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Decision tree analysis for prostate cancer prediction

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SUMMARY

Introduction/Objective The use of serum prostate-specific antigen (PSA) test has dramatically increased the number of men undergoing prostate biopsy. However, the best possible strategies for selecting appropriate patients for prostate biopsy have yet to be defined.

The aim of the study was to develop a classification and regression tree (CART) model that could be used to identify patients with significant prostate cancer (PCa) on prostate biopsy in patients referred due to abnormal PSA, digital rectal examination (DRE) findings, or both, regardless of the PSA level.

Methods The data on clinicopathological characteristics regarding prebiopsy assessment collected from patients who had undergone ultrasound-guided prostate biopsies included the following: age, PSA, DRE, volume of the prostate, and PSA density (PSAD). The CART analysis was carried out using all predictors identified by univariate logistic regression analysis. Different aspects of predictive performance and clinical utility risk prediction model were assessed.

Results In this retrospective study, significant PCa was detected in 92 (41.6%) out of 221 patients. The CART model had three splits based on PSAD, as the most decisive variable, prostate volume, DRE, and PSA. Our model resulted in an 83.3% area under the receiver operating characteristic curve. Decision curve analysis showed that the regression tree provided net benefit for relevant threshold probabilities compared with the logistic regression model, PSAD, and the strategy of biopsying all patients.

Conclusion The model helps to reduce unnecessary biopsies without missing significant PCa.

Keywords: prostatic neoplasms; prostate-specific antigen density; decision trees

INTRODUCTION

Prostate cancer (PCa) is the second most frequently diagnosed malignancy and the sixth leading cause of cancer-associated mortality in men worldwide [1]. The use of serum prostate-specific antigen (PSA) test dramatically increased the number of men undergoing prostate biopsy over the last decades. However, PSA and the digital rectal exam (DRE) have moderate sensitivity but low specificity for cancer diagnosis, potentially causing unnecessary treatment complications with prostate biopsy. Furthermore, 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, PSA density (PSAD), PSA velocity, transition-zone (TZ) PSAD, percentage of free PSA, or the presence of hypoechoic lesions on transrectal ultrasound [3–7]. The most advanced blood-based PCa biomarkers include [-2]proPSA, %p2PSA, Prostate Health Index (PHI), 4-kallikrein panel or urine-based biomarkers such as PCa gene 3 (PCA3) and TMPRSS2:ERG (T2:ERG) gene fusions [8, 9, 10]. Numerous multivariate models based on the combination of various clinical and demographic variables expressed by nomograms [7, 11, 12, 13], artificial neural networks [5, 14], risk calculators [15, 16, 17] provide better clinical performance than the results obtained by individual predictors [5, 7, 16]. Although they are reported to produce useful results, these approaches are still in the evaluation phase and they are not used in daily clinical practice. Furthermore, only limited reductions in the rate of unnecessary biopsies are possible. Therefore, 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 PCa in the prediction of aggressive PCa on biopsy [18, 19], or bone scan positivity [20]. *Chi*-squared Automatic Interaction Detector (CHAID) is one of the oldest tree classification methods. 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 the CART analysis are presented as a decision tree, which is intuitive and easier to understand than the results of many other statistical methods.

The aim of the study was to develop and compare the predictive accuracy and clinical usefulness of classification trees with that of the traditional statistical method (logistic regression – LR) and individual most important predictor for predicting clinically significant PCa on biopsy in patients referred due to abnormal PSA, DRE findings, or both, regardless of PSA level.

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METHODS

Patient population

This is a retrospective study carried out using the database of 239 patients at the Kragujevac Clinical Centre, who had undergone ultrasound-guided prostate biopsies, from September 2016 through September 2017. Patient referrals were obtained in the course of routine clinical care, regardless of prostate-specific antigen level or clinical findings, and not as part of a population-based screening trial. After obtaining institutional review board approval, the collected data on clinicopathological characteristics for each patient regarding prebiopsy assessment included the following: age, PSA, DRE, prostate volume, 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 primary outcome was the detection of clinically significant PCa on biopsy. Clinically insignificant PCa was defined histopathologically according to the Prostate Cancer Research International Active Surveillance (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 ≤ 6 [2].

A member of the urology team performed a DRE on all the patients. The DRE was classified as normal or suspicious/positive. At presentation, the serum PSA measurement (UniCel DxI 600 Access Immunoassay System; Beckman Coulter, Brea, CA, USA) was performed. Before the biopsy procedure, all the patients received a cleansing enema and prophylactic broad-spectrum antibiotics. A Toshiba (Aplio 300; Toshiba, Tokyo, Japan) ultrasound device with a 5–10 MHz probe was used to obtain ultrasound data and prostate biopsy. All the patients underwent ultrasound-guided prostate biopsy performed using an 18-gauge biopsy instrument (Pro-Mag I 2.5, Md-Tech, Houston, TX, USA). A median of 10 biopsy cores were obtained (range: 2–12 cores), and 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. Univariate and multivariate LR were used to identify and quantify the potential and independent predictors of significant PCa with Backward–Wald stepwise regression. The results of the regressions were expressed in odds ratio with 95% confidence interval.

CRT classification tree

The CHAID analysis was carried out on the whole sample using all the predictors identified by the univariate LR analysis. We selected the category of significant PCa as the category of primary interest in the analysis. For both significance value for splitting nodes and merging categories, we specified a default significance level of 0.05. The χ^2 statistic was calculated using the Pearson method. We checked "Allow resplitting of merged categories" within a node, which allows the procedure to resplit merged categories if that provides a better solution. We controlled the stopping rules by the maximum tree depth of three levels and the minimum numbers of cases for nodes by specifying that the parent node must have at least 20 cases and a child node at least five 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. By comparing the classification rate of the entire sample to the cross-validated classification rate, we can assess the generalizability and stability of the classification tree.

Comparison of predictive models

For each model we calculated the area under the receiver operating characteristic (ROC) curve (AUC), sensitivity, specificity, positive (PPV), negative predictive value (NPV), accuracy, and calibration for the CHAID model. The comparisons of AUC were performed using the method proposed by DeLong et al. [21].

Clinical usefulness was assessed by using the decision curve analyses [22]. These analyses estimate a "net benefit" for prediction models by summing the benefits (true positives) and subtracting the harms (false positives). An assumption is made that the identification of clinically significant PCa would lead to biopsy. Net benefit is plotted against threshold probabilities compared with the 'Biopsy for all' and 'Biopsy for none' strategies. The interpretation of a decision curve is that the model with the highest net benefit should be chosen. We calculated the net benefit in Excel using the recommended formula [22]. All other analyses were performed using IBM SPSS Statistics, Version 23.0 (IBM Corp., Armonk, NY, USA). Statistical significance was set at $p < 0.05$.

RESULTS

Patients' characteristics

A total of 221 patients were analyzed. PCa was detected in 100 (45.2%) patients, but significant PCa was detected in 92 (41.6%) patients. Table 1 shows the clinicopathological characteristics of patients with/without significant PCa included in the study. There were significant differences in age, PSA levels, volume of prostate, PSAD, and DRE findings between patients with or without significant PCa.

The logistic regression analysis

In a univariate analysis, all five risk factors displayed significant correlation with significant PCa (Table 2). During the multivariate analysis, three factors sustained their prognostic significance (Table 2). The analysis demonstrated

Table 1. Baseline patients' clinicopathological characteristics (n = 221).

Characteristics		All	BPH/Insignificant PCa (n = 129)	Significant PCa (n = 92)	p
Age	mean ± SD, years	69.8 ± 7.3	68.5 ± 6.9	71.6 ± 7.4	0.002
PSA	median (IQR), ng/ml	11.2 (15.1)	9.8 (8.4)	17.8 (42.3)	0.000
Volume prostate	median (IQR), ml	49 (32.5)	55 (40)	44 (27)	0.003
PSAD	median (IQR), ng/ml/ml	0.24 (0.41)	0.17 (0.23)	0.43 (0.72)	0.000
DRE	abnormal n, (%)	53 (24)	14 (10.9)	39 (42.4)	0.000
Number of biopsy cores	median (IQR)	10 (0)	10 (0)	10 (0.75)	0.039
GS ≤ 6	n (%)	40 (18.1)	8 (3.6)	32 (14.5)	NA
GS = 7	n (%)	25 (11.3)		25 (11.3)	NA
GS 8–10	n (%)	35 (15.8)		35 (15.8)	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

Table 2. The logistic regression analysis of predictors for significant prostate cancer

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Age	1.062 (1.022–1.104)	0.002		
PSA	1.025 (1.012–1.038)	0.000	1.020 (1.007–1.033)	0.003
Prostate volume	0.988 (0.978–0.998)	0.024	0.980 (0.967–0.992)	0.001
PSAD	3.735 (1.870–7.458)	0.000		
DRE	6.044 (3.026–12.074)	0.000	4.024 (1.877–8.626)	0.000

PSA – prostate-specific antigen; PSAD – prostate-specific antigen density; DRE – digital rectal examination; OR – odds ratio; CI – confidence interval

that the PSA, volume of prostate, and DRE have strong prognostic value of significant PCa (Table 2).

CHAID tree

A tree-based CHAID prediction model is shown in Figure 1. There are nine terminal and five non-terminal nodes, resulting from three 'if–then' conditions. The most decisive variable at the moment of classification was the PSAD, which stratified the patients into four classes in relation to the value: ≤ 0.15, 0.15–0.24, 0.24–1.47, and ≥ 1.47 ng/ml/ml, respectively. Ultimate nodes (nodes 1 and 4) are also terminal with low and very high prevalence of significant PCa (10.6% and 86.4%, respectively). Node 2, associated with PCa in 34.1% of cases, was further split on the basis of the prostate volume being less than, equal to, or greater than 54 ml. Larger prostate was associated with low prevalence of PCa (12.5%), compared to smaller (46.4%) ones. Finally, the non-terminal node (5) split on the basis of the presence of abnormal DRE, with more PCa (83.3%) cases when DRE was abnormal. Node 3, associated with PCa in 57.3% of the cases, was further split on the basis of the presence of abnormal DRE. Abnormal DRE was associated with more PCa (79.3%) compared to normal DRE (46.7%). Node 7 was further split on the basis of the PSA value: ≤ 8.2 ng/ml, 8.2–11.2 ng/ml, and ≥ 11.2 ng/ml (terminal nodes 11, 12, and 13). The misclassification rates of the entire sample and of the cross-validated estimate were 21.3% *vs*. 29%. The overall model prediction accuracy of the CHIAD model was 78.7%, and it was higher in the absence of significant PCa (90.7%) than in the significant PCa group (62%).

Diagnostic performance of PSAD at various cut-off values

Since the CHAID analysis indicated that the PSAD was the most useful variable in predicting significant PCa, what we tried next was to define the optimum cut-off value for PSA density. The diagnostic performance of different thresholds for PSAD is shown in Table 3. 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 92.4% and 45.7%, respectively; the number of patients requiring biopsy could have been reduced to 155 (30%) from 221, with a PCa detection rate of 92.4% (87/92). However, according to our analysis, a PSAD of > 0.25 was considered optimum because it gave the highest sum of sensitivity and specificity.

Predictive performance for each of the modelling strategies and PSAD is reported in Table 3. AUC for all the models were shown to have moderate/good discriminatory ability (77.8–83.3%) (Figure 2), and in pairwise comparison of receiver operating characteristic curves, the difference between the areas of the CHAID tree and the LR

Table 3. Diagnostic performance of prostate-specific antigen density at diverse cut-off values

PSAD cut-off value	TP	FN	TN	FP	Sensitivity (%)	Specificity (%)	Biopsy spread (%)	Missed (%)
0.07	92	0	14	115	100	10.85	6	0
0.10	90	2	19	110	97.83	14.73	10	2
0.15	85	7	59	70	92.39	45.74	25	8
0.18	82	10	64	65	89.13	49.61	33	11
0.21	79	13	72	57	85.87	55.81	38	14
> 0.25	69	23	89	40	75	68.99	51	25

PSAD – prostate-specific antigen density; TP – true positive; FN – false negative; TN – true negative; FP – false positive

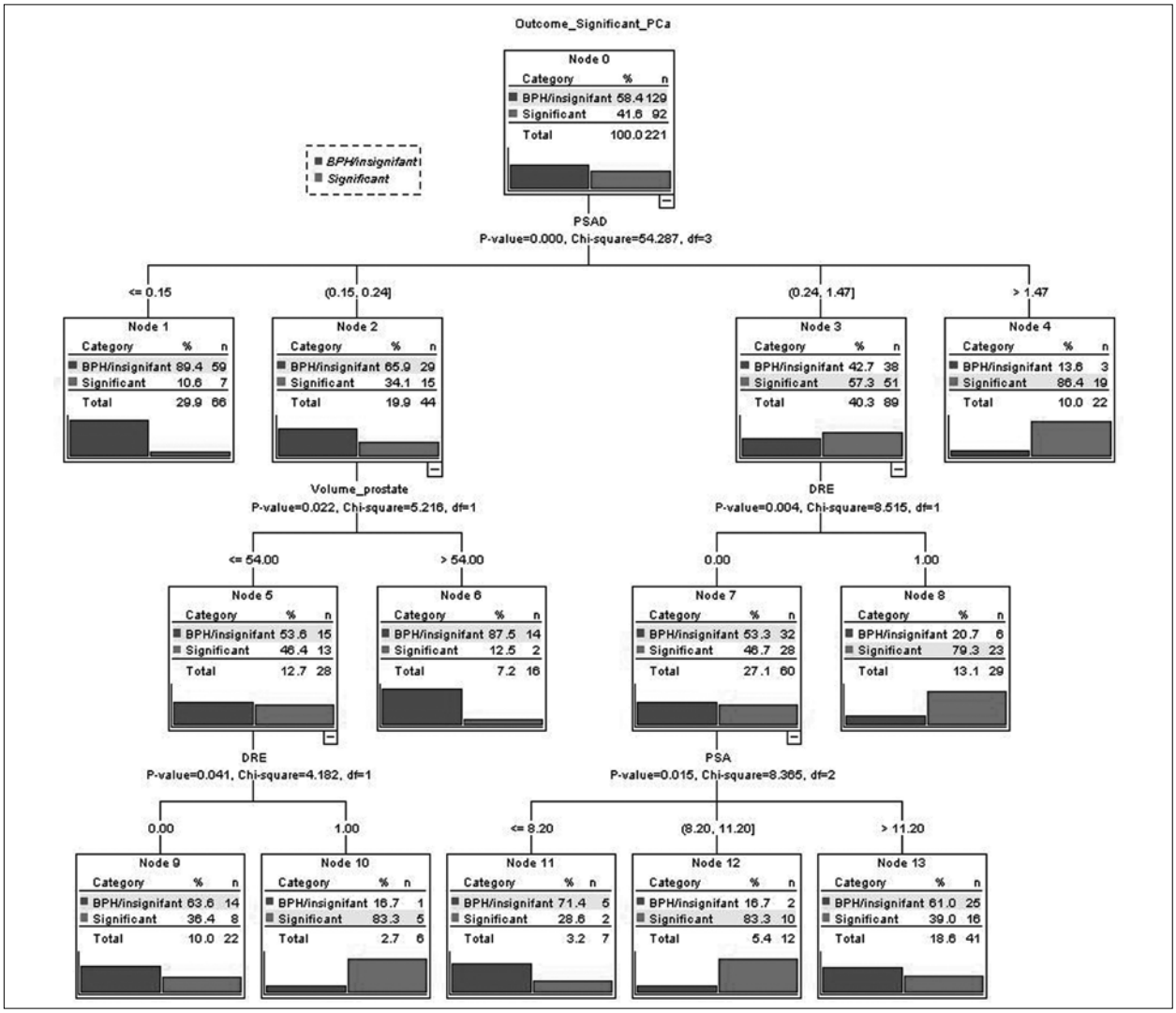

Figure 1. A tree-based Chi-squared Automatic Interaction Detector prediction model

Table 4. Predictive performance of classification methods

Efficacy measure	Classification method		
	PSAD	Logistic regression	CHAID tree
AUC (95% CI)	77.8 (71.5–83.1)	78 (72–83.3)	83.3 (77.8–88.9)
Sensitivity (95% CI)	33.7 (24.2–44.3)	50 (39.4–60.6)	61.9 (51.2–71.8)
Specificity (95% CI)	93 (87.2–96.8)	88.4 (81.5–93.3)	90.7 (84.3–95.1)
PPV (95% CI)	77.5 (61.5–89.2)	75.4 (62.7–85.5)	82.6 (71.6–90.7)
NPV (95% CI)	66.3 (58.9–73.1)	71.2 (63.5–78.1)	76.9 (69.4–83.4)
Accuracy (95% CI)	68.3 (61.7–74.4)	72.4 (66–78.2)	78.7 (72.7–83.9)

AUC – area under the curve; CI – confidence interval; NPV – negative predictive value; PPV – positive predictive value; PSAD – prostate-specific antigen density; CHAID – *Chi*-squared Automatic Interaction Detector

model (5.3%) and the CHAID tree and the PSAD (5.5%) were significant (p = 0.011, and p = 0.002, respectively), and between LR and PSAD areas (0.2%) not significant (p = 0.931). Graphical assessments of the CHAID model calibration are presented in Figure 3. The model was well calibrated (R^2 = 0.997).

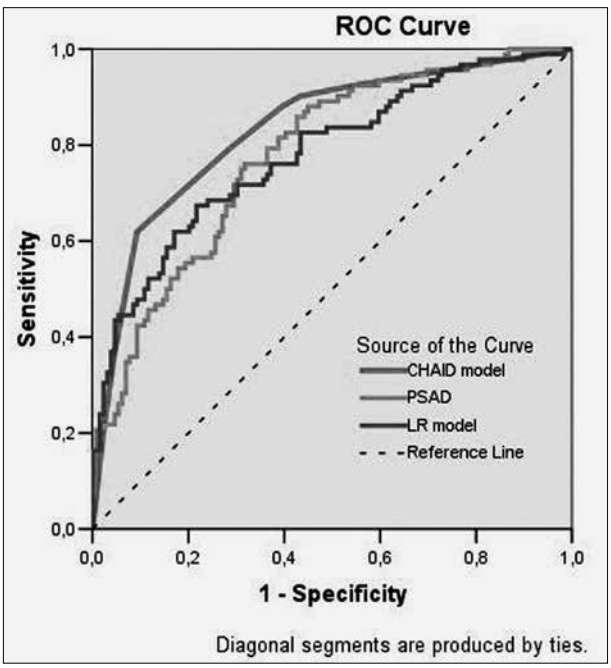

Figure 2. Receiver operating characteristic curves' analyses

PSAD – prostate-specific antigen density; LR – logistic regression; CHAID – Chi-squared Automatic Interaction Detector

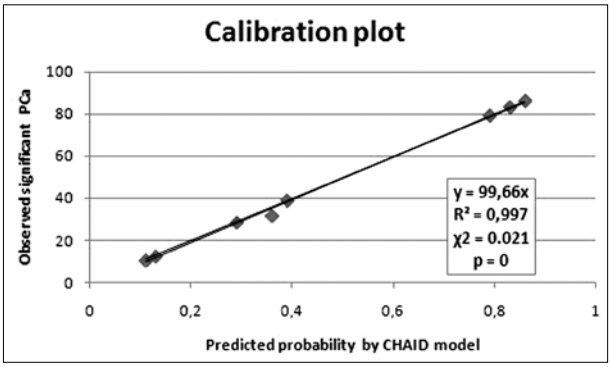

Figure 3. Calibration in the *Chi*-squared Automatic Interaction Detector method (CHAID)

In the decision curve analysis (Figure 4a), both models predicting significant PCa provided net benefit for threshold probabilities of approximately 11% or higher as compared with the strategy of biopsying all patients, or alternatively, biopsying no one. The CHAID model (red line) leads to the higher net benefit compared with the LR model (blue line) or the PSAD (green line). The reduction in the number of unnecessary biopsies per 100 patients is net of false negatives, without a decrease in the number of patients with significant PCa who duly have PCa. Also, in this case, the CHAID model (red line) outperformed the LR model (blue line) or the PSAD (green line) for threshold probabilities above approximately 12% and above 29% for PSAD (Figure 4b). For example, at a probability threshold of 15% and 30%, the use of the model reduces the number of unnecessary biopsies by 9 and 23 per 100 patients, respectively, without missing any significant PCa.

DISCUSSION

In the current study, we used the CART analysis to develop a prostate biopsy decision algorithm in patients referred due to an abnormal PSA or DRE finding, or both, regardless of the PSA level. The CART analysis selected PSAD as an indication for further work-up in several subclasses. Some common predictors (prostate volume, DRE, PSA) may serve in further risk stratification. The CHAID model has shown to have good discriminatory ability. It outperformed the logistic model and PSAD as an individual predictor. Application of the model would lead to notably superior clinical outcomes than the current strategy of biopsying all men with elevated PSA, and consequently resulted in the reduction number of unnecessary biopsies.

Previous existing models have established the criteria associated with the higher risk of significant PCa. They included age [7, 11, 12, 13, 15, 18, 19, 23], race [15, 23], digital rectal examination [7, 11, 12, 13, 15, 16, 17, 23], total PSA [5, 12, 13, 15, 16, 17, 19, 23], percentage of free PSA [5, 12, 13], PSAD [7, 18, 19], PHI [11], prostate volume [11, 12, 16–19], PSAD of the TZ [5], TZ volume [5], hypoechoic lesions on ultrasound [7, 17,19], biopsy history [11, 15, 16, 23] and family history [15]. A wide variety of different combinations of predictive factors have been identified. In line with previous studies, several of those predictors have reached statistical significance in the univariate or multivariate analysis or tree-based methods in our study. However, many of these parameters did not sustain their independent value. Nevertheless, according to the analysis, PSAD was the most decisive variable at the moment of classification. The PSAD has been suggested to differentiate benign from malignant prostate disease especially in cases belonging in the grey zone [3]. Although there is controversy about the cut-off of PSAD, our result showed that western reference (PSAD 0.15) has good sensitivity (92.4%) and only 3% of patients would have been missed, and at the same time 30% of unnecessary biopsies would have been avoided. In studies with similar design that included patients with serum PSA value of ≤ 10 ng/ml, PSAD greater or less than 0.158–0.165 was the main splitting criterion [18, 24]. However, these results do not support those of prior investigators such as Catalona et al. [6], who reported that the commonly used PSAD cut-off of 0.15 detected only 59% of cancers in men with normal DRE and PSA value of 4–10 ng/ml. These disparities can be explained by different populations and a diverse defining outcome. 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 [25].

We found that significant variables constructing the CHAID model were different (prostate volume, DRE, PSA) according to the PSAD level. In the patients with PSAD between 0.15 and 0.24, we demonstrated that prostate volume was the only useful parameter. It is in concordance

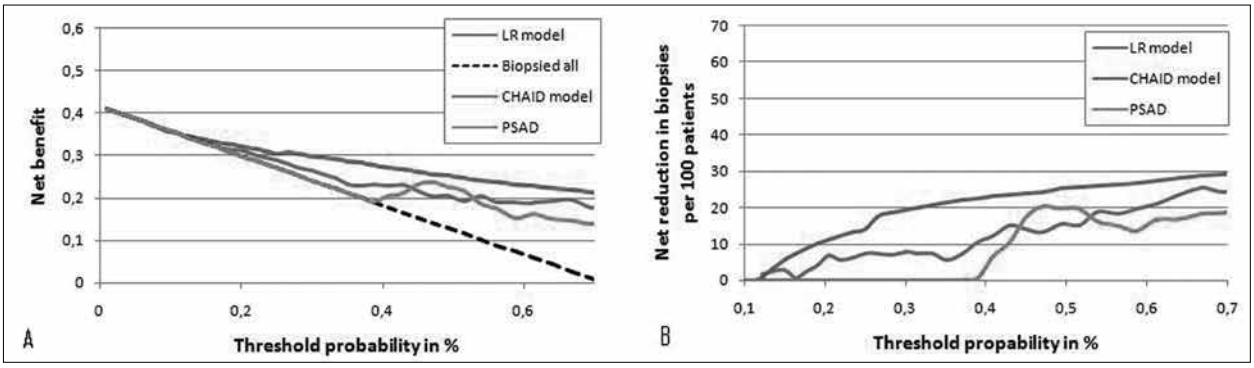

Figure 4. Decision curve analyses

PSAD – prostate-specific antigen density; LR – logistic regression; CHAID – *Chi*-squared Automatic Interaction Detector

with many studies that have shown a reduction in PCa risk with the increase in prostate size. The DRE is considered to be mandatory in the diagnosis and staging of PCa. This variable has reached clinical significance in some subclasses of our model, similar to other reports [7, 11, 12, 13, 15, 16, 17, 23]. Overall, this supports that clinical information and laboratory tests are not of equal importance for predicting the probability of a PCa-positive biopsy result at various PSA concentrations [24]. According to the PRIAS criteria, we found 8% of insignificant PCa, which is not in agreement with mathematical models that estimate that 23–42% of PSA-detected cancers are overdiagnosed [2, 26].

It was found that the accuracy of the present models were higher than the accuracy of many earlier ones. Our model resulted in an AUC of 83.3%, which is better than many others (73–82%) [7, 11, 12, 13, 16, 19], and similar to some other reports [9, 17]. However, metrics of accuracy do not address the clinical value of a model. Net benefit is a tool for evaluating the clinical implications of models [22]. However, determining a reasonable range of threshold probabilities is a critical aspect of net benefit approaches [27]. For PCa screening, a reasonable range of 10–40% was defined [22]. According to this criterion, the net benefit for the PSAD marker is equal to that for the "biopsy all" strategy for threshold probabilities below approximately 30%. This means that the best clinical outcome would be achieved by conducting the biopsy irrespective of the PSAD results across relevant threshold probabilities. On the other hand, in our decision curve analysis, we identified the range of threshold probabilities (> 11%) in which our models were of value. Furthermore, the decision tree is valuable because it defines two subgroups of patients who have a very low possibility of being cancer: (a) men who have PSAD below 0.15, and (b) men who have PSAD 0.15–0.24 ng/ml/ml, and prostate volume above 54 ml. In comparison with other clinically relevant risk assessment algorithms that showed a number of unnecessary biopsies, our model outperformed some [18], was comparable to some [11], and inferior to others [9, 10]. Our model showed excellent calibration but a correction for the misclassification might need to be made.

The limitation of this study resides in its retrospective design, in a single tertiary center with a relatively small patient cohort that restricted the generalization of the rules. Secondly, we included only those variables that were available to us. Because others 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 a clinically significant disease [28]. Next, the criteria for insignificant PCa are not generally accepted. A modern study suggests that not all Gleason 3 + 4 patients will have the aggressive form of the disease [29]. Finally, determination of prostate volume by transrectal ultrasound may vary considerably [30]. The lack of measurement precision of prostate volume has prevented the widespread clinical acceptance of PSAD. Nevertheless, to the best of our knowledge, to date, the CHAID analysis has not yet been used in the prediction of significant PCa in routine clinical settings. Our study provides clear evidence that the statistical model could be used in everyday clinical practice in order to decrease the number of unnecessary biopsies without substantially affecting the diagnosis of significant PCa. Furthermore, our CART analysis had a very small numbers of splits (7 splits), unlike others, which can be easily applied in clinical practice [19]. The prediction model represents another step towards accurately estimating individualized risk of PCa in a patient population lacking optimal prediction procedures.

CONCLUSION

In summary, CART analysis chose PSAD for the identification of patients at minimal risk for a positive biopsy. The model showed good discrimination, outperformed the LR model, and was the most important individual predictor. Despite favorable global metrics, PSAD has no clinical implication across relevant threshold probabilities. This prediction model could help avoid unnecessary biopsy and reduce overdiagnosis and overtreatment in clinical settings. However, before recommending its use in clinical practice, a larger and more complete database may be used to further clarify the magnitude of the model in terms of prediction of significant PCa.

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Анализа стабла одлучивања у предвиђању карцинома простате

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САЖЕТАК

Увод/Циљ Тестирање на антиген специфичан за простату (АСП) драматично је повисило број особа код којих се изводи биопсија простате. Међутим, оптимална стратегија селекције болесника за биопсију простате још није дефинисана. Циљ ове студије је креирање модела класификационог и регресионог стабла одлучивања (КРСО) који би се могао користити у предвиђању сигнификантних карцинома простате (*PCa*) током биопсије простате, код болесника са абнормалним АСП, дигиторектални налазом (ДРН), или оба, независно од нивоа АСП.

Методе Прикупљане су следеће клиничкопатолошке карактеристике болесника код којих је учињена ултразвуком вођена трансректална биопсија простате: старост, АСП, ДРН, волумен простате и густина АСП (ГАСП). Анализа КРСО је изведена коришћењем свих предиктора идентификованих у униваријатној логистичкој регресионој анализи. Процењени су различити аспекти перформанси и клиничке корисности предикционог модела.

Резултати У овој ретроспективној студији сигнификантни *PCa* су утврђени код 92 (41,6%) од укупно 221 болесника. Модел КРСО има три нивоа гранања на основу вредности ГАСП, као најпресуднije варијабле, волумена простате, ДРН и АСП. Наш модел је показао површину испод криве од 83,3%. Анализа криве одлучивања је показала да регресионо стабло у релевантном прагу вероватноћа пружа нетбенефит у поређењу са логистичким регресионим моделом, ГАСП и стратегијом извођења биопсије код свих болесника.

Закључак Модел помаже у смањењу непотребних биопсија без пропуштања било којег сигнификантног *PCa*.

Кључне речи: неоплазме простате; густина антигена специфичног за простату; стабло одлучивања