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The Predictive Value of Free PSA/PSAD, (F/T)/PSAD in Detect of Prostate Cancer Between PSA Values 4-10 ng/ml: A Single-Center Study Results

PSA Değeri 4-10 Arasında Olan Hastalarda Prostat Kanserini Öngörmede Serbest PSA/PSAD, (Serbest/Total PSA)/PSAD' nin Tanısal Değeri; Tek Merkezli Çalışma Sonuçları

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Öz

Amaç: Bu çalışmada, Türk popülasyonunda prostat kanseri tespiti için (Serbest/Toplam PSA)/PSAD ve FPSA/PSAD' nın tanısal değerini araştırmayı amaçladık.
Hastalar ve Yöntem: Ocak 2007-Aralık 2017 tarihleri arasında prostat spesifik antijen (PSA) değerleri 4-10 ng/ml arasında olan hastaların dosyaları retropesktif olarak incelendi. Veriler prostat biyopsi sonuçlarına göre prostat kanseri (PCa) ve benign prostat hiperplazisi (BPH) gruplarına ayrılan hastalardan toplandı. Gruplar arasında prostat hacmi (PV), Serbest PSA (FPSA), Total PSA (TPSA), serbest-total PSA oranı (F/T), PSA Yoğunluğu (PSAD), (F/T)/PSAD ve FPSA/PSAD gibi değerler kaydedildi ve karşılaştırıldı. Bu değerlerin prostat kanserini öngörmede kullanılabilirliği incelendi.
Bulgular: Çalışmaya toplam 327 hasta (131 PCa ve 196 BPH) dahil edildi. (F/T)/PSAD ve FPSA/PSAD' nin duyarlılık ve özgüllük değerleri PSAD, PSA, F/T'den daha iyiydi. Optimum kesme değerine bağlı olarak, (F/T)/PSAD ve FPSA/PSAD' nin duyarlılığı benzerdi. F/T, (F/T)/PSAD ve FPSA/PSAD' nin negatif öngörü değerleri benzerdi. Yaş, PV, FPSA/PSAD ve (F/T)/PSAD kombinasyonunu kullanan lojistik regresyon modeli, tek başına her birinden daha yüksek AUC gösterdi.
Sonuç: Nispeten yeni parametreler olan FPSA/PSAD ve (F/T)/PSAD prostat kanserini ön görmede benzer teşhis doğruluğuna sahiptir parametrelerdir. İncelenen bu iki parametre, F/T ve tek başına PSAD' den daha yüksek duyarlılığa ve özgüllüğe sahiptir. Bununla birlikte, bu parametrelerin tanısal değerinin etkinliğini değerlendirmek için daha fazla araştırmaya ihtiyaç vardır.

Anahtar Kelimeler: Serbest PSA, Total PSA, PSA Yoğunluğu, Prostat kanseri, Benign prostat hiperplazisi

Abstract

Aim: The present study aimed to investigate the predictive value of (F/T)/PSAD and Free PSA/PSAD in PCa detection in Turkish males.
Patients and Methods: A retrospective analysis of patients' files, from January 2007 to December 2017, with prostate-specific antigen (PSA) values between 4-10 ng/ml was conducted. According to the prostate biopsy outcomes, data were collected from patients and divided into prostate cancer (PCa) and/or benign prostatic hyperplasia (BPH) groups. Among the groups, prostate volume (PV), Free PSA (FPSA), Total PSA (TPSA), free-to-total PSA ratio (F/T), PSA Density (PSAD), (F/T)/PSAD, and FPSA/PSAD values were evaluated and compared. The utilization of these values in PCa detection was examined.
Results: The present study participants were 131 PCa and 196 BPH patients, 327 in total. Sensitivity and specificity values of (F/T)/PSAD and FPSA/PSAD were better than PSAD, PSA, F/T. According to the optimal cut-off value, the sensitivity of (F/T)/PSAD and FPSA/PSAD was similar. Likewise, NPV of F/T, (F/T)/PSAD, and FPSA/PSAD were also similar. The logistic regression model using a combination of age, PV, FPSA/PSAD, and (F/T)/PSAD displayed a higher AUC than each of these values per se.
Conclusion: FPSA/PSAD and (F/T)/PSAD, the relatively new parameters, have similar predictive accuracy in PCa detection. They have higher sensitivity and specificity than F/T PSA and PSAD alone. However, more research is needed to evaluate the efficiency of predictive value of these parameters.

Key words: Free PSA, Total PSA, PSA Density, Prostate cancer, Benign prostatic hyperplasia

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INTRODUCTION

According to Turkish cancer statistics data, prostate cancer (PCa) was the second most present cancer in 2017 (12%, 9%) (1). Prostate-specific antigen (PSA) has had led to significant progress in early PCa diagnosis and treatment (2, 3). The presence of prostate malignancy is not the only cause of elevation in PSA levels. Inflammation of the prostate (prostatitis) and benign prostatic hyperplasia (BPH) can also lead to increased serum PSA levels (4, 5). More than 80% of men who present high PSA are between 4.0 and 10.0 ng/ml, and 2/3 of these patients have been detected benign pathologies when referred to prostate biopsy (6). Additional parameters other than PSA was needed to avoid unnecessary biopsies. PSA density (PSAD) and free-to-total PSA ratio (F/T) are the two most commonly used parameters to evaluate this condition. In clinical practice, these parameters are used frequently because they are accessible and practically applicable. These parameters were found to have higher specificity in predicting PCa than PSA (7, 8).

Free PSA/PSAD and (F/T)/PSAD ratios are two new parameters used in predicting of PCa and have not been widely evaluated in the literature, and the number of studies on these parameters is limited. In studies that were evaluating these parameters, it was stated that the (F/T)/PSAD ratio was a superior new parameter than PSA, PSAD, and F/T in predicting PCa (9-11). In the light of these studies, we aimed to evaluate the efficiency of (F/T)/PSAD and FPSA/PSAD in cases with PSA values ranging from 4-10 ng/ml in predicting PCa. We also aimed to evaluate the usability of these parameters to avoid unnecessary biopsies.

PATIENTS AND METHODS

The files of patients whose PSA values ranged between 4-10 ng/ml in Meram Faculty of Medicine from January 2007 to December 2017 were analyzed retrospectively. A total of 327 patients were included in the study. Patients with a history of urinary tract infection, prostatitis, previous cystoscopy, prostate surgery, and 5-alpha reductase inhibitor medication were excluded from the retrospective evaluation process. Patients with PSA values from 4 to10 and performed transrectal ultrasonography-guided needle biopsy (TRUS-GB) were included in the study. The patients were divided into PCa and BPH groups according to their biopsy results. Three hundred twenty-seven patients (113 patients with PCa and 214 patients with BPH) were included in the study. PSA values before biopsy and digital rectal examination (DRE) findings were recorded. Moreover, prostate volume (PV), free PSA (FPSA), total PSA (TPSA), F/T PSA, PSAD, (F/T PSA)/PSAD ratio, and FPSA/PSAD values were also recorded among the groups, and the efficiency of these values in predict of PCa was evaluated. Informed consent was taken from the patients before the biopsy. A 10-12 quadrant biopsy was performed. During the biopsy, the sample was taken from the suspect nodule (if present).

The following parameters were calculated:

- PSAD=TPSA/PV;
- FPSA/TPSA;
- (F/T)/PSAD= (F/T)/(TPSA/PV);
- FPSA/PSAD= (FPSA×PV)/TPSA.

The institutional human research ethics committee (Necmettin Erbakan University, Faculty of Meram Medicine, Interventional Ethics Committee) approved the protocol numbered "2021/2992.

Statistical Analyses

SPSS 22 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Data with a p-value of <0.05 were considered statistically significant. Continuous variables were defined using the mean ± standard deviation (SD). Mann-Whitney U test and t-tests were used for parametric and non-parametric data. A comparison of the percentages was made with the Chi-square test. The values of TPSA, FPSA, PV, F/T PSA, PSAD, FPSA/PSAD ratio, and (F/T PSA)/PSAD ratio were compared between the groups.

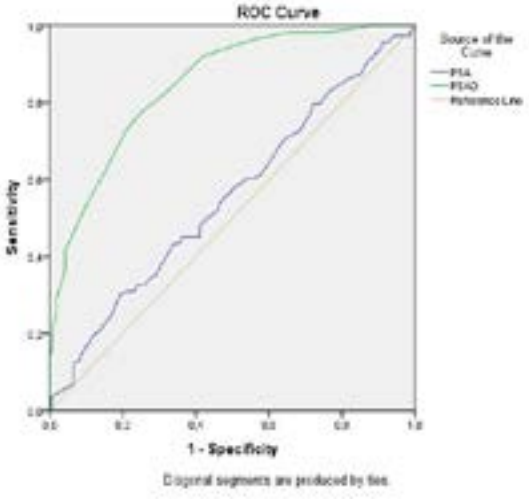

Figure 1. The ROC curves of TPSA, PSAD, for diagnosis of PCa are shown in Figure1

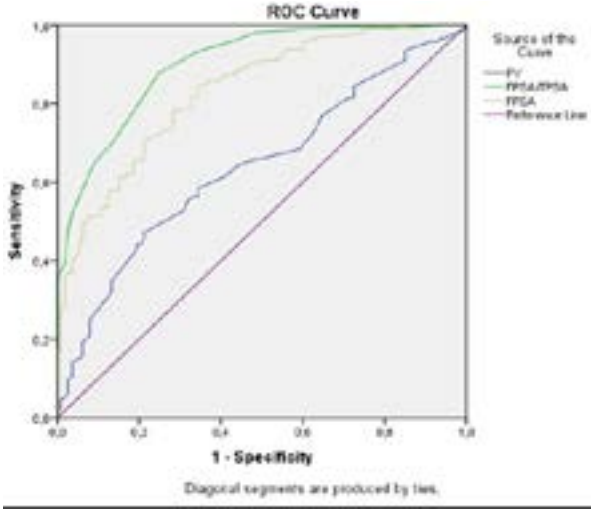

Figure 2. The ROC curve of the FPSA, PV, FPSA/PSA are shown in Figure 2

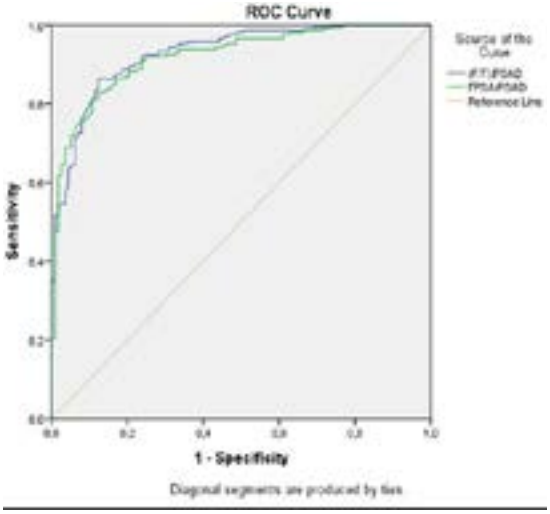

Figure 3. The ROC curve of the new parameter FPSA/PSAD and (FPSA/PSA)/PSAD are shown in Figure 3

Considering these values, ROC was calculated. In the determination of the optimum cut-off value, the Youden index was used. The area under the curve (AUC) was calculated, and the results were mutually statistically compared. Sensitivity, specificity, PPV, and NPV were evaluated using the optimum cut-off value. Logistic regression analysis was performed to find an optimal risk prediction model. With the Hosmer-Lemeshow test, p-value> 0.05 was taken as a threshold value, and the higher p value showed a better fit.

RESULTS

A total of 337 patients were included, 113 patients

Table 1. CENP-H and Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) Genes Primers and Probes

	BPH Group	PCa Group	p value	z value
Age (years)	63.2±7.62	65.1±7.51	.078	-2271
PV (ml)	51.07±19.11	42.29±14.69	.000	-4177
PSA (ng/ml)	6.7±1.88	7.2±1.95	.002	-1763
F/T	0.21±0.7	0.11±0.4	.000	-11883
PSAD(ng/ml/cm^3)	0.13±0.04	0.2±0.05	.000	-10351
(F/T) / PSAD	1.77±1.01	0.6±0.32	.000	-12732
FPSA (ng/ml)	1.42±0.56	0.8±0.37	.000	-9840
FPSA / PSAD	11.4±6.01	4.17±2.32	.000	-12506

BPH: Benign prostatic hyperplasia, PCa: Prostate cancer, PV: Prostate volume, PSA: Prostate-specific antigen, F/T: Free-to-total PSA ratio, PSAD: PSA Density, FPSA: Free PSA, TPSA: Total PSA, p value: Asymp. Sig. (2-tailed) <.05

Table 2. Paired-Sample Area Difference under the ROC Curves

Test Result Pair(s)	z value	p value
FPSA/PSA vs PSAD	24.294	.000
FPSA/PSA vs (FPSA/TPSA)/PSAD	-2.391	.017
FPSA/PSA vs FPSA/PSAD	-1.454	.146
FPSA/PSA vs PSA	11.346	.000
PSAD vs (FPSA/TPSA)/PSAD	-23.294	.000
PSAD vs FPSA/PSAD	-24.005	.000
PSAD vs PSA	-8.309	.000
FPSA/PSAD vs (FPSA/TPSA)/PSAD	.723	.470
(FPSA/PSA)/PSAD vs PSA	12.280	.000
FPSA/PSAD vs PSA	14.260	.000

PSA: Prostate-specific antigen, F/T: Free-to-total PSA ratio, PSAD: PSA Density, FPSA: Free PSA, TPSA: Total PSA, p value: Asymp. Sig. (2-tailed) < .05

Table 3. The comparison of diagnostic predictive parameters

Parameter	AUC	Cut-off Value	Sensitivity	Specificity	PPV	NPV
TPSA	.445	6.35 (ng/ml)*	0.504	0.669	0.518	0.702
PV	.635	40.52 cm^{3}#	0.611	0.602	0.586	0.681
F/T	.771	0.14#	0.742	0.767	0.696	0.810
PSAD	.743	0.17(ng/ml/cm^{3})*	0.700	0.755	0.626	0.806
FPSA/PSAD	.852	6.76 (cm^{3})#	0.794	0.811	0.710	0.835
(F/T PSA)/PSAD	.862	0.54#	0.811	0.824	0.729	0.841

PV: Prostate volume, PSA: Prostate-specific antigen, F/T: Free-to-total PSA ratio, PSAD: PSA Density, FPSA: Free PSA, TPSA: Total PSA, AUC: Area under the ROC Curve, PPV: Positive predictive values, NPV: Negative predictive values

* If the data was greater than or equal to this value, the patients can be diagnosed with prostate cancer when using this parameter for predicting prostate cancer;

If the data was lower than or equal to this value, the patients can be diagnosed with prostate cancer when using this parameter for predicting prostate cancer.

with PCa (33.5%), and 214 patients with BPH (63.5%). When we compared the data between the PCa and BPH groups, there was a statistically significant difference between all other data except age. Table 1 shows these demographic data. In the predict of PCa, the ROC curve, PSA, PSAD (Figure 1), FPSA, PV, F/T PSA (Figure 2) and FPSA/PSAD ratio and (F/T PSA)/PSAD ratio (Figure 3) are presented, respectively. The AUCs of TPSA, PV, F/T PSA, PSAD, FPSA/PSAD and (F/T)/PSAD were 0.445, 0.635, 0.771, 0.743, 0.852, 0.862. All these parameters had significant predictive value (p <0.001). Table 2 shows a comparison of results between the AUC of the ROC curves. The results showed that FPSA/PSAD ratio and (F/T)/PSAD had significantly higher AUC (p <0.001) than F/T PSA, TPSA, and PSAD. However, there was no statistical difference in the comparison of FPSA/PSAD ratio and (F/T)/PSAD ratio (p <0.470).

In predict of PCa in Table 3, 40.52 ml, 6,35 ng/ml, ≥0.17 (ng/ml)/cm^{3}, 0,14, ≤6.76 cm^{3} and ≤0,54 for PV, PSA, PSAD, F/T PSA, FPSA/PSAD, and (F/T)/PSAD ratio, respectively, it shows the optimum cutting data for 54. The sensitivity, specificity, PPV, and NPV were calculated according to these cut-off values. Among them, (F/T)/PSAD ratio and FPSA/PSAD sensitivities, sensitivity, PPV and NPV values was 0.81, 0.82, 0.72, 0.84 and 0.79, 0.81, 0.71, 0, 83 respectively. Sensitivity and specificity values of FPSA/PSAD and (F/T)/PSAD were higher than F/T PSA and PSAD only. Although the NPV values were above 0.80, they were similar to F/T PSA and PSAD. PPV was more significant than PSAD and FPSA/PSAD ratio. PV and PSA had lower values when compared to all other parameters.

All the parameters (including age, TPSA, FPSA, PV, F/T PSA, PSAD, and (F/T)/PSAD ratio) were analyzed using multiple regression analysis. The results showed that PV (OR=1,053, 95% CI=1,021–1,086, p<0.001), FPSA/PSAD ratio (OR=0,595, 95%=0,463–0,766, p<0.000), and (F/T)/PSAD ratio (OR=0.066, 95% CI=0.13–0.326, p<0.001) were independent predictors of PCa disregarding age (Table 4). Hosmer-Lemeshow test showed good regression model fitting (p=0.815).

DISCUSSION

The newly calculated parameters, which FPSA/PSAD and (F/T)/PSAD ratios, analyzed in the present study, showed higher predictive accuracy than PSA, PSAD, and F/T. Prostate-specific antigen has been used for 25 years in the early diagnosis of PCa. Repeated PSA levels >4 ng/ml or abnormal DRE indicate a TRUS-GB necessity for diagnosis (4). TRUS-GB can cause complications such as

Table 4. Results of logistic regression analysis

	B	S.E.	Wald	df	P-value	OR	95% CI of OR	
							Lower	Upper
AGE	.080	.027	9198	1	.002	1.084	1.029	1.141
(FPSA/PSA)/PSAD	-2.719	.815	11117	1	.001	.066	.013	.326
FPSA/PSAD	-.518	.129	16253	1	.000	.595	.463	.766
PV	.051	.016	10551	1	.001	1.053	1.021	1.086
Constant	-1.944	1633	1418	1	.234	.143		

PV: Prostate volume, PSA: Prostate-specific antigen, F/T: Free-to-total PSA ratio, PSAD: PSA Density, FPSA: Free PSA, TPSA: Total PSA, S.E: standart error, OR: odds radio, CI: Confidence interval

hematuria, hematospermia, and rectal bleeding, as well as under 1% serious procedure-related urosepsis (5). Unnecessary biopsy should be avoided due to complications. In Turkey, PSA and FPSA are the most used parameter in patients with suspected PCa. The use of the F/T PSA provides more specificity than only PSA and FPSA in the predict of PCa. However, no definitive data are available indicating the optimal use of F/T PSA in detecting of PCa. When we evaluated the literature, it was stated that F/T PSA is more effective than PSA in the comparisons made in the predict of prostate cancer (12-15). Partin et al. proposed using F/T PSA ratio 0,15 to detect all advanced, non-organ confined, and large volume tumors while avoiding 80% of biopsies in men with the insignificant disease, particularly in the intermediate range of TPSA (4.1-10 ng/ml) (16). In the same study, an F/T PSA ratio of 0.15 indicated that 20% unnecessary biopsy would be avoided (16). Another study in Turkey determined that F/T PSA cut-off point was AUC of 0.81 for all age groups in detecting PCa, while the value of sensitivity and specificity was found between 0.63 and 0.83 (17). A further one reported a 29% PPV for F/T PSA (cut-off value was set at 20%) in men with a PSA level within the gray zone (18). In our study, the F/T PSA ratio cut-off value was 0.14 and similar to the findings in the relevant literature.

There are large series related to the predictive value of F/T PSA in the literature. However, the studies associated with F/T PSA and (F/T)/PSAD are limited. In study of Yan et al., they found that the cut-off point of F/T PSA, PSAD, and (F/T)/PSAD values were 0.16, 0.15, and 0.8 in their study of 88 patients (10). They found that (F/T)/PSAD ratio's sensitivity was more significant in the early diagnosis of PCa than other parameters (66.7% vs. 76.2% vs. 85.7%). They did not find any significant difference in the specificity of these parameters (10). However, in their study (F/T)/PSAD ratio was stated that it is a parameter that should be used to detect PCa. They also stated that the low number of patients was the most important disadvantage in their study (10). In this present study, both the sensitivity and specificity of (F/T)/PSAD ratio were more significant than PSA, F/T PSA, and PSAD. The high number of patients may be one of the most important factors that reveal both parameters' meaningfulness.

In a study by Li-Bin Nan et al. (11), they found that (F/T)/PSAD and FPSA/PSAD ratios' sensitivity was higher than PSAD. In addition to, AUC rates were higher than F/T PSA and PSA in their studies (11). There was no difference between specificity, NPV, and PPV between PSAD, PV, FPSA/PSAD ratio, and (F/T)/PSAD ratio. They also stated that the cut-off value was 0.773 for FPSA/PSAD and 6.263 for (F/T)/PSAD. However, according to Chinese guidelines, they performed biopsy in patients with PSA values of 4-10 ng/ml or F/T PSA<0.16, and PSAD>0.15. In their manuscript, they stated that this might also indirectly affect their results. In our study, (F/T)/PSAD and FPSA/PSAD ratios cut-off value was 0.54 and 6.76, respectively. The sensitivity, specificity, NPV, and PPV values of both were similar.

Likewise, the sensitivity and specificity were higher than FPSA/PSAD and (F/T)/PSAD ratio, while F/T PSA, FPSA/PSAD, and (F/T)/PSAD values' NPV and PPV ratios were similar. Similar to these studies, our results show that these relatively new parameters are more effective than PSA and PSAD in predict of prostate cancer. However, many factors (patients' number, age, race, territory, etc.) that will affect the results should also be considered. In the early detection of PCa, many new parameters and imaging techniques such as multiparametric prostate MRI are being discovered. It is obvious that studies are needed in these new parameters by combining predictive accuracy and new imaging techniques. Age is an essential factor causing an increased risk of PCa (19, 20). Multiple regression analysis was performed in our study and showed that PV, FPSA/PSAD, and (F/T)/PSAD as unconstrained determinants of PCa, disregarding age. In the study by Li-Bin Nan et al., they stated that the combination with PV, age, and PSAD in addition to new parameters is a good predictive model in logistic regression analysis (11). In the study by Erol et al., they evaluated the distribution of the F/T PSA ratio in 657 patients with PSA ranging from 4-10 according to age groups in the Turkish population. In this study, the F/T PSA cut-off points were determined to be 10%, 15%, 15%, and 10% in 50-59 years, 60-69 years,> 70 years, and all ages categories, respectively (17). However, they did not evaluate PV in their studies (17). In another study conducted in the Turkish population, they compared the patients with BPH and PCa ranging from PSA 2.5-10. PV was significantly lower in the cancer group (18). In this present study, we did not evaluate by age groups. We stated that the combination of the new parameters, age, and PV might have an advantage in predicting PCa.

In our study, when we considered the biopsy results we received in our region, we got some extra results.

Considering PV, the cut-off value is 40.5 ml, and the risk of PCa increases in patients below. Former studies have determined that PV might influence PSA's predictive accuracy (21) and an increase in the detection rate of PCa, along with a decrease in PV (18). In addition, the calculated parameters which analyzed in this study FPSA/PSAD and (F/T)/PSAD ratios, were showed similar predictive accuracy.

The present study is the first study to comparing these parameters in our country. Further prospective studies are needed to compare the predictive accuracy of these parameters in detect of PCa. Moreover, there are some inherent limitations of the present study to be considered. First of all, the present study is single-centered and only patients from a particular region are included in the study. The second is that our study was a retrospective study, and therefore some data (such as voiding symptoms, family history, and cancer history) could not be integrated into the analysis of the findings as these were not of use for the purpose of the present study.

CONCLUSION

The predictive values of (F/T)/PSAD and FPSA/PSAD give better results than F/T PSA, PSA, and PSAD in patients with 4-10 ng/ml PSA range, and they have higher sensitivity and spesivity. In addition to being the first study to be conducted in our country, we believe that PSA, FPSA, and Prostate volume can be formulated in a simple way to have an idea in the pre-diagnosis of prostate cancer. The use of these parameters may be beneficial in predicting PCa, and to avoid unnecessary biopsies. More series and prospective studies are needed.

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