Original Article

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The Predictive Ability of Prostate-Specific Antigen (PSA) Density and Free/Total PSA Ratio in Diagnosing Clinically Significant Prostate Cancer (PCa) in Patients with Histologically Confirmed PCa with a PSA Level of 2.5-10 Ng/ML

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Abstract

Objective: Many men with non-clinically significant prostate cancer (N-CSPCa) will not progress to symptomatic forms within their lifetime. So, predicting clinically significant PCa (CSPCa) will prevent unnecessary biopsies, overdiagnoses, and overtreatment of patients. Thus, we aimed at demonstrating the predictive ability of prostate-specific antigen (PSA) density (PSAD) and f/t PSA in revealing CSPCa (Gleason score ≥7) in patients diagnosed with prostate cancer on biopsy with a PSA level of 2.5-10 ng/mL.

Materials and Methods: We evaluated 78 patients with PSA 2.5-10.0 ng/mL who underwent transrectal ultrasound guided (TRUSG)-guided prostate biopsy in our clinic between March 2017 and August 2020 and whose histology reported as prostate adenocarcinoma. In addition to the demographic content of the patients, PSA, free PSA, prostate size (with TRUSG), rectal examination findings, and prostate biopsy results were recorded. Clinically significant prostate cancer was defined as a minimum Gleason score of 7.

Results: The mean age of the patients was 66.9±8.4 years, PSA value was 6.9±1.8 ng/mL, free/total PSA ratio was 18±8.1%, and PSAD was 0.150±0.078. The p-values of PSA, free PSA, PSAD, f/t PSA, and prostate volume between CSPCa and N- CSPCa groups were 0.010, 0.780, 0.001, 0.084, and 0.030, respectively. The area under the curve of the PSAD for predicting CSPCa was 0.719 with a 95% CI (0.604-0.835), and the standard errors were 0.062 and 0.059, respectively. When PSAD cut-off was 0.130 for predicting CSPCa, sensitivity and specificity rates were 75% and 63%, respectively.

Conclusion: PSAD can be used in predicting CSPCa, but not f/t PSA. PSAD is not a strong stand-alone tool owing to its sensitivity and specificity, but can be a part of future nomograms for predicting CSPCa and future protocols for active surveillance.

Keywords: Prostate-specific antigen, clinically significant prostate cancer, PSA density

Introduction

Prostate cancer (PCa) is the second most common cancer in men. An estimated 1.1 million cases were diagnosed with PCa worldwide in 2012, accounting for 15% of cancers diagnosed in men (1). For several years, the combination of prostate-specific antigen (PSA) and digital rectal examination (DRE) has been used to diagnose PCa early. Catalona et al. (2) proposed that a total PSA cut-off value of 4 ng/mL should prompt the need for a prostate biopsy to diagnose PCa. However, more than 20% of men diagnosed with PCa have PSA levels lower than 4 ng/mL and early detection would result in a higher probability of curative treatment (3). PSA is not specific for PCa; benign prostate hyperplasia, prostatitis, and other benign events can elevate PSA levels. Therefore, PSA has a low specificity for the diagnosis of PCa at 2.5-10 ng/mL (4). Free/total PSA ratio (f/t PSA), PSA density (PSAD), PSA velocity, and age-specific PSA can be used for early PCa detection in PSA levels of 2.5-10 ng/mL (3,5).

Many men with non-clinically significant PCa (N-CSPCa) will not progress to symptomatic forms within their lifetime (6,7). Currently, there is no universally accepted definition of clinically significant PCa (CSPCa) (8). However, in most studies referenced in recent The European Association of Urology guidelines, CSPCa is defined as an International Society of Urological Pathology

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(ISUP) grade group ≥2 (Gleason ≥7) (9). Thus, predicting clinically significant PCa (CSPCa) prevents unnecessary biopsies, over diagnoses, and overtreatment in patients. Some studies have shown that PSA, PSAD, f/t PSA can predict a Gleason score and CSPCa at a PSA level of 4-10 ng/dL (10,11). Therefore, we aimed at demonstrating the predictive ability of PSAD and f/t PSA in revealing CSPCa (Gleason ≥7) in patients diagnosed with PCa on biopsy with a PSA level of 2.5-10 ng/mL.

Materials and Methods

The data of the patients who received transrectal ultrasound guided (TRUS) biopsies due to high PSA levels or suspicious findings during DRE were evaluated retrospectively between March 2017 and August 2020. We included all the patients (78 patients) who had PSA levels between 2.5-10 ng/mL, with a histologically confirmed adenocarcinoma of the prostate on TRUS biopsies. We excluded patients who had PSA levels <2.5 or >10 and patients with PSA levels between 2.5-10 ng/mL with benign conditions, ASAP (atypical small acinar proliferation), HGPIN (high-grade prostatic intraepitelial neoplasia), and prostatic malignancy other than adenocarcinoma. In addition to the demographic data of the patients, PSA, free PSA, prostate volume (based on TRUS), DRE findings, and prostate biopsy reports were recorded. Our primary endpoint was to assess the associations of PSAD and f/t PSA with CSPCa. PSAD is the level of serum PSA divided by the prostate volume (9). CSPCa was defined as Gleason score ≥7. Our secondary endpoints were to assess the associations of PSA, free PSA, prostate volume with CSPCa and the associations of PSA, free PSA, PSAD, f/t PSA, and prostate volume with Gleason subgroups. We used the ISUP grading for Gleason subgroups (12) (Table 1). All patients underwent TRUS biopsies in the lateral decubitus position with periprostatic prilocaine block. An 18-gauge automatic disposable needle was used in each case.

Statistical Analysis

Statistical analysis was carried out using the IBM Statistical Package for Social Sciences version 20 software. The suitability of the variables to normal distribution was examined using the Shapiro-Wilk Test. The Mann-Whitney U test was used to compare continuous outcome variables in two groups; One-Way analysis of variance and Kruskal-Wallis H tests were used in three or more groups. Post-hoc Tukey-HSD, LSD, and Tamhane's T2 were used in groups showing normal distribution, and post-hoc Mann-Whitney U test in groups that did not show normal distribution for multiple comparisons. The significance level was set at $p<0.05$. Two receiver operating characteristic (ROC) curves were drawn to obtain the best PSA and PSAD cut-off values for CSPCa.

The study was approved by the Local Ethical Board of our hospital prior to recruitment of files (University of Health Sciences Turkey, Trabzon Kanuni Training and Research Hospital, approval number: 2021/03-01, date: 13.01.2021).

Results

The mean age of the patients was 66.9±8.4 years (44-88), PSA was 6.92±1.85 ng/mL (2.69-9.91), free PSA was 1.20±0.52 ng/mL (0.15-2.56), f/t PSA was 18.04±8.1% (4-46), prostate volume was 53.6±19.4 (18-108), and PSAD was 0.150±0.078 (0.045-0.357). ISUP grade groups of the patients were as follows: 46 patients (59%) in grade group 1, 21 patients (26.9%) in grade group 2, 7 patients (9%) in grade group 3, 4 patients (5.1%) in grade group 4, and none in group 5. We recorded 32 patients (41%) with CSPCa (Gleason ≥7, ISUP group ≥2).

The p-values of PSA, free PSA, PSAD, f/t PSA, and prostate volume between CSPCa and N-CSPCa groups were 0.010, 0.780, 0.001, 0.084, and 0.030, respectively (Table 2).

The p-values of PSA, free PSA, PSAD, f/t PSA, and prostate volume between ISUP grade groups were 0.013, 0.850, 0.001, 0.379, and 0.022, respectively (Table 3).

The area under the ROC curve (AUC) of the PSA and PSAD for predicting CSPCa was 0.671 with a 95% CI (0.549-0.793), 0.719 with a 95% CI (0.604-0.835), and the standard errors were 0.062 and 0.059, respectively. When PSA cut-off was 6.29 ng/mL for predicting CSPCa, sensitivity and specificity were 78.1% and 50%, respectively. When PSAD cut-off was 0.130, sensitivity and specificity were 75% and 63%, respectively (Figure 1).

Discussion

PCa is one of the malignancies with a serum-based biomarker. Since PSA's discovery in 1979 until clinical application in the late 1980s, PSA has evolved into an invaluable tool for detecting, staging, and monitoring PCa in men. For several years, an abnormal DRE, elevated PSA, or both were used to diagnose

Table 1. The International Society of Urological Pathology (ISUP) grading system

ISUP grade groups	Gleason score
Grade group 1	Gleason score ≤6
Grade group 2	Gleason score 3+4=7
Grade group 3	Gleason score 4+3=7
Grade group 4	Gleason score 4+4=8; 3+5=8; 5+3=8
Grade group 5	Gleason score 4+5=9; Gleason score 5+4=9; Gleason score 5+5=10

ISUP: International Society of Urological Pathology

Table 2. Clinically significant (Gleason ≥7) and non-clinically significant (Gleason <7) prostate cancer distributions accordindg to patient's PSA, free PSA, PSA density, free / total PSA ratio and prostate volume

	Gleason ≥7 (ISUP grade group ≥2) (n=32)	Gleason <7 (ISUP grade group 1) (n=46)	p-value
PSA	7.6±1.7[A] (7.66)	6.5±1.8 (6.52)	0.010[Aa]
Free PSA	1.2±0.5 (1.13)	1.2±0.5 (1.10)	0.780[a]
PSA density	0.2±0.07[A] (0.16)	0.1±0.07 (0.106)	0.001[Aa]
Free/total PSA ratio	16.1±7 (15.5)	19.1±8.6 (19)	0.084[a]
Prostate volume	47.9±16.4 (48.5)	57.6±20.6A (61)	0.030[Ab]

ISUP: International Society of Urological Pathology, PSA: Prostate-specific antigen
[A]Represents a statistically significant difference (P<0.05).
[a]Mann-Whitney U Test
[b]2 sample independent t test

Table 3. ISUP grade group distributions accordindg to patient's PSA, free PSA, PSA density, free/total PSA ratio and prostate volume						
	All patients (n=78)	**ISUP grade group 1 (n=46)**	**ISUP grade group 2 (n=21)**	**ISUP grade group 3 (n=7)**	**ISUP grade group 4 (n=4)**	**p-value**
PSA	6.9±1.9 (7.08)	6.5±1.8 (6.52)	7.4±1.8 (7.37)	7.3±1.4 (7.36)	9.2±0.4A (9.22)	0.013[Aa]
Free PSA	1.2±0.5 (1.11)	1.2±0.5 (1.10)	1.2±0.6 (1.09)	1.2±0.4 (1.11)	1.5±0.7 (1.29)	0.850[b]
PSA density	0.150±0.08 (0.131)	0.1±0.08 (0.106)	0.2±0.07 (1.89)	0.1±0.03 (0.11)	0.3±0.08A (0.25)	0.001[Ab]
Free/total PSA ratio	18±8.1 (17)	19.4±8.6 (19)	16.1±7.6 (16)	16.4±6.2 (15)	15.6±7.1 (13,5)	0.379[b]
Prostate volume	53.6±19.5 (54)	57.6±20.6 (61)	45.0±16.3 (47)	61.6±11.5[A] (60)	39.3±12.8 (38)	0.022[Aa]

ISUP: International Society of Urological Pathology, PSA: Prostate-specific antigen
[A]Represents a statistically significant difference (p<0.05).
[a]One-Way ANOVA
[b]Kruskal-Wallis H test

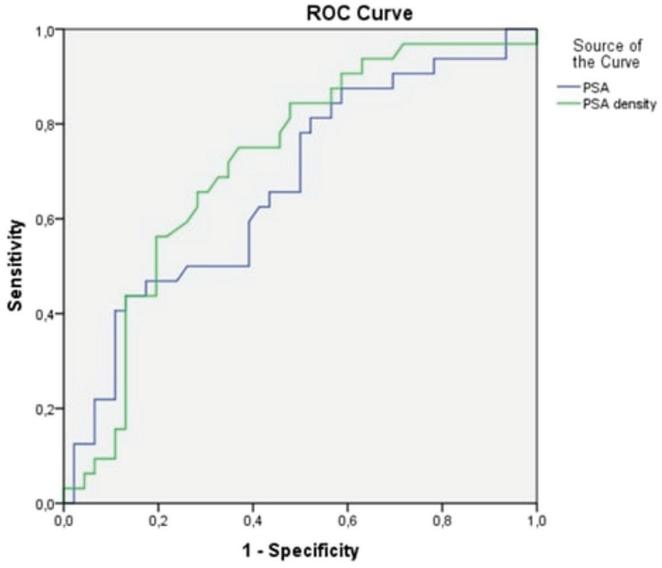

Figure 1. The AUC of PSA, PSA density for predicting clinically significant PCa

PSA: Prostate-specific antigen, ROC: Receiver operating characteristics, PCa: Prostate cancer, AUC: Area undar the curve

PCa. Today, most PCa are diagnosed as clinically non-palpable (stage T1c) with PSA levels between 2.5 and 10 ng/mL (13). PSA screening for PCa leads to a small reduction in disease-specific mortality over 10 years but does not affect overall mortality (14). Nowadays, attention has turned from the detection of any PCa to a focus on detecting CSPCa, often interpreted as a Gleason score ≥7 (13). PSAD and f/t PSA are well-known for PCa detection, especially in PSA levels <10 ng/mL, and this prompted us to carry out this study (3,5).

Recent studies have shown that PSAD is associated with CSPCa. Omri et al. (15) found that PSAD is correlated with CSPCa (based on radical prostatectomy histology reports) in small (<50 cc) and medium (50-75 cc) size prostates and level of PSAD is directly associated with the ISUP grade groups. Liu et al. (11) demonstrated that PSAD predicted CSPCa (based on prostate biopsy pathology reports) in the PSA level ranging 4-10 ng/mL. Compatible with these studies, we found clinical significance between PSAD and CSPCa (Gleason ≥7, ISUP grade group ≥2) (p<0.001). This was not surprising because we found clinical significance between PSA and CSPCa (p<0.010) and prostate volume and CSPCa (p<0.030) (Table 2). Moreover, we also found clinical significance between PSAD and ISUP grade groups, especially for ISUP grade group 4 (Table 3). However, there was no correlation between ISUP grade groups and PSAD as well as between prostate volume and ISUP grade groups. ISUP grade group 3 had the biggest mean prostate volume in our study, and when we excluded that group, we could see a correlation between PSAD and ISUP grade groups (groups 1, 2, and 4). We had no correlation between PSAD and CSPCa for large prostates as in Omri et al. (15) but not fully certain because all ISUP grade groups mean prostate volume were <75 cc in our study.

Ceylan et al. (10) revealed a relationship between a higher Gleason score and decreased f/t PSA and f/t PSA can be an indicator for predicting the Gleason score. Unlike that, there was no clinical significance between f/t PSA and CSPCa in our study. Apart from PSA values, there was no clinical significance between free PSA and CSPCa. The mean free PSA was similar between the CSPCa and N-CSPCa groups in our study (Table 2). Additionally, there was no correlation between free PSA and ISUP grade groups (Table 3).

There was clinical significance between prostate volume and CSPCa in our study. We did not have any inclusion or exclusion criteria related to prostate volume. We postulated that prostate volume differences were also a reason for PSAD significance between CSPCa and N-CSPCa groups. PSAD is the level of serum PSA divided by the prostate volume. Loeb et al. (16) identified 658 men age ≥50 years with PSA levels from 4-10 ng/mL and normal DRE that underwent prostate biopsy. Prostate volume had clinically significant difference between Gleason score <7 and ≥7 groups, as in our study.

PSAD is beneficial, available, cost-effective, and can be used as a tool for predicting CSPCa. Nowadays, PSAD can be combined with MRI for superior predictive ability to detect CSPCa (17,18). PSAD can also be used for predicting N-CSPCa. Therefore, PSAD can be used for better identification of candidates for active surveillance in the future, as Ha et al. (19) stated. They found that adopting a lower PSAD threshold of 0.085 decreased the risk of advanced disease to 17.5-21.7%. In our study, the PSAD cut-off was 0.130 for predicting CSPCa (sensitivity 75% and specificity 63%).

Study Limitations

The first limitation of our study is its sample size. The second limitation is that we used prostate biopsy reports for deciding clinically significant PCa as reported in Liu et al. (11) and Ceylan

et al. (10) However, the latest pathology can upgrade in radical prostatectomy specimens. It may be that some of our N-CSPCa patients had CSPCa in reality. Corcoran et al. (20) revealed that 418 of 1312 patients had an upgrade in Gleason score. Among the1312 patients, 363 had upgraded Gleason 6 to >6. This study found that PSAD was also a predictor of upgrade of biopsy Gleason 6. We could not use radical prostatectomy pathology reports for deciding CSPCa because some of our patients had chosen active surveillance or radiation therapy in our center, while others lost to follow-up or had chosen focal therapy alternatives in other centers.

Conclusion

According to the results of this study, PSAD can be used for predicting CSPCa, but not f/t PSA. PSAD is not a strong stand-alone tool owing to its sensitivity and specificity, but we suggest that PSAD can be a part of future nomograms for predicting CSPCa and future protocols for active surveillance. Therefore, we can prevent patients from overdiagnoses and overtreatment through this predictive ability.

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Ethics

Ethics Committee Approval: The study was approved by the Local Ethical Board of our hospital prior to recruitment of files (University of Health Sciences Turkey, Trabzon Kanuni Training and Research Hospital, approval number: 2021/03-01, date: 13.01.2021).

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Authorship Contributions

Critical Review: H.R.A., Concept: F.B., H.R.A., Design: F.B., Data Collection or Processing: F.B., A.Ö.G., H.Z.A., Analysis or Interpretation: F.B., A.Ö.G., H.Z.A., Literature Search: F.B., A.Ö.G., H.Z.A., Writing: F.B.

References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359-386.
2. Catalona WJ, Smith DS, Ratliff TL, et al. Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. N Engl J Med 1991;324:1156-1161.
3. Djavan B, Zlotta A, Kratzik C, et al. PSA, PSA density, PSA density of transition zone, free/total PSA ratio and PSA velocity for early detection of prostate cancer in men with serum PSA 2.5 to 4.0 ng/mL. Urology 1999;54:517-522.
4. Yoshida K, Honda M, Sumi S, et al. Levels of free prostate-specificantigen (PSA) can be selectively measured by heat treatment of serum: free/ total-PSA ratios improve detection of prostate carcinoma. Clin Chim Acta 1999;280:195-203.
5. Catalona WJ, Southwick PC, Slawin KM, et al. Comparison of percent free PSA, PSA density, and age-specific PSA cutoffs for prostate cancer detection and staging. Urology 2000;56:255-260.
6. Albertsen PC, Hanley JA, Fine J. 20-year outcomes following conservative management of clinically localized prostate cancer. JAMA 2005;293:2095-2101.
7. Lu-Yao GL, Albertsen PC, Moore DF, et al. Outcomes of localized prostate cancer following conservative management. JAMA 2009;302:1202-1209.
8. Fütterer JJ, Briganti A, De Visschere P, et al. Can clinically significant prostate cancer be detected with multiparametric magnetic resonance ımaging? A systematic review of the literature. Eur Urol 2015;68:1045-1053.
9. Mottet N, Cornford P, van den Bergh RCN, et al. EAU-EANM-ESTROESUR-ISUP-SIOG guidelines on prostate cancer. Arnhem: European Association of Urology.
10. Ceylan C, Gazel E, Keleş İ, et al. Can the free/total PSA ratio predict the Gleason score before prostate biopsy? Curr Urol 2016;9:24-27.
11. Liu J, Wang ZQ, Li M, et al. Establishment of two new predictive models for prostate cancer to determine whether to require prostate biopsy when the PSA level is in the diagnostic gray zone (4-10 ng ml(-1)). Asian J Androl 2020;22:213-216.
12. Epstein JI, Egevad L, Amin MB, et al. The 2014 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma: definition of grading patterns and proposal for a new grading system. Am J Surg Pathol 2016;40:244-252.
13. Salami SS, Palapattu GS, Partin AW, Morgan TM. Campbell Walsh Wein Urology. In: Partin AW, Dmochowski RR, Kavoussi LR, Eds. C Section XIV Prostate; 108. Prostate cancer biomarkers. 12th ed. Marylans: Elsevier; 2020.
14. Ilic D, Djulbegovic M, Jung JH, et al. Prostate cancer screening with prostate-specific antigen (PSA) test: a systematic review and meta-analysis. BMJ 2018;362:k3519. doi: 10.1136/bmj.k3519.
15. Omri N, Kamil M, Alexander K, et al. Association between PSA density and pathologically significant prostate cancer: the impact of prostate volume. Prostate 2020;80:1444-1449.
16. Loeb S, Sanda MG, Broyles DL, et al. The prostate health index selectively identifies clinically significant prostate cancer. J Urol 2015;193:1163-1169.
17. Han C, Liu S, Qin XB, et al. MRI combined with PSA density in detecting clinically significant prostate cancer in patients with PSA serum levels of 4~10ng/mL: biparametric versus multiparametric MRI. Diagn Interv Imaging 2020;101:235-244.
18. Wei C, Chen T, Zhang Y, et al. Biparametric prostate MRI and clinical indicators predict clinically significant prostate cancer in men with "gray zone" PSA levels. Eur J Radiol 2020;127:108977.
19. Ha YS, Yu J, Salmasi AH, et al. Prostate-specific antigen density toward a better cutoff to identify better candidates for active surveillance. Urology 2014;84:365-371.
20. Corcoran NM, Casey RG, Hong MKH, et al. The ability of prostate-specific antigen (PSA) density to predict an upgrade in Gleason score between initial prostate biopsy and prostatectomy diminishes with increasing tumour grade due to reduced PSA secretion per unit tumour volume. BJU Int 2012;110:36-42.