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

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 PCa, 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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Amaç: Bu çalışmada, Türk popülasyonunda prostat kanseri tespiti için (Serbest/Toplam PSA)/PSAD ve FPSA/PSAD'ın tanısal değeri araştırılmayı amaçladık.

Hastalar ve Yöntem: Ocak 2007-Aralık 2017 tarihleri arasında prostat spesifik antijen (PSA) değerleri 4-10 ng/ml arasında olan hastaların dosyaları retrospektif olarak incelendi. Veriler prostat biyopsis sonuçlarına göre prostat kanseri (PCa) ve benign prostat hiperplazisi (BPH) gruplarına ayrılan hastalardan toplandı. Gruplar arasında hastanın (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 değerler prostat kanserini öngörmede kullanılabileceğini incelendi.

Bulgular: Çalışmaya toplam 327 hasta (131 PCa ve 196 BPH) dahil edildi. (F/T)/PSAD ve FPSA/PSAD’nin duyarlılık ve özgülük 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 kombinasyonu kullanılan lojistik regresyon modeli, tek başına her birinden daha yüksek AUC gösterdi.

Sonuç: Nispeten yeni parametreler olan FPSA/PSAD ve (F/T)/PSAD prostat kanserini öngörmede benzer şekilde doğruluklu daha yüksek değerler sahipti. Bununla birlikte, bu parametrelerin tanısal değerinin etkinliğini değerlendirmek için daha fazla araştırılarak ihtiyaç duyulur.

Anahtar Kelimeler: Serbest PSA, Total PSA, PSA Yoğunluğu, Prostat kanseri, Benign prostat hiperplazisi
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 to 10 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
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 2. Paired-Sample Area Difference under the ROC Curves

| Test Result Paired(s)                  | z value | p value |
|--------------------------------------|---------|---------|
| FPSA/PSAD vs PSAD                   | 24.294  | .000    |
| FPSA/PSAD vs (FPSA/TPSA)/PSAD        | -2.391  | .017    |
| FPSA/PSAD vs FPSA/PSAD              | -1.454  | .146    |
| FPSA/PSAD 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) < 0.05
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 ratio 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)/cm³, 0.14, ≤0.17 cm³, 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).

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

| 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 cm³#   | 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/cm³)* | 0.700       | 0.755       | 0.626 | 0.806 |
| FPSA/PSAD      | .852 | 6.76 (cm³)#  | 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.

Table 4. Results of logistic regression analysis

| B             | S.E. | Wald | df | P-value | OR    | 95% CI of OR |
|---------------|------|------|----|---------|-------|--------------|
| AGE           | .080 | .027 | 9198 | 1       | .002  | 1.084        |
| (FPSA/PSA)/PSAD | -2.719 | .815 | 11117 | 1       | .001  | .066        |
| FPSA/PSAD     | -.518 | .129 | 16253 | 1       | .000  | .595        |
| PV            | .051 | .016 | 10551 | 1       | .001  | 1.053        |
| 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 ratio, CI: Confidence interval
higher than F/T PSA and PSA in their studies (11). In addition to, AUC rates were (F/T)/PSAD and FPSA/PSAD ratios' sensitivity was higher than FPSA/PSAD. In a study by Li-Bin Nan et al. (11), they found that the (F/T)/PSAD ratio was stated that it is a parameter that should be used to detect PCa. 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 the 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 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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REFERENCES

1. Bakanlığı S. Sağlık İstatistikleri Yılılığı 2016 Haber Bülteni. Sağlık Araştırma Genel Müdürlüğü, Ankara. 2017.
2. Catalona WJ, Richie JP, Ahmann FR, et al. Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: Results of a multicenter clinical trial of 6,630 men. J Urol 1994;151(5):1283-90.
3. Stamey TA, Caldwell M, McNEAL JE, et al. The prostate specific antigen era in the United States is over for prostate cancer: What happened in the last 20 years? J Urol 2004;172(4 Part 1):1297-301.
4. Shariat SF, Roehrborn CG. Using biopsy to detect prostate cancer. Rev Urol 2008;10(4):262.
5. Sarwar S, Adil MAM, Nyamath P, et al. Biomarkers of prostatic cancer: An attempt to categorize patients into prostatic carcinoma, benign prostatic hyperplasia, or prostatitis based on serum prostate specific antigen, prostatic acid phosphatase, calcium, and phosphorus. Prostate Cancer 2017;2017:5687212.
6. Djavan B, Zlotta A, Remzi M, et al. Optimal predictors of prostate cancer on repeat prostate biopsy: A prospective study of 1,051 men. J Urol 2000;163(4):1144-9.
7. Matsuyama H, Baba Y, Yamakawa GI, et al. Diagnostic value of prostate-specific antigen-related parameters in discriminating prostate cancer. Int J Urol 2006;7(11):409-14.
8. Yilmaz H, Ciftci S, Yavuz U, et al. Percentage of free prostate-specific antigen (PSA) is a useful method in deciding to perform prostate biopsy with higher core numbers in patients with low PSA cut-off values. Kaohsiung J Med Sci 2015;31(6):315-9.
9. Veneziano S, Pavlica P, Compagnone G, et al. Usefulness of the (F/T)/PSA density ratio to detect prostate cancer. Urol Int 2005;74(1):13-8.
10. Yan D, Hu E, Zhang H, et al. The significance of PSA modified parameters (F/T)/PSAD for diagnosing prostatic cancer in the grey zone of 4–10 ng/ml. Chinese J Clin Oncol 2007;4(5):347-50.
11. Nan L-B, Yin X-T, Gao J-P. Significant diagnostic value of free-serum PSA (FPSA)/prostate-specific antigen density (PSAD) and (F/T)/PSAD for prostate cancer of the chinese population in a single institution. Med Sci Monit: Int Med J Expier Clin Res 2019;25:8345.
12. Guazzoni G, Nava L, Lazzari M, et al. Prostate-specific antigen (PSA) isofrom p2PSA significantly improves the prediction of prostate cancer at initial extended prostate biopsies in patients with total PSA between 2.0 and 10 ng/ml. Results of a prospective study in a clinical setting. Eur Urol 2011;60(2):214-22.
13. Loeb S, Sokoll LJ, Broyles DL, et al. Prospective multicenter evaluation of the Beckman Coulter Prostate Health Index using WHO calibration. J Urol 2013;189(5):1702-6.
14. Stephan C, Vincendeau S, Houlgatte A, et al. Multicenter evaluation of [-2] proprostate-specific antigen and the prostate health index for detecting prostate cancer. Clin Chem 2013;59(1):306-14.
15. Lazzari M, Haese A, De La Taille A, et al. Serum isoform [-2] proPSA derivatives significantly improve prediction of prostate cancer at initial biopsy in a total PSA range of 2–10 ng/ml: A multicentric European study. Eur Urol 2015;63(6):986-94.
16. Partin AW, Mangold LA, Lamm DM, et al. Contemporary update of prostate cancer staging nomograms (Partin Tables) for the new millennium. Urology 2001;58(6):843-8.
17. Erol B, Gulpinar MT, Bozdogan G, et al. The cutoff level of free/total prostate specific antigen (f/t PSA) ratios in the diagnosis of prostate cancer: A validation study on a Turkish patient population in different age categories. Kaohsiung J Med Sci 2014;30(11):545-50.
18. Özden E, Turgut AT, Talas H, et al. Effect of dimensions and
volume of the prostate on cancer detection rate of 12 core prostate biopsy. Int Urol Nephrol 2007;39(2):525-9.
19. Pettersson A, Robinson D, Garmo H, et al. Age at diagnosis and prostate cancer treatment and prognosis: A population-based cohort study. Ann Oncol 2018;29(2):377-85.
20. Braga SFM, de Souza MC, Cherchiglia ML. Time trends for prostate cancer mortality in Brazil and its geographic regions: An age-period-cohort analysis. Cancer Epidemiol 2017;50:53-9.
21. Partin AW, Catalona WJ, Southwick PC, et al. Analysis of percent free prostate-specific antigen (PSA) for prostate cancer detection: Influence of total PSA, prostate volume, and age. Urology 1996;48(6):55-61.