SERBIAN ARCHIVES OF MEDICINE Est.1872

Address: 1 Kraljice Natalije Street, Belgrade 11000, Serbia
☏+38111 4092 776, Fax: +38111 3348 653
E-mail: office@srpskiarhiv.rs, Web address: www.srpskiarhiv.rs

Paper Accepted* **ISSN Online 2406-0895**

Original Article / Оригинални рад

Miroslav M. Stojadinović[1†], Milorad M. Stojadinović[2], Damjan N. Pantić[1]

Decision tree analysis for prostate cancer prediction

Анализа стабла одлучивања у предвиђању карцинома простате

[1]KragujevacClinical Centre, Clinic of Urology and Nephrology, Department of Urology, Kragujevac, Serbia;
[2]University of Kragujevac, Faculty of Medical Sciences, Kragujevac, Serbia

Received: November 27, 2017
Accepted: May 18, 2018
Online First: June 1, 2018
DOI: https://doi.org/10.2298/SARH181127039S

*__Accepted papers__ are articles in press that have gone through due peer review process and have been accepted for publication by the Editorial Board of the *Serbian Archives of Medicine*. They have not yet been copy edited and/or formatted in the publication house style, and the text may be changed before the final publication.
Although accepted papers do not yet have all the accompanying bibliographic details available, they can already be cited using the year of online publication and the DOI, as follows: the author's last name and initial of the first name, article title, journal title, online first publication month and year, and the DOI; e.g.: Petrović P, Jovanović J. The title of the article. Srp Arh Celok Lek. Online First, February 2017.
When the final article is assigned to volumes/issues of the journal, the Article in Press version will be removed and the final version will appear in the associated published volumes/issues of the journal. The date the article was made available online first will be carried over.

†**Correspondence to:**
Miroslav M. STOJADINOVIĆ
Deparment of Urology, Clinic of Urology and Nephrology, Kragujevac Clinical Centre
Zmaj Jovina 30, 34000 Kragujevac, Serbia
E-mail:**midinac@gmail.com**

Decision tree analysis for prostate cancer prediction

Анализа стабла одлучивања у предвиђању карцинома простате

SUMMARY

Introduction/Objective Usage of serum prostate-specific antigen (PSA) test dramatically increases in 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 for an abnormal PSA, digital rectal examination (DRE), or both, regardless of PSa level.

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

Results In this retrospective study significant PCa was detected in 92 (41.6%) of a total of 221 patients. The CART model had 3 splits based on PSAD, as the most decisive variable, prostate volume, DRE, and PSA. Our model resulted in an area under the receiver operating characteristic curve of 83.3%. Decision curve analysis showed that regression tree provided net benefit for relevant threshold probabilities as compared with the logistic regression model, PSAD and strategy of biopsied all patients.

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

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

САЖЕТАК

Увод/Циљ Тестирање на простата специфични антиген (ПСА) драматично је повисила број особа код којих се изводи биопсија простате. Међутим, најоптималнија стратегија селекције болесника за биопсију простате још није дефинисанат. Циљ ове студије је креирање модела класификационог и регресионог стабла одлучивања (*CART*) који би се могао користити у предвиђању сигнификантних карцинома простате (*PCa*) током биопсије простате, код болесника са абнормалним ПСА, дигиторектални налазом (*DRE*), или оба, независно од нивоа ПСА.

Методе Прикупљане су следеће клиничкопатолошке карактеристика болесника код којих је учињена ултразвуком вођена трансректална биопсија простате: старост, ПСА, *DRE*, волумен простате, и густина ПСА (ПСАД). *CART* анализа 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. *CART* модел има три нивоа гранања на основу вредности ПСАД, као најпресудније варијабле, волумена простате, *DRE*, и ПСА. Наш модел је показао површину испод криве од 83.3%. Анализа криве одлучивања је показала да регресионо стабло у релевантном прагу вероватноћа пружа нет бенефит у поређењу са логистичким регресионим моделом, ПСАД, 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 простата специфичног антигена; стабло одлучивања

INTRODUCTION

Prostate cancer (PCa) is the second most frequently diagnosed malignancy and the sixth leading cause of cancer-associated mortality in men worldwide [1]. Usage of serum prostate-specific antigen (PSA) test dramatically increases in 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 biopsy. Multiple PSA derivatives have been advanced as early detection biomarkers, including age-specific PSA reference ranges, PSA density (PSAD) [3], PSA velocity [4], transition-zone (TZ) PSAD [5], percentage of free PSA [6], or presence of hypoechoic lesions on transrectal ultrasound (TRUS) [7]. The most advanced blood-based PCa biomarkers including [-2]proPSA, %p2PSA, Prostate Health Index (PHI) [8], 4-kallikrein panel [9] or urine-based biomarkers such as prostate cancer gene 3 (PCA3) and TMPRSS2:ERG (T2:ERG) gene fusions [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] provides better clinical performance than the results obtained with 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. So, best possible strategies for selecting appropriate patients for prostate biopsy have yet to be defined.

Classification and regression tree analysis (CART) were applied in urology especially for prostate cancer in the prediction of aggressive prostate cancer 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 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 traditional statistical method (logistic regression, LR) and individual most important predictor for predicting clinically significant PCa on biopsy in patients referred for an abnormal PSA, DRE, or both, regardless of PSA level.

METHODS

Patient population

This is a retrospective study carried out using the database of 239 patients at Clinical Centre Kragujevac, 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 data were collected about clinicopathological characteristics for each patient as regards prebiopsy assessment and included following: age, PSA, DRE, volume of prostate, PSAD, total number of cores taken, Gleason score, and number of positive cores 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 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 (UniCelDxI 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 5-10-MHz probe was used to obtain ultrasound data and prostate biopsy. 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 (range, two to 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 was used for demographic and baseline characteristics. Univariate and multivariate LR was used to identify and quantify the potential and independent predictors of significant PCa with Backward–Wald stepwise. The results of regressions were expressed in odds ratios (ORs) with 95% confidential interval (CIs).

CRT classification tree

The CHAID analysis was carried out on the whole sample using all predictors identified by univariate LR analysis. We selected 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 0.05. Chi-Square 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 stopping rules by the maximum tree depth of 3 levels and the minimum numbers of cases for nodes by specified that the parent node

must have at least 20 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. 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 area under the receiver operating characteristic (ROC) curve (AUC), sensitivity, specificity, positive (PPV), negative predictive value (NPV), accuracy, and calibration for CHAID model. The comparisons of AUC were performed using the method proposed by DeLong et al. [21].

Clinical usefulness was assessed by using 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). Assumption is made that the identification of clinically significant PCa would lead to biopsy. Net benefit is plotted against threshold probabilities compared with ‘Biopsy for all’ strategy and ‘Biopsy for none’.The interpretation of a decision curve is that the model with the highest net benefit should be chosen. We calculated and graphic net benefit in Excel using the recommended formula [22]. All other analyses were performed using SPSS version 23.0 (SPSS Inc., Chicago, IL). Statistical significance was set at $p < 0.05$.

RESULTS

Patients’ characteristics

A total of 221 patients were analyzed. Prostate cancer was detected in 100 (45.2%), but significant PCa detected in 92 (41.6%) of 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 5 risk factors displayed significant correlation with significant PCa (Table 2). During multivariable analysis three sustained their prognostic significance (Table 2). The analysis demonstrated 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 Fig. 1. There are 9 terminal and 5 non-terminal nodes, resulting from 3 "*if-then*" conditions. The most decisive variable at the moment of classification was the PSAD, which stratified patients in 4 classes in relation to the value: ≤ 0.15, 0.15–0.24, 0.24–1.47, and ≥1.47 ng/ml/ml, respectively. Ultimate nodi (node 1 and 4) are also terminal with low and very high prevalence of significant PCa (10.6% and 86.4%, respectively). The node two associated with PCa in 34.1% was further split on the basis of the volume prostate of higher or less or equal 54 ml. Larger prostate were 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%) was when DRE was abnormal. The node three associated with PCa in 57.3% 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%). The node 7 was further split on the basis of the PSA value: less or equal 8.2, 8.2–11.2, and ≥11.2 ng/ml (terminal node 11, 12, 13). The misclassification rates of the entire sample and of the cross-validated estimate were 21.3% vs. 29%, respectively. The overall model prediction accuracy of CHIAD model was 78.7%, and it was higher in absence of significant PCa (90.7%) than in significant PCa group (62%).

Diagnostic performance of PSA density 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 is to define the optimum cutoff value for PSA density. The diagnostic performance of different thresholds for PSAD is shown in Table 3. If the PSA density cutoff 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 biopsies 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 ROC curves difference between areas CHAID tree and LR model (5.3%) and CHAID tree and PSAD (5.5%) were significant (P = 0.011, and P = 0.002, respectively), and between areas LR and PSAD (0.2%) not significant (P = 0.931). Graphical assessments of CHAID model calibration are presented in Figure 3. The model was well calibrated (R^2=0.997).

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 biopsied all patients, or alternatively, biopsied no one. CHAID model (red line) leads to the higher net benefit compared with LR model (blue line) or 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, CHAID model (red line) outperformed LR model (blue line) or 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, without missing any of significant PCa.

DISCUSSION

In the current study, we used CART analysis to develop a prostate biopsy decision algorithm in patients referred for an abnormal PSA, DRE, or both, regardless of PSA level. CART analysis selected PSAD as an indication for further work-up in several subclasses. Some common predictors (volume prostate, DRE, PSA) may serve in further risk stratification. CHAID model have shown to have good discriminatory ability. It outperformed logistic model and PSAD as 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 criteria associated with 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 [19, 17, 7], 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 cutoff 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 avoid 30% of unnecessary biopsy. In studies that included patients with serum PSA 10 ng/ml or less with similar design, 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 Catalonaet al. [6], who reported that

the commonly used PSADcutoff of 0.15 detected only 59% of cancers in men with a normal DRE and PSA between 4.0 and 10.0 ng/ml. These disparities can be explained by different populations and 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 CHAID model were different (volume prostate, DRE, PSA) according to PSAD level. In the patients with PSAD between 0.15 and 0.24, we demonstrated that only prostate volume was useful parameter. It is in concordance with many studies that have shown a reduction in prostate cancer risk with increasing prostate size. The DRE is considered to be mandatory in the diagnosis and staging of prostate cancer. 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 prostate cancer-positive biopsy result at various PSA concentrations [24]. According to PRIAS criteria [2] we found 8% of insignificant PCa, which are not in agreement with mathematical models that estimate 23–42% of PSA-detected cancers are overdiagnosed [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 other (73-82%) [7, 11, 12, 13, 16, 19], and similar to 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]. But, determining a reasonable range of threshold probabilities is a critical aspect of net benefit approaches [27]. For PCa screening reasonable range of 10–40% was defined [22]. According to this criterion the net benefit for the marker PSAD is equal than that for the strategy of “biopsy all” for threshold probabilities below about 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 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 men who have PSAD between 0.15–0.24 ng/mL/mL, and volume prostate above 54 ml. In comparison with other clinically relevant risk assessment algorithms that showed a number of unnecessary biopsy, our model outperformed some [18], was comparable [11] and inferior than others [9, 10]. Our model shown 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 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 others advanced biomarkers were not available, we

were unable to assess its 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 [28]. Next, criteria for insignificandPCa are not generally accepted. Modern study suggests that not all Gleason 3+4 will have aggressive disease [29]. Finally, determination of prostate volume by TRUS may vary considerably [30]. The lack of measurement precision of prostate volume has prevented the widespread clinical acceptance of PSAD. Nevertheless, to our best knowledge, up to now, 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 unnecessary biopsies without substantially affecting the diagnosis of significant PCa. Furthermore, our CART analysis had very small numbers of splits unlike other (7 splits) [19] that can be easily applied in clinical practice. 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 a PSAD for the identification of patients at minimal risk for a positive biopsy. The model showed good discrimination and outperformed LR model and individual the most important predictor. Despite favourable global metrics, PSAD have 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 the significant PCa.

ACKNOWLEDGMENT

The authors were financially supported through a research grant No. 175014 of the Ministry of Education, Science and Technological Development of the Republic of Serbia. The authors thank the Ministry for this support.

REFERENCES

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015 Mar;65(2):87-108. doi:10.3322/caac.21262. PMID: 25651787.

2. Bul M, Zhu X, Valdagni R, Pickles T, Kakehi Y, Rannikko A, et al. Active surveillance for low-risk prostate cancer worldwide: the PRIAS study. Eur Urol. 2013;63(4):597-603. doi: 10.1016/j.eururo.2012.11.005. PMID: 23159452.

3. Benson MC, Whang IS, Pantuck A, Ring K, Kaplan SA, Olsson CA, et al. Prostate specific antigen density: a means of distinguishing benign prostatic hypertrophy and prostate cancer. J Urol. 1992 Mar;147(3 Pt 2):815-6. PMID:1371554.

4. Carter HB, Pearson JD. Prostate-specific antigen velocity and repeated measures of prostate-specific antigen. Urol Clin North Am. 1997 May;24(2):333-8. PMID: 9126231.

5. Djavan B, Remzi M, Zlotta A, Seitz C, Snow P, Marberger M. Novel artificial neural network for early detection of prostate cancer. J Clin Oncol. 2002; 20(4):921-9. PMID: 11844812.

6. Catalona WJ, Partin AW, Slawin KM, Brawer MK, Flanigan RC, Patel A, et al. Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: a prospective multicenter clinical trial. JAMA. 1998;279(19):1542-7. PMID: 9605898.

7. Garzotto M, Hudson RG, Peters L, Hsieh YC, Barrera E, Mori M, et al. Predictive modeling for the presence of prostate carcinoma using clinical, laboratory, and ultrasound parameters in patients with prostate specific antigen levels < or = 10 ng/mL. Cancer. 2003 Oct 1;98(7):1417-22. PMID: 14508828.

8. Filella X, Giménez N. Evaluation of [-2] proPSA and Prostate Health Index (phi) for the detection of prostate cancer: a systematic review and meta-analysis. Clin Chem Lab Med. 2013;51(4):729-39. doi:10.1515/cclm-2012-0410. PMID: 23154423.

9. Parekh DJ, Punnen S, Sjoberg DD, Asroff SW, Bailen JL, Cochran JS, et al. SM. A multi-institutional prospective trial in the USA confirms that the 4Kscore accurately identifies men with high-grade prostate cancer. Eur Urol. 2015;68(3):464-70. doi: 10.1016/j.eururo.2014.10.021. PMID: 25454615.

10. Tomlins SA, Day JR, Lonigro RJ, Hovelson DH, Siddiqui J, Kunju LP, et al. Urine TMPRSS2:ERG Plus PCA3 for Individualized Prostate Cancer Risk Assessment. Eur Urol. 2016;70(1):45-53. doi: 10.1016/j.eururo.2015.04.039. PMID: 25985884.

11. Lughezzani G, Lazzeri M, Larcher A, Lista G, Scattoni V, Cestari A, et al. Development and internal validation of a Prostate Health Index based nomogram for predicting prostate cancer at extended biopsy. J Urol. 2012;188(4):1144-50. doi: 10.1016/j.juro.2012.06.025. PMID: 22901589.

12. Chun FK, Graefen M, Briganti A, Gallina A, Hopp J, Kattan MW, et al. Initial biopsy outcome prediction--head-to-head comparison of a logistic regression-based nomogram versus artificial neural network. Eur Urol. 2007;51(5):1236-40; PMID: 16945477.

13. Karakiewicz PI, Benayoun S, Kattan MW, Perrotte P, Valiquette L, Scardino PT, et al. Development and validation of a nomogram predicting the outcome of prostate biopsy based on patient age, digital rectal examination and serum prostate specific antigen. J Urol 2005; 173: 1930-4. PMID: 15879784.

14. Stephan C, Cammann H, Semjonow A, Diamandis EP, Wymenga LF, Lein M, et al. Multicenter evaluation of an artificial neural network to increase the prostate cancer detection rate and reduce unnecessary biopsies. Clin Chem. 2002 Aug;48(8):1279-87. PMID: 12142385.

15. Ankerst DP, Hoefler J, Bock S, Goodman PJ, Vickers A, Hernandez J, et al. Prostate Cancer Prevention Trial risk calculator 2.0 for the prediction of low- vs high-grade prostate cancer. Urology. 2014;83(6):1362-7. doi: 10.1016/j.urology.2014.02.035. PMID: 24862395.

16. Roobol MJ, Schröder FH, Hugosson J, Jones JS, Kattan MW, Klein EA, et al. Importance of prostate volume in the European Randomised Study of Screening for Prostate Cancer (ERSPC) risk calculators: results from the prostate biopsy collaborative group. World J Urol. 2012; 30(2):149–55. doi: 10.1007/s00345-011-0804-y.PMID: 22203238

17. Park JY, Yoon S, Park MS, Choi H, Bae JH, Moon DG, et al. Development and External Validation of the Korean Prostate Cancer Risk Calculator for High-Grade Prostate Cancer: Comparison with Two Western Risk Calculators in an Asian Cohort. PLoS One. 2017;12(1):e0168917. doi: 10.1371/journal.pone.0168917. PMID: 28046017.

18. Spurgeon SE, Hsieh YC, Rivadinera A, Beer TM, Mori M, Garzotto M. Classification and regression tree analysis for the prediction of aggressive prostate cancer on biopsy. J Urol. 2006 Mar;175(3 Pt 1):918-22. PMID:16469580.

19. Garzotto M, Beer TM, Hudson RG, Peters L, Hsieh YC, Barrera E, et al. Improved detection of prostate cancer using classification and regression tree analysis. J Clin Oncol. 2005;23(19):4322-9. DOI: 10.1200/JCO.2005.11.136. PMID: 15781880.

20. Briganti A, Passoni N, Ferrari M, Capitanio U, Suardi N, Gallina A, et al. When to perform bone scan in patients with newly diagnosed prostate cancer: external validation of the currently available guidelines and proposal of a novel risk stratification tool. Eur Urol. 2010;57(4):551-8. doi:10.1016/j.eururo.2009.12.023. PMID: 20034730.

21. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988;44(3):837-45. PMID: 3203132.

22. Vickers AJ. Decision analysis for the evaluation of diagnostic tests, prediction models and molecular markers. Am Stat. 2008;62(4):314-320. PMID: 19132141.

23. Moyer VA; U.S. Preventive Services Task Force. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2012;157(2):120-34. doi: 10.7326/0003-4819-157-2-201207170-00459. PMID: 22801674.

24. Hwang SH, Pyo T, Oh HB, Park HJ, Lee KJ. Combined application of information theory on laboratory results with classification and regression tree analysis: analysis of unnecessary biopsy for prostate cancer. Clin Chim Acta. 2013;415:133-7. doi: 10.1016/j.cca.2012.10.012. PMID: 23078854.

25. Milkovic B, Dzamic Z, Pejcic T, Kajmakovic B, Nikolic D, Cirovic D, et al. Evaluation of free-to-total prostate specific antigen (F/T PSA), prostate specific antigen density (PSAD) and (F/T)/PSAD sensitivity on reduction of unnecessary prostate biopsies for patients with PSA in gray zone. Ann Ital Chir. 2014;85(5):448-53. PMID: 25599711.

26. Draisma G, Etzioni R, Tsodikov A, Mariotto A, Wever E, Gulati R, et al. Lead time and overdiagnosis in prostate-specific antigen screening: importance of methods and context. J Natl Cancer Inst. 2009;101(6):374-83. doi: 10.1093/jnci/djp001. PMID: 19276453.

27. Vickers AJ, Van Calster B, Steyerberg EW. Net benefit approaches to the evaluation of prediction models, molecular markers, and diagnostic tests. BMJ. 2016;352:i6. doi: 10.1136/bmj.i6.PMID: 26810254

28. Bjurlin MA, Taneja SS. Standards for prostate biopsy. Curr Opin Urol. 2014;24(2):155-61. doi: 10.1097/MOU.0000000000000031. PMID: 24451092.

29. Schiavina R, Borghesi M, Brunocilla E, Romagnoli D, Diazzi D, Giunchi F, et al. The biopsy Gleason score 3+4 in a single core does not necessarily reflect an unfavourable pathological disease after radical prostatectomy in comparison with biopsy Gleason score 3+3: looking for larger selection criteria for active surveillance candidates. Prostate Cancer Prostatic Dis. 2015;18(3):270-5. doi: 10.1038/pcan.2015.21. PMID: 26055663.

30. Kim SB, Cho IC, Min SK. Prostate volume measurement by transrectal ultrasonography: comparison of height obtained by use of transaxial and midsagittal scanning. Korean J Urol. 2014;55(7):470-4. doi: 10.4111/kju.2014.55.7.470. PMID: 25045446.

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

Characteristics	All	BPH / Insignificant PCa (n = 129)	Significant PCa (n = 92)	p-value
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 (%)	35 (15.8)		35 (15.8)	NA

BPH – benign prostatic hyperplasia; 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		Multivariable 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
Volume prostate	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

Table 3. Diagnostic performance of PSA density at diverse cutoff values

PSAD cut-off value	p	n	n	p	Sensitivity (%)	Specificity (%)	Biopsy spread (%)	Missed (%)
0.07	2		4	15	100	10.85	6	0
0.10	0		9	10	97.83	14.73	10	2
0.15	5		9	0	92.39	45.74	25	8
0.18	2	0	4	5	89.13	49.61	33	11
0.21	9	3	2	7	85.87	55.81	38	14
>0.25	9	3	9	0	75	68.99	51	25

TP – true positive; FN – false negative; TN – true negative; FP – false positive

Table 4. Predictive performance of classification method

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

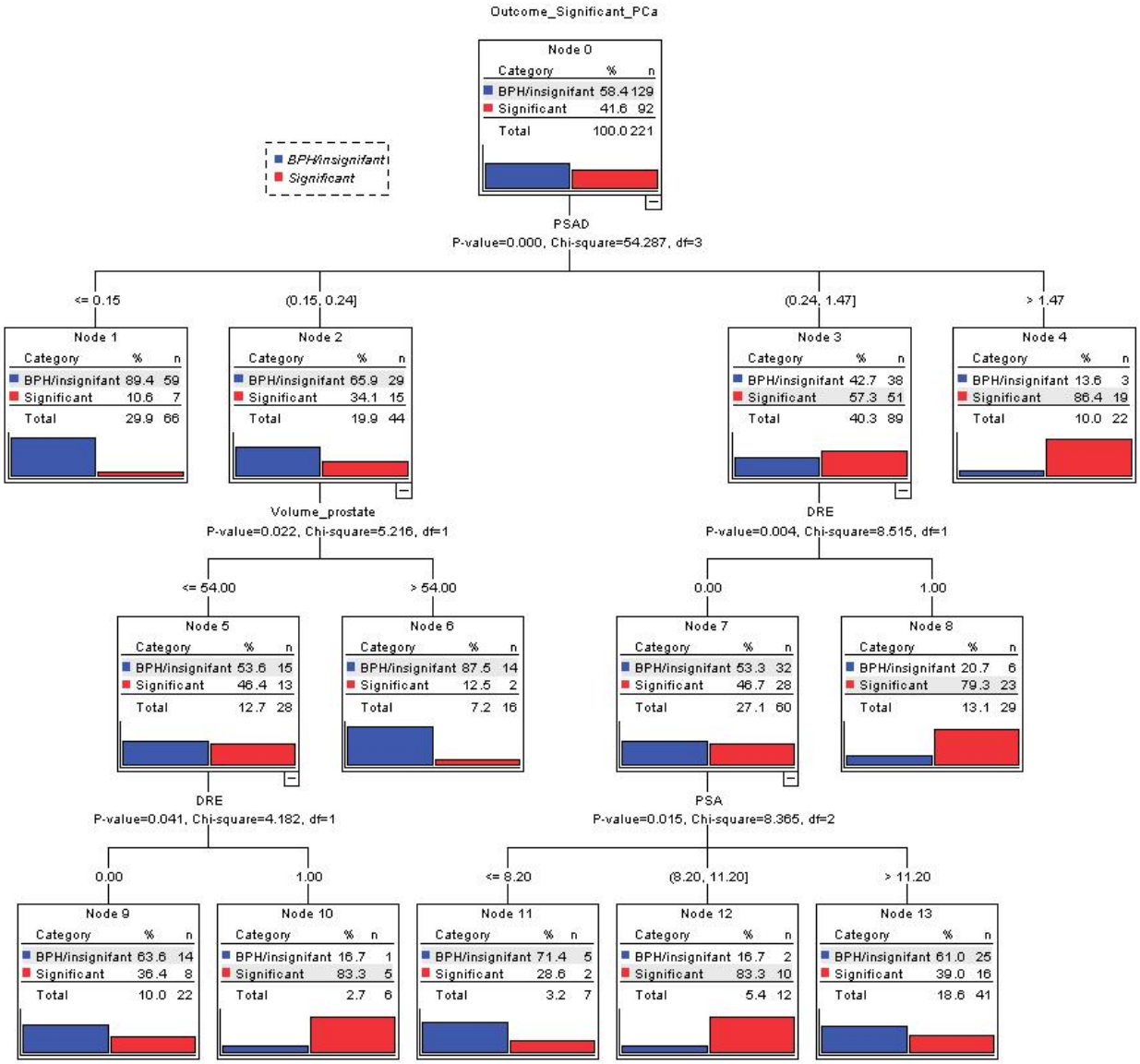

Figure 1. A tree-based CHAID prediction model

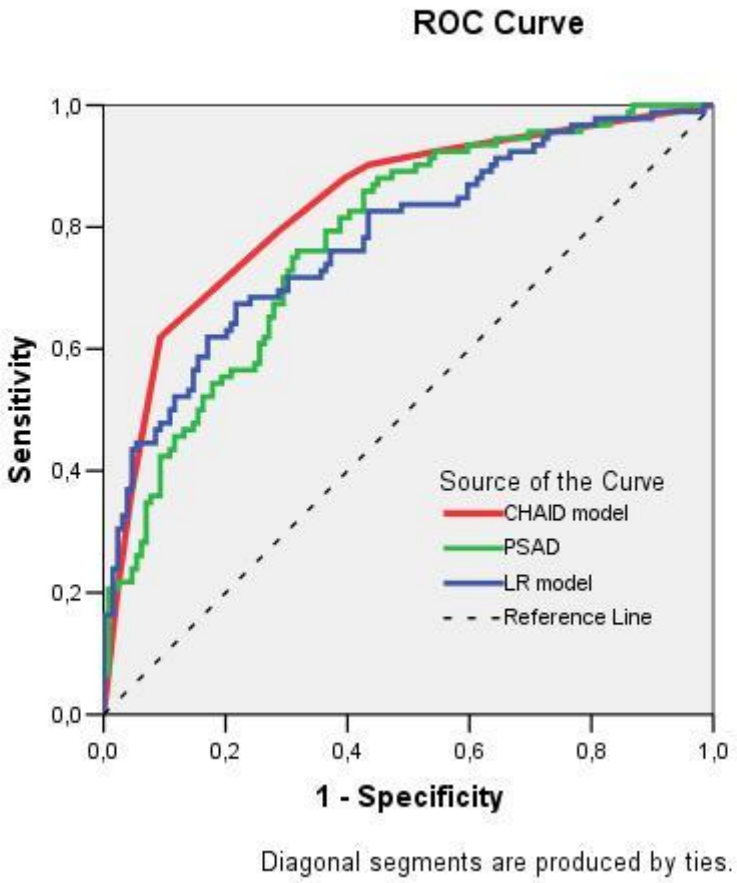

Figure 2. ROC curves analyses

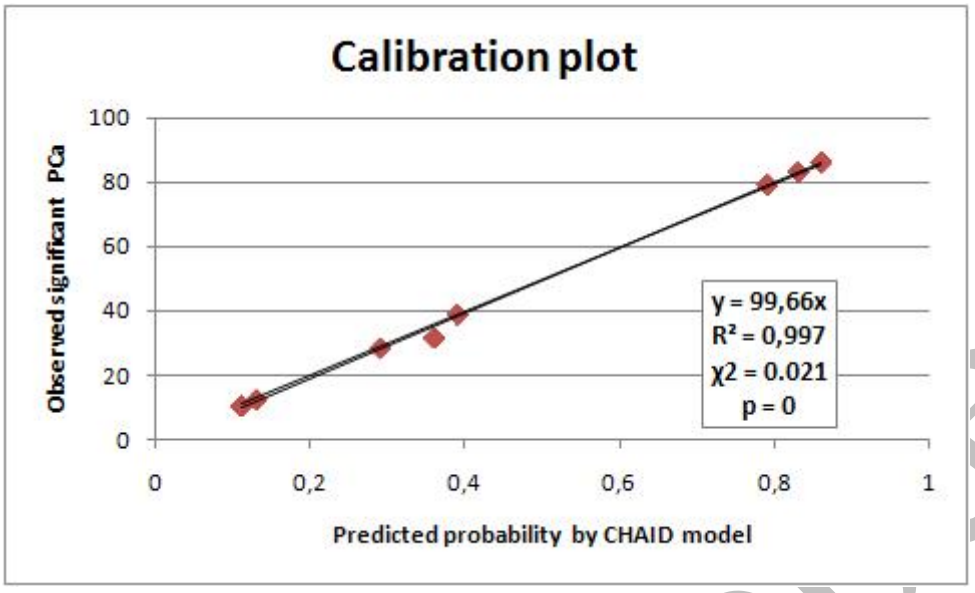

Figure 3. Calibration in CHAID method

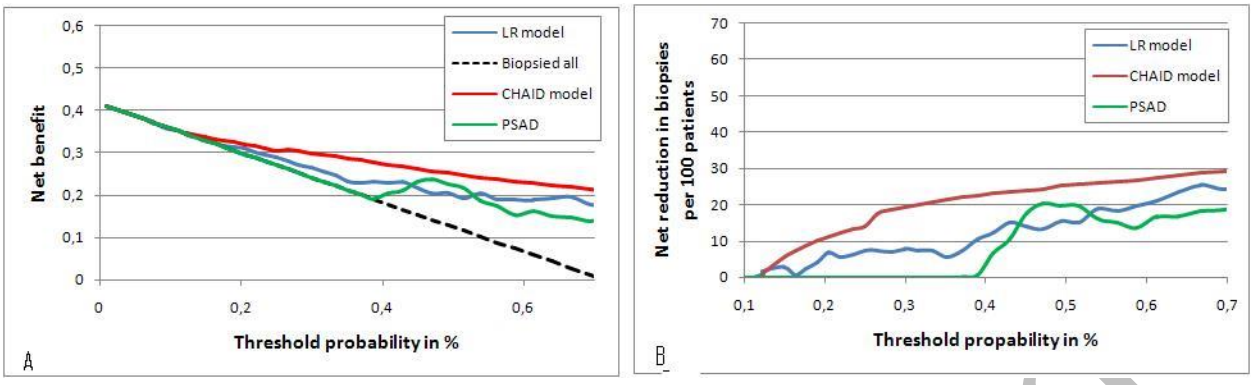

Figure 4. Decision curve analyses

