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ORIGINAL ARTICLE

Comparison of methods for prediction of prostate cancer in Turkish men with PSA levels of 0-10 ng/mL

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Summary

Purpose: *Several concepts to improve the diagnostic accuracy of prostate specific antigen (PSA) for prediction of prostate cancer have been studied. The aim of this study was to examine and compare the methods used for improving the diagnostic accuracy of PSA in a country with low incidence of prostate cancer.*

Methods: *997 patients with prostate biopsy were included into study. Predictive models using PSA, PSA density (PSAD), free PSA/total PSA (f/tPSA), binary logistic regression (LR) analysis, artificial neural networks (ANNs), and decision trees (DTs) have been developed. For LR, ANNs and DTs, a validation group consisting of 241 cases was reserved.*

Results: *193 (19%) biopsies out of 997 showed prostatic cancer. Median PSAD in patients with malignant and benign lesions were 0.21 and 0.16, respectively (p <0.001). According to 25% f/tPSA cut-off level, 18.4% of the patients with PSA <25% and 16.0% of the patients with PSA > 25% had prostate cancer (p=0.423). Receiver operating characteristics (ROC) area under the curve (AUC) values for PSA, PSA density, f/tPSA, LR, ANNs, and DTs were 0.587, 0.625, 0.560, 0.678, 0.644, and 0.698, respectively. ROC AUCs in the validation group for LR, ANNs and DTs were 0.717, 0.516 and 0.629 respectively.*

Conclusions: *For cases with f/tPSA < 25%, no increased probability for prostatic carcinoma was observed. Multivariate models have higher AUCs than PSA, PSAD or f/tPSA. LR, DTs and ANNs showed similar results, however application of ANNs to the validation group produced a significantly lower AUC, limiting the value of ANNs in this situation.*

Key words: decision trees, logistic models, neural networks (computer), prostatic neoplasms, prostate specific antigen, Turkey

Introduction

In men, the most common malignant tumor is prostatic adenocarcinoma (186,320 new cases, 28,660 deaths estimated in USA in 2008) [1]. Luckily, there are some predictors used for early detection of prostatic carcinoma. Serum PSA level, age, digital rectal examination (DRE), and clinical symptoms are helpful for early detection of this tumor [2].

When a patient is suspected to have a prostate tumor, a biopsy from the prostate is advised by the physician. Sometimes, because of the presence of strong indicators such as a very high serum PSA level, the decision for biopsy is easy. However, when the findings are in the grey zone, physicians and patients have to make a choice between the risk of missing an early detection of a tumor and the risk of an unnecessary biopsy [3]. There are several studies [3,4] trying to establish methods to improve the sensitivity and specificity of different examinations in these grey zone cases.

Generally, a PSA level between 4-10 ng/ml is accepted as having a 70% sensitivity and a 70% specificity [4]. Since 1989, several concepts to further improve the diagnostic accuracy of PSA have been developed with the aim of avoiding unnecessary biopsies. The use of PSAD [5-7] and the ratio of f/tPSA [8,9] have yielded promising results.

Another approach to predict prostatic carcinoma is to prepare nomograms [10-13]. A nomogram (or nomograph) is a graphical calculating device, a 2-di-

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mensional diagram designed to allow the approximate graphical computation of a function. It can be based on any type of function, such as logistic regression or Cox regression models. Binary logistic regression (LR)-based nomograms have been reported to be the most useful [14,15].

The use of DT in this problem has also been examined in several studies [16-18]. There are several algorithms for building DTs. These algorithms build DT structures and classify subjects into several risk levels. They can be used to simply explore data, identify possible high-risk subgroups, and uncover interactions or effect modifications among prognostic factors. The most widely known is the classification and regression tree (CRT, also known as CART).

ANNs is another method which intended to increase the predictive value of PSA. The results of relevant studies [19-25] show that ANNs may be useful in the prediction of prostatic carcinoma. However, the nature of ANNs limits their practical applicability. These models are not amenable to a paper-based, portable and clinically applicable format. ANNs require computer support since they require complex calculations. Therefore, they cannot be distributed to a wide array of clinical users in a format similar to prostate cancer nomograms [13].

In the USA the estimated annual incidence of prostatic carcinoma is 161 per 100,000 men [1]. However, prostatic carcinoma is an indolent disease which can be silent for years. It is a cancer all men will get if they live long enough [26]. An autopsy study in men also serves to emphasize the critical relationship of prostate cancer with age; 2% of men in their twenties had prostate cancer, rising steadily and linearly with each decade until 64% had prostate cancer in their sixties [27]. Most of the cases are not known, and they usually die because of other causes after decades. Some authors suspect that overtreatment for prostate cancer is carried out caused by the use of PSA levels in the USA [26].

In an epidemiologic study performed in Izmir, Turkey, the incidence of prostate cancer was 4.2 per 100,000 male population, similar to that observed in other Asian populations. The incidence of prostate cancer varies widely between countries and ethnic groups, and differences in genes associated with androgen metabolism or inherited susceptibility may explain some of this variability. The incidence in Turkish men who have migrated to Australia was 6-fold higher, suggesting that underdiagnosis accounts for the low recorded rates, which are readily inflated by examination of prostatic tissue obtained during transurethral prostatectomies, or by PSA screening [28]. Another cause of this drastic difference in rates may be overdiagnosis in USA [26]. The value of predictive tests is closely related to the prevalence of the disease. Naturally, the prevalence of prostatic carcinoma may change according to geographical location and time.

The aim of this study was to examine and compare the methods used for improving the diagnostic accuracy of serum PSA in Turkey, a country with low incidence of prostate cancer.

Methods

Patients

All the transrectal ultrasound (TRUS)-guided prostatic biopsy cases who were admitted to Akdeniz University Hospital, Department of Urology, between January 2000-April 2007 were retrospectively evaluated. TRUS-guided biopsy could be performed only in Akdeniz University in Antalya district which has a population around 1,800,000. Included were 997 patients whose serum PSA level ranged between 0 and 10. In patients with multiple biopsies only the first one was included in the study.

Data

Akdeniz University Hospital Information System (HIS) and the patients' medical records of the Department of Urology were used as data sources. HIS contains the demographic information about all patients, laboratory data of the last 8 years, and patient pathology reports. The prostate volume was calculated by the ellipsoid formula (length [cm] * width [cm] * height [cm] * p/6) [29].

Statistical analysis

SPSS 15.0 (Statistical Package for Social Sciences, SPSS Inc, Chicago, Illinois, USA) was used for the statistical analyses including chi-square test, Mann-Whitney U test and DTs. Some specifications and additional software are listed below:

Logistic regression analysis: Forward conditional stepwise analysis with 0.5 entry and 0.10 removal criteria was performed. Hosmer-Lemeshow goodness of fit test was also performed for each model. Forward and backward conditional stepwise methods were applied because of multicollinearity of the variables. The forward method was selected because of better performance in Hosmer-Lemeshow goodness of fit test.

Decision trees: In the analysis, the dependent variable was diagnosis which is composed of two class-

es, namely benign and malignant. Independent variables were age (numeric), PSA (numeric), free PSA (numeric), percent free PSA (numeric), DRE I (DRE I, class I: negative, class II: suspicious, class III: positive), DRE II (class I: negative, class II: suspicious or positive). CRT algorithm in SPSS was used for decision tree classification.

Artificial neural networks: The ANN program SimMine (SimWorld Limited, London, UK, www.simworld.co.uk) was used in this study. The system uses the back-propagation algorithm. A design with 3 hidden nodes was used and a total of 5300 iterations were performed.

Validation group: For ANN, LR, and DT, the data set was divided into a study group and a validation group. Near one-fourth of the cases (241 of 997 cases) were reserved as the validation group.

Results

The general patient characteristics are shown in Table 1.

Patients were classified according to their DRE result and prebiopsy serum PSA level. The results are shown in Table 2.

Prostate volume data was available for 946 patients. The median PSAD densities in patients with malignant and benign conditions were 0.21 and 0.16, respectively ($p < 0.001$).

fPSA serum level was available in 750 patients. According to 25% f/tPSA cut-off level, 18.4% of the patients with PSA < 25% and 16.0% of the patients with PSA >25% had prostate cancer ($p=0.423$). The sensitivity for 25% cut-off value was 0.71.

Because some patients did not have TRUS and/or fPSA results, 3 different LR analyses were performed. The summary of these analyses is shown in Table 3.

In the ANN model, when the cut-off value was taken as 0.2, the system had 0.95 sensitivity and 0.33 specificity for the study group. However, the validation group failed to show a statistically significant ROC AUC.

A DT with 7 terminal nodes was obtained. One of these nodes included no malignant case and 3 of them included malignant cases over 20%.

The summary of the methods applied to cases is shown in Table 4.

Table 1. General characteristics of the cases

Characteristics	*n*	*Mean*	*Standard deviation*	*Median*	*Minimum*	*Maximum*
Age (years)	997	63.3	8.3	63.0	38	88
PSA (ng/ml)	997	5.6	2.6	6.0	0.05	10
Free PSA	750	1.1	0.8	1.0	0.03	6.8
Free/total PSA	750	23.0	13.7	20.0	1	100
Volume	946	33.0	17.6	28.8	2.0	151.5
PSA density	946	0.20	0.13	0.17	0.01	1.31

Table 2. Percent of malignant and benign biopsy results according to prebiopsy PSA level and digital rectal examination (DRE)

PSA (ng/ml)	*DRE (–)*			*DRE (+)*			*Total*		
	Benign	*Malignant*	*Subtotal*	*Benign*	*Malignant*	*Subtotal*	*Benign*	*Malignant*	*Total*
0-2.5, n (%)	24 (89)	3 (11)	27 (100)	122 (85)	22 (15)	144 (100)	146 (85)	25 (15)	171 (100)
2.51-4, n (%)	17 (89)	2 (11)	19 (100)	68 (88)	9 (12)	77 (100)	85 (89)	11 (12)	96 (100)
4.01-6, n (%)	125 (92)	11 (8)	136 (100)	83 (78)	24 (22)	107 (100)	208 (86)	35 (14)	243 (100)
6.01-10, n (%)	245 (83)	49 (17)	294 (100)	120 (62)	73 (38)	193 (100)	365 (75)	122 (25)	487 (100)
Total, n (%)	411 (86)	65 (14)	476 (100)	393 (75)	128 (25)	521 (100)	804 (81)	193 (19)	997 (100)

Table 3. Results of three logistic regression sets

	N	*Input variables*	*Significant variables*
LR1	525	Age, PSA, fPSA, f/t PSA, prostate volume, PSAD, DRE, TRUS	Age, PSA, PSAD, DRE
LR2	562	Age, PSA, fPSA, f/t PSA, DRE	Age, PSA, DRE
LR3	756	Age, PSA, DRE	Age, PSA, DRE

LR: logistic regression, f/tPSA: free/total PSA, PSAD: PSA density, DRE: digital rectal examination, TRUS: transrectal ultrasonography

Table 4. Summary of the methods applied to the cases

Method	*n*	*AUC*	*95% CI*	*p-value*	*Validation AUC*
PSA	997	0.587	0.543-0.631	<0.001	–
PSAD	946	0.625	0.577-0.673	<0.001	–
f/tPSA	750	0.560	0.504-0.616	0.031	–
LR1	525	0.678	0.625-0.731	<0.001	0.717
LR2	562	0.660	0.608-0.712	<0.001	0.656
LR3	756	0.661	0.609-0.712	<0.001	0.662
ANN	756	0.644	0.596-0.692	<0.001	0.516
DT	756	0.698	0.653-0.743	<0.001	0.629

PSAD: PSA density, f/tPSA: free/total PSA, LR: logistic regression, ANN: artificial neural network, DT: decision tree, AUC: area under the curve, CI: confidence interval

Discussion

Prediction studies with the help of PSA in prostate cancer is important because PSA is the first serum marker which can be used in cancer screening and the experience from these studies [7-13, 15-25] can be used in future possible cancer markers. Despite the importance of predicting prostate cancer, so far there are no studies evaluating a variety of methods on the same data set. Additionally, the problem has not been studied sufficiently in detail on the Turkish population.

The present study included 997 biopsied patients. A small fraction of the patients in the included data set were deficient of TRUS data, although all of them had TRUS-guided biopsy. The strong aspect of the study is that it reflects one geographic region, Antalya district, because nearly all the patients in this region were referred to Akdeniz University hospital which had the only TRUS centre in the region during the study period.

In this study, analysis of the cases whose PSA levels ranged between 0 and 10 was performed because it is widely accepted that a substantial proportion of individuals have prostate cancer if their PSA is over 10 and hence a biopsy should be performed. The grey zone is in the 0-10 range, so further evaluation of these persons may reveal useful results.

According to previous studies, the carcinoma rate is 10-20%, and 25% for serum PSA levels 2.5-4, and 4-10 ng/ml, respectively, in DRE-negative patients [30]. The corresponding rates in our study were 11 and 14%. The incidence of this disease is lower in our country, and the rates may reflect the effect of the incidence [28]. However, in our study the malignancy rate was unexpectedly high (11%) in 0-2.5 range, in contrast to a previous study that reported a rate under 2% [4]. An explanation of this result could possibly be connected with the absence of screening in our country. The patients in this range must be clinically symptomatic cases who complain to their physician of lower urinary tract symptoms.

In the 0-10 ng/ml PSA range, PSAD in malignant (median 0.21) and benign (median 0.16) cases was statistically different. This result shows the value of PSAD also in the problematic range of PSA.

A fPSA >25% is 95% sensitive in excluding prostate cancer when PSA values are in the ambiguous range of 4-10 ng/ml (4-10 μg/L) [8]. fPSA serum level was available in 750 of our patients. Of the cases with f/tPSA ratio < 25%, 18% were malignant, whereas-of the remaining-16% were malignant. The difference was not statistically significant. The sensitivity for 25% cut-off value was 0.71 in contrast to the reported 0.95 value [8]. The suggested 25% threshold was not predictive in our series. ROC AUC for f/tPSA (0.560, p=0.031) could not show a powerful predictive value. According to literature, several pre-analytical and clinical factors may influence the f/tPSA ratio, e.g. instability of fPSA both at 4° C and at room temperature, assay characteristics (equimolar vs. skewed response), and a "dilution effect" in large prostates due to concomitant benign prostate hyperplasia (BPH) [31].

In this study, multivariate models, namely LR, ANNs and DTs had higher AUCs than PSA, PSAD or f/tPSA. LR analysis of the cases showed that, in the first LR set, f/tPSA could not take place in multivariate model, but age, PSA, PSAD, and DRE were significant. In a similar previous study which did not contain free/total PSA in the analysis, age, PSAD, DRE, and TRUS were significant variables [11]. Another study which did not contain f/tPSA in the analysis revealed only prostate volume as significant variable, a quite different result from our study [32]. In the second and third LR analyses, age, PSA and DRE were significant. The ROC AUCs of 3 LR sets were 0.678, 0.660, and 0.661, respectively. The first LR analysis seemed most successful, but the presence of PSAD in the model limited its practical use because, when TRUS is performed, taking prostate biopsy is an easy intervention. The other 2 sets had very close ROC AUCs (0.660 and 0.661), which were slightly lower compared with a previous study in which it was 0.73 [11].

ANN was another method that was applied in this study. The evaluation in the study group revealed good results with an AUC ROC value of 0.644, however it failed to show a statistically significant performance in the validation group. This result does not confirm previous studies which reported successful ANN results [20-23]. The reason for this difference may be defects in our ANN design that might have caused overfitting [23]. Overfitting is a frequent complication of classification algorithms. In case of overfitting, the system

is adjusted to learn a specific training data rather than producing generalized results [33]. Further studies with different number of layers and/or neurons and different number of iterations may produce more successful results.

A summary of the multivariate approaches as comparisons of ROC AUCs have shown that 3 LR methods, DT and ANN have very close results, however the application of ANN in the validation group showed a significantly lower AUC, limiting the value of ANN use for prediction of prostate cancer.

The patients whom we evaluate are usually symptomatic patients, as screening is not common in our country. So our sample does not reflect the real patient profile in the region. Additionally, the sample of the study was mainly from the Southwest Anatolia, so that the results may not be applicable to the whole country. A screening study for the Turkish population is needed for a more reliable profile. This study was retrospective, so some data could not be obtained. Body mass index and prostate carcinoma in relatives were shown as important predictors in some studies [34].

According to multivariate analyses, age, serum PSA level and DRE seem to be most important variables for prediction of prostatic carcinoma in our study. The models which contain f/tPSA and PSAD could not demonstrate a prominent superiority compared to models with only age, PSA and DRE. For the cases with f/tPSA < 25%, no increased probability for prostatic carcinoma was observed in our study population.

This is the first study extensively evaluating the prediction and decision-making on the issue of prostate biopsy in Turkey. Because the incidence of prostate cancer is low in Turkey, the results of this study may be partially conflicting with previous studies. Some clues for decision-making strategies in countries with low incidence of prostate cancer may emerge from this investigation. The results show that models for prediction of prostate cancer and biopsy decision in a country, or in a geographic region can be designed by using local data that provides insights for similar settings.

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References

1. Jemal A, Siegel R, Ward E et al. Cancer statistics, 2008. CA Cancer J Clin 2008; 58: 71-96.
2. Thompson IM, Ankerst DP. Prostate-specific antigen in the early detection of prostate cancer. CMAJ 2007; 176: 1853-1858.
3. Tricoli JV, Schoenfeldt M, Conley BA. Detection of prostate cancer and predicting progression: current and future diagnostic markers. Clin Cancer Res 2004; 10 (12 Pt 1): 3943-3953.
4. Roscigno M, Scattoni V, Bertini R, Pasta A, Montorsi F, Rigatti P. Diagnosis of prostate cancer. State of the art. Minerva Urol Nefrol 2004; 56: 123-145.
5. Babaian RJ, Fritsche HA, Evans RB. Prostate-specific antigen and prostate gland volume: correlation and clinical application. J Clin Lab Annal 1990; 4: 135-137.
6. Veneziano S, Pavlica P, Querzé R, Nanni G, Lalanne MG, Vecchi F. Correlation between prostate-specific antigen and prostate volume, evaluated by transrectal ultrasonography: usefulness in diagnosis of prostate cancer. Eur Urol 1990; 18: 112-116.
7. Benson MC, Whang IS, Olsson CA, McMahon DJ, Cooner WH. The use of prostate specific antigen density to enhance the predictive value of intermediate levels of serum prostate specific antigen. J Urol 1992; 147 (3 Pt 2): 817-821.
8. Catalona WJ, Partin AW, Slawin KM 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: 1542-1547.
9. Recker F, Kwiatkowski MK, Huber A, Stamm B, Lehmann K, Tscholl R. Prospective detection of clinically relevant prostate cancer in the prostate specific antigen range 1 to 3 ng/ml combined with free-to-total ratio 20% or less: the Aarau experience. J Urol 2001; 166; 851-855.
10. Eastham JA, May R, Robertson JL, Sartor O, Kattan MW. Development of a nomogram that predicts the probability of a positive prostate biopsy in men with an abnormal digital rectal examination and a prostate-specific antigen between 0 and 4 ng/mL. Urology 1999; 54: 709-713.
11. Garzotto M, Hudson RG, Peters L et al. Predictive modeling for the presence of prostate carcinoma using clinical, laboratory, and ultrasound parameters in patients with prostate specific antigen levels. Cancer 2003; 98: 1417-1422.
12. Lopez-Corona E, Ohori M, Scardino PT, Reuter VE, Gonen M, Kattan MW. A nomogram for predicting a positive repeat prostate biopsy in patients with a previous negative biopsy session. J Urol 2003; 170 (4 Pt 1): 1184-1188.
13. Karakiewicz PI, Benayoun S, Kattan MW 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: 1930-1934.
14. Chun F, Karakiewicz P, Briganti A et al. A critical appraisal of logistic regression-based nomograms, artificial neural networks, classification and regression-tree models, look-up tables and risk-group stratification models for prostate cancer. BJU Int 2007; 99: 794-800.
15. Kawakami S, Numao N, Okubo Y et al. Development, validation, and head-to-head comparison of logistic regression-based nomograms and artificial neural network models predicting prostate cancer on initial extended biopsy. Eur Urol 2008; 54: 601-611.
16. Garzotto M, Park Y, Mongoue-Tchokote S et al. Recursive partitioning for risk stratification in men undergoing repeat prostate biopsies. Cancer 2005; 104: 1911-1917.
17. Garzotto M, Beer TM, Hudson RG et al. Improved detection of prostate cancer using classification and regression tree analysis. J Clin Oncol 2005; 23: 4322-4329.
18. Nam RK, Toi A, Trachtenberg J et al. Making sense of prostate

specific antigen: improving its predictive value in patients undergoing prostate biopsy. J Urol 2006; 175: 489-494.
19. Snow PB, Smith DS, Catalona WJ. Artificial neural networks in the diagnosis and prognosis of prostate cancer: a pilot study. J Urol 1994; 152 (5 Pt 2): 1923-1926.
20. Babaian RJ, Fritsche H, Ayala A et al. Performance of a neural network in detecting prostate cancer in the prostate-specific antigen reflex range of 2.5 to 4.0 ng/mL. Urology 2000; 56: 1000-1006.
21. Finne P, Finne R, Auvinen A et al. Predicting the outcome of prostate biopsy in screen-positive men by a multilayer perceptron network. Urology 2000; 56: 418-422.
22. Stephan C, Cammann H, Semjonow A et al. Multicenter evaluation of an artificial neural network to increase the prostate cancer detection rate and reduce unnecessary biopsies. Clin Chem 2002; 48: 1279-1287.
23. Remzi M, Anagnostou T, Ravery V et al. An artificial neural network to predict the outcome of repeat prostate biopsies. Urology 2003; 62: 456-460.
24. Matsui Y, Utsunomiya N, Ichioka K et al. The use of artificial neural network analysis to improve the predictive accuracy of prostate biopsy in the Japanese population. Jpn J Clin Oncol 2004; 34: 602-607.
25. Porter CR, Gamito EJ, Crawford ED et al. Model to predict prostate biopsy outcome in large screening population with independent validation in referral setting. Urology 2005; 65: 937-941.
26. Stamey TA. The era of serum prostate specific antigen as a marker for biopsy of the prostate and detecting prostate cancer is now over in the USA. BJU Int 2004; 94: 963-964.
27. Sakr W, Grignon D, Crissman J et al. High grade prostatic intraepithelial neoplasia (HGPIN) and prostatic adenocarcinoma between the ages of 20-69: an autopsy study of 249 cases. In Vivo 1994; 8: 439-443.
28. Fidaner C, Eser SY, Parkin DM. Incidence in Izmir in 1993-1994: first results from Izmir Cancer Registry. Eur J Cancer 2001; 37: 83-92.
29. Kälkner K, Kubicek G, Nilsson J, Lundell M, Levitt S, Nilsson S. Prostate volume determination: differential volume measurements comparing CT and TRUS. Radiother Oncol 2006; 81: 179-183.
30. Schmid HP, Riesen W, Prikler L. Update on screening for prostate cancer with prostate-specific antigen. Crit Rev Oncol Hematol 2004; 50: 71-78.
31. Stephan C, Lein M, Jung K, Schnorr D, Loening SA. The influence of prostate volume on the ratio of free to total prostate specific antigen in serum of patients with prostate carcinoma and benign prostate hyperplasia. Cancer 1997; 79: 104-109.
32. Shigemura K, Arakawa S, Yamanaka K et al. Potential predictive factors of positive prostate biopsy in the Japanese population. Int Urol Nephrol 2008; 40: 91-96.
33. Dunham MH (Ed). Data mining. Introductory and advanced topics. New Jersey: Pearson Education Inc, 2003.
34. Bernal-Delgado E, Latour-Perez J, Pradas-Arnal F, Gomez-Lopez LI. The association between vasectomy and prostate cancer: a systematic review of the literature. Fertil Steril 1998; 70: 191-200.