and baseline characteristics. We expressed continuous variables as the means and standard deviations (SDs) when normally distributed or as the medians and interquartile ranges (IQRs) if their distributions were skewed, and discrete variables as percentages. Categorical variables (frequencies) were compared using Fisher's exact or Chi-square test. Continuous numerical data were analysed using the t-test or the Mann-Whitney U test when the data were not normally distributed.

CART classification tree

We choose the CART growing method to attempt to maximize the within-node homogeneity. CART analysis was carried out on the whole sample using all the predic-

Table 1. Patients' baseline clinicopathological characteristics (N=97).

Characteristics		BPH/Insignificant Pca (n=71)	Significant Pca (n=26)	p
Age	mean ± SD, years	67.7 ± 7.1	68.6 ± 6.3	0.548
PSA	mean ± SD, ng/ml	6.7 ± 2.1	7.6 ± 1.6	0.059
Volume prostate	median (IQR), ml	52 (35)	37 (18.7)	0.002
PSAD	median (IQR), ng/ml/ml	0.12 (0.10)	0.21 (0.12)	0.000
DRE	abnormal n, (%)	6 (8.5)	5 (19.2)	0.158
Number of biopsy cores	median (IQR)	10 (0)	10 (0)	0.140
GS ≤ 6	n (%)	8 (8.2)	14 (14.4)	NA
GS = 7-10	n (%)	0 (0)	12 (12.3)	NA

PCa–prostate cancer; SD–standard deviation; PSA–prostate-specific antigen; PSAD–prostate-specific antigen density; IQR–interquartile range; DRE–digital rectal examination; GS–Gleason score; NA–not applicable

tors identified in the patient population. We selected the category of significant PCa as the category of primary interest in the analysis. We select the GINI impurity measure, which splits and maximizes the homogeneity of child nodes with respect to the value of the dependent variable. We controlled stopping rules with a maximum tree depth of 3 levels and the minimum numbers of cases for nodes by specifying that the parent node must have at least 10 cases and a child node at least 5 cases. The optimal number of leaves was determined by identifying the tree size that minimized the tree deviance when 10-fold cross-validation was used in the derivation sample.

For models derived from CART analysis, we calculated the sensitivity, the specificity, the positive predictive value (PPV), the negative predictive value (NPV), the accuracy, and the area under the receiver operating characteristic curve (AUC). Comparisons of AUCs between models and individual predictors were performed using the method proposed by DeLong et al. (20) The SPSS (version 23.0) software package was used for all analyses. Statistical significance was set at $p < 0.05$.

RESULTS

A total of 97 patients with serum PSA levels of 10 ng/ml or less were analysed. Cancer was detected in 34 (35.1%), and significant PCa was detected in 26 (26.8%) of patients. The majority of tumours (64.7%) were determined to be Gleason score 6 or less. Table 1 shows the clinical characteristics of patients with/without significant PCa included in the study. The mean age of the patients was 68 years. The mean PSA level in all patients was 6.9 ng/ml. The DRE was abnormal in 11.3% of patients. The median prostate volume was 47 ml. The median PSAD was 0.13 ng/ml/ml. There were no significant differences in age, PSA levels and DRE findings between patients with or without significant PCa. The most decisive variables at the moment of classification were PSAD and prostate volume (Table 1).

CART tree

A tree-based CART prediction model is shown in Fig. 1 and details the total number of patients (n) and the possible outcome of the class variables with high probability. There are 5 terminal and 4 non-terminal nodes, resulting from 3 *"if-then"* conditions. The most decisive variable at the moment of classification was the PSAD, which stratified patients into two classes in relation to the cut-off value of more or less than 0.16 for further work-up. The non-terminal nodes (node 1 and 2) represented patients in low- and high-risk groups (prevalence rates of 10.5% and 50%, respectively). Both nodes were further split on the basis of the patient's age: more or less than 70.5 years in low-risk group and more or less than 61.5 years in high-risk group. The incidence rates of cancer detection in the low-risk group after splitting were 15% and 0%, respectively (nodes 3 and 4). Younger patients in the high-risk group were associated with low prevalence of PCa (14.3%) compared to older patients (57.6%) (nodes 5 and 6). These nodes are also terminal

Table 2. Diagnostic performance of PSA density at diverse cut-off values and CART model.

PSAD cut-off value	TP	FN	TN	FP	Sensitivity (%)	Specificity (%)	Biopsy spread (%)	Missed (%)
0.07	26	0	6	65	100	8.45	6	0
0.10	24	2	19	52	92.31	26.76	22	8
0.15	20	6	47	24	76.92	66.20	55	23
0.18	17	9	53	18	65.38	74.65	64	35
0.21	15	11	57	14	57.69	80.28	70	42
0.24	8	18	62	9	30.77	87.32	82	69
CART model	19	7	57	14	73.1	80.3	66	27

TP–true positive; FN–false negative; TN–true negative; FP–false positive; CART–classification and regression tree analysis

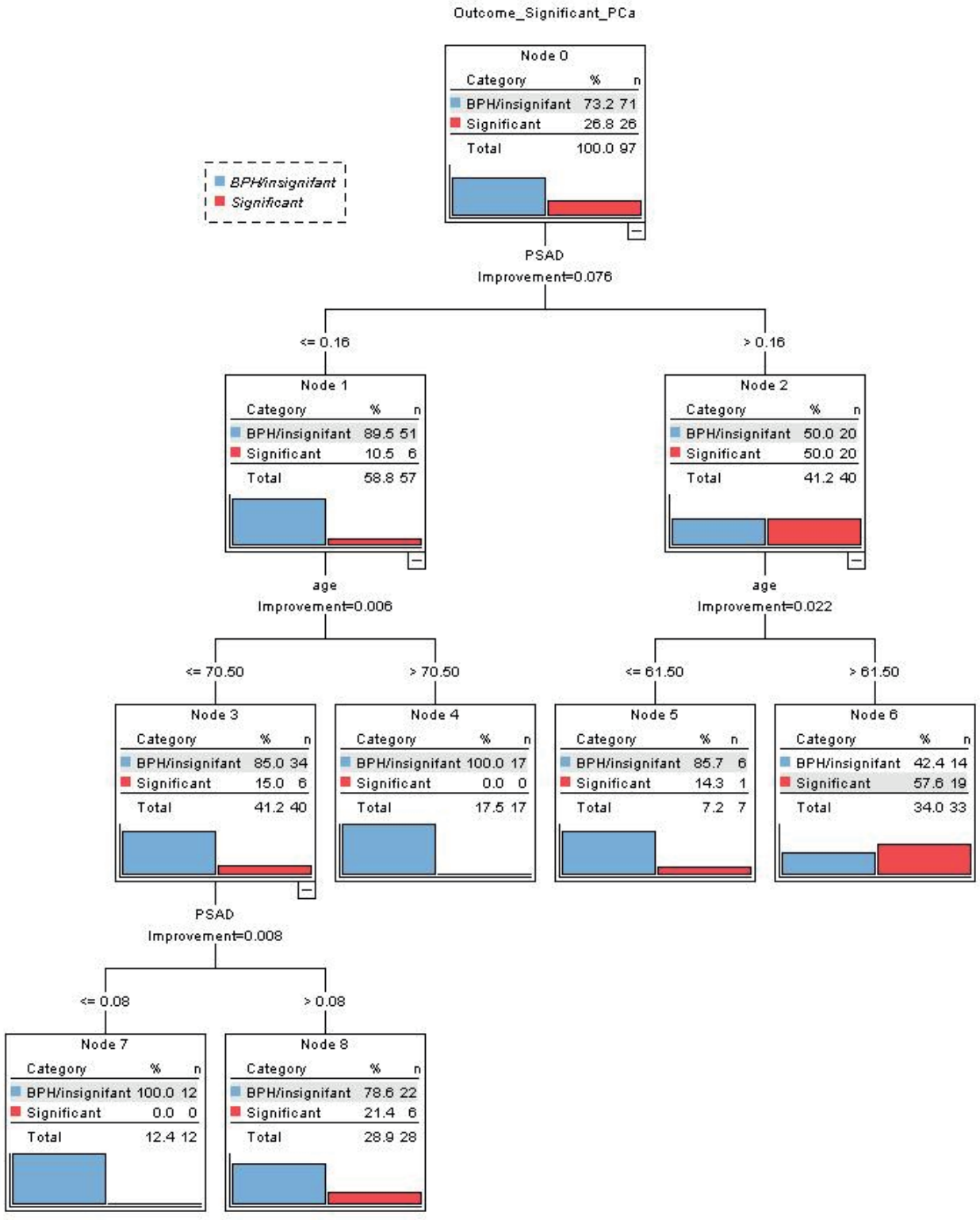

Figure 1. Tree-based CART prediction model.
The CART analysis was carried out on the whole sample using the all the predictors identified in the patients' population.

nodes. Finally, the non-terminal node 3 was further split on the basis of the PSAD of more or less than 0.08 (nodes 7 and 8). No patients had cancer if the PSAD was less than 0.08 (node 7). The misclassification rates of the entire sample and of the cross-validated estimate were 21.6% vs. 29.9%, respectively. The overall prediction accuracy of the CART model was 78.4%, and it was higher in the absence of significant PCa (80.3%) than in the significant PCa group (73.1%).

Diagnostic Performance of PSA Density at Various Cut-off Values

Since the CART analysis indicated that the PSAD was the most useful variable in predicting significant PCa, we next attempted to define the optimum cut-off value for PSAD. The diagnostic performances of different thresholds for PSAD are shown in Table 2. If the PSAD cut-off value was set at 0.15, which has been widely used for PCa detection, the sensitivity and specificity would be 76.6 and 66.2%, respectively; the number of patients requiring biopsies could have been reduced to 43 (55%) from 97, but 23% of the PCa patients would have been missed, with a PCa detection rate of 76.6% (20/26). Reducing the cut-off value to 0.07 (ng/ml/ml) resulted in a sensitivity of 100% and a specificity of 8.45%. Utilizing this parameter, the number of biopsies could have been reduced to 91 (6%) from 97, and none of the PCa patients would have been missed. However, according to our analysis, a PSA of ≤ 7.17 was considered optimum because it gave the highest sum of sensitivity and specificity.

Global metrics of test accuracy (AUC) for model and individual predictors are shown in Figure 2 and Table 3. The AUC for the model was shown to have moderate/good discriminatory capacity (82.6%), and in the pairwise comparison of ROC curves, the difference between the areas for CART and PSAD (5.4%) was not significant (P = 0.188), while that between the areas for CART and PSA (20.6%) was significant (P < 0.001). Graphical assessments of the CART model calibration are presented in Figure 3. The model was well calibrated (R^2=0.942). The CART model was found to have an overall sensitivity of 73.1% (95% confidence interval (CI) 52.2 – 88.4%) and a specificity of 80.3% (95% CI 69.1 – 88.8%). The positive predictive value was 57.6% (95% CI 39.2 – 74.5%), the negative predictive value was 89.1% (95% CI 78.5 – 95.5%), and the accuracy was 78.3% (95% CI 68.8 – 88.1%).

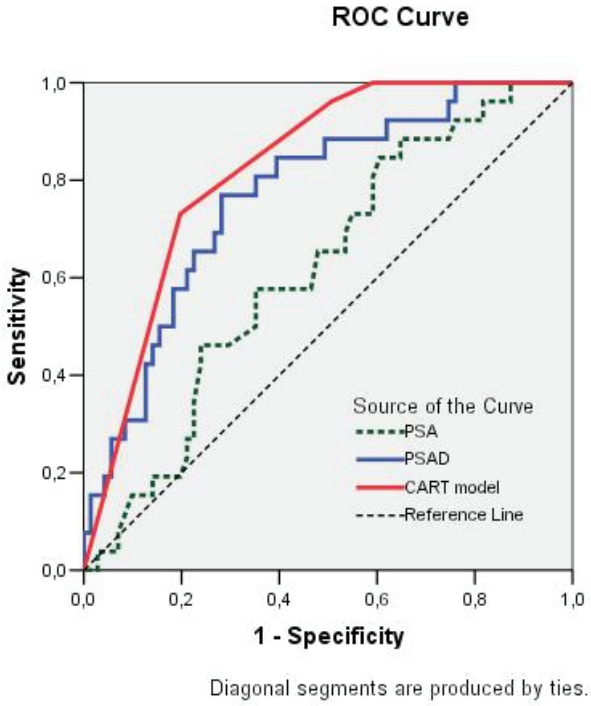

Figure 2. ROC curve analyses
A global metric of test accuracy (AUC) for the model and individual predictors (PSAD and PSA).

Table 3. Areas under the receiver operating characteristic curve of PSA, PSAD, and the CART model.

Predictors	AUC (95% CI)
CART model	82.6% (73.5 – 89.5%)
PSAD	77.1% (67.5 – 85.1%)
PSA	61.9% (51.5 – 71.6%)

AUC–area under the receiver operating characteristic curve; PSA–prostate-specific antigen; PSAD–prostate-specific antigen density; CART–classification and regression tree analysis

DISCUSSION

In the current study, we used CART analysis to develop a prostate biopsy decision algorithm in patients with serum PSA levels of 10 ng/ml or less. CART analysis selected PSAD as an indication for low- and high-risk groups. Age as common predictor may serve in further risk stratification. The CART model was shown to have good discriminatory capacity and outperformed PSA and PSAD as individual predictors. Application of the model would lead to notably superior clinical outcomes than the current strategy of biopsying all men with elevated PSA, consequently resulting in a reduction of the number of unnecessary biopsies.

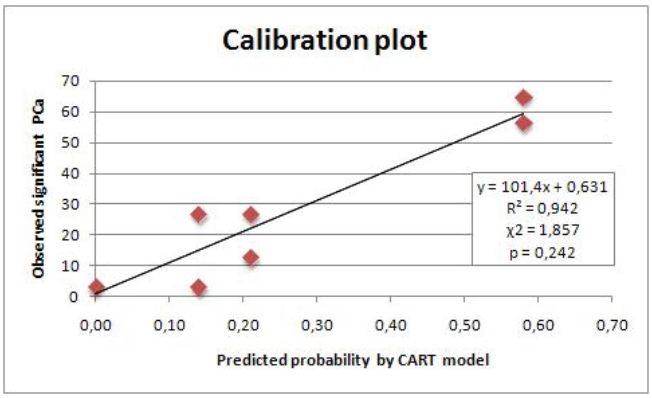

Figure 3. CART model calibration.
Graphical assessments of the CART model calibration.

Previous studies have established criteria associated with higher risk of significant PCa. They included age (7, 11-14, 17, 18), race (14), digital rectal examination (7, 11-16), total PSA (6, 12-16, 18), percentage of free PSA (6, 12, 13), PSAD (7, 17, 18), PHI (11), prostate volume (11, 12, 15-18), PSAD of the TZ (6), TZ volume (6), hypoechoic lesions on ultrasound (7, 16, 18), biopsy history (11, 14, 15) and family history (14). A wide variety of different

combinations of predictive factors has been identified. In line with previous studies, two of those predictors have reached statistical significance in the tree-based methods in our study. In our study ,, there were no significant differences in PSA levels between patients with or without significant PCa, which is in accordaence with many previous reports that serum PSA level alone, in the intermediate range, lacks proper the specificity. According to the analysis, PSAD was the most decisive variable at the moment of classification. The PSAD measurement is based upon the observation that PCa can produce an approximately 10-fold higher PSA concentration per volume of prostate tissue than in benign conditions. The PSAD has been suggested to differentiate benign from malignant prostate disease, especially in cases belonging in the grey zone (5). The PSAD asas an individual predictors outperformed PSA in our analysis,s as shown in thea global metric of test accuracy. Although there is controversy about cut-offs for PSAD, our result showed that the western reference (PSAD 0.15) (3) has moderate sensitivity (77%), and 23% of patients would have been missed, at the same time avoiding 55% of unnecessary biopsies. However, by reducing the value to 0.07 ng/ml/ml, a complete sensitivity similar to the value of 95% obtained by Catalona et al. (3) could be achieved. In studies that included patients with serum PSA levels of 10 ng/ml or less with similar design, a PSAD greater or less than 0.158–0.165 was the main splitting criterion (17, 21). These results support those of prior investigators, such as Catalona et al. (3), who reported that the commonly used PSAD cut-off of 0.15 detected only 59% of cancers in men with normal DREs and PSA levels between 4.0 and 10.0 ng/ml. Patients with cancer with lower PSAD values (0.15 or less) tended to have less aggressive disease (3), which is one of criteria for identifying very-low-risk prostate cancer. According to the findings of a recent study in our circumstances, patients with PSAD values above 0.17±0.06 should be included for biopsy (22). Furthermore, PSAD is an accurate predictor for adverse pathology prediction in patients with localized prostate cancer who undergo radical prostatectomy (23, 24). A previous study showed that PSAD could be a reliable clinical parameter for predicting prostate behaviour in cases of active surveillance. Patients with clinically localized prostate cancer and PSAD values <0.15 can be followed up safely on active surveillance, whereas cases with PSAD values >0.15 are at a higher risk of tumour progression and may be better managed by definitive therapy (25).

Our CART analysis identified two critical values for patient age, which is similar to critical values in other studies (younger than 60, 60 to 70 and older than 70 years) that examined survival after radical prostatectomy in relation to age, suggesting that men older than 70 years had a higher risk of disease and poorer survival (26). In addition, the detection rate of aggressiveness of PCa progressively increased with the age at diagnosis (27).

The accuracy levels of the present models were higher than the accuracy level of many earlier models. Our model resulted in an AUC of 82.6%, which is better than many other (73-82%) (7, 11-13, 15, 18) and similar to other reports (9, 16). In line with previous studies, our summary results suggest that the discriminative accuracy of the prediction model was better than PSAD and PSA testing (28). A systematic review that assesses the model's performance in the prediction of PCa suggested that none has clearly shown superiority over the others or can be considered as optimal (28). However, metrics of accuracy do not address the clinical value of a model.

The limitation of this study resides in its retrospective design, as the study was conducted in a single tertiary centre with a relatively small patient cohort that restricted generalization of the rules. Secondly, we included only those variables that were available to us. Because other advanced biomarkers were not available, we were unable to assess their utility in the current model. Furthermore, this analysis is limited by the bias introduced by false-negative biopsies. Recent studies have suggested that extended biopsy schemes and MR-targeted biopsies have demonstrated superiority over systematic biopsies for the detection of clinically significant disease (29). Next, criteria for insignificant PCa are not generally accepted. A recent study suggests that not all Gleason 3+4 cases will have aggressive disease (30). Furthermore, the prostate volumes of the study patients were measured by multiple operators. Therefore, inter-operator bias might interfere with our results. Finally, determination of prostate volume by TRUS may vary considerably (31). The lack of measurement precision for prostate volume has prevented the widespread clinical acceptance of PSAD. Nevertheless, using CART analysis, we could classify patients into a low-risk group (PSAD ≤ 0.16), which could avoid the biopsy procedure, and a high-risk group. Men in the low-risk group (positive biopsy result: 10.5%) could be selected with the CART model according to the following criteria: a PSAD of ≤ 0.16, age > 70.5 years or a PSAD of ≤ 0.08, age ≤ 70.5 years. Our study provides clear evidence that the statistical model could be used in everyday clinical practice to decrease unnecessary biopsies and had very small numbers of splits, unlike other models (7 splits) (18). The prediction model represents another step towards accurately estimating individualized risk of PCa in a patient population lacking optimal prediction procedures.

CONCLUSION

In summary, the CART analysis chose PSAD for the identification of patients at minimal risk for a positive biopsy. The model showed good discrimination and outperformed the most important individual predictors. However, before recommending its use in clinical practice, a larger and more complete database should be used to further clarify the magnitude of the model in terms of the prediction of significant PCa.

Conflicts of Interest

None.

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