CAN PROSTATE-SPECIFIC ANTIGEN DENSITY AND FREE / TOTAL PROSTATE-SPECIFIC ANTIGEN RATIO PREDICT CLINICALLY SIGNIFICANT PROSTATE CANCER (GLEASON [?] 7) IN PATİENTS DIAGNOSED PROSTATE CANCER ON BIOPSY WITH A PROSTATE-SPECIFIC ANTIGEN LEVEL OF 2.5 -10 NG/ML?

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Abstract

Introduction Many men with non-clinically significant PCa (N-CSPCa) will not progress to become symptomatic within their lifetime. If we can predict clinically significant PCa (CSPCa), we can prevent patients from unnecessary biopsies, overdiagnoses, and overtreatment. The purpose of this study was to determine whether PSAD and f/t PSA can predict CSPCa (Gleason [?] 7) in patients diagnosed with prostate cancer on biopsy with a PSA level of 2.5-10 ng/ml or not. Materials and Methods 78 patients who underwent TRUSG-guided prostate biopsy with PSA 2.5-10.0 in our clinic between March 2017 - August 2020 and whose pathology result was reported as prostate adenocarcinoma, were retrospectively evaluated. In addition to the demographic content of the patients, PSA, free PSA, prostate size (with TRUSG), rectal examination findings and prostate biopsy pathology results were recorded. Clinically significant prostate cancer was defined as a Gleason score 7. Results The mean age of the patients was 66.9 ± 8.4, PSA value was 6.9 ± 1.8, free / total PSA ratio was 18 ± 8.1%, and PSA density 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 ROC curve (AUC) of the PSAD for predicting CSPCa was 0.719 with a 95% Cl (0.604–0.835), and the standard errors were 0.062 and 0.059, respectively. When PSAD cutoff was 0.130 for predicting CSPCa, sensitivity and specificity were 75% and 63%, respectively. Conclusion PSAD can be used for predicting CSPCa, but f/t PSA can not. PSAD is not a strong stand-alone tool with 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. Key words:prostate-specific antigen; clinically significant prostate cancer

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GLEASON [?] 7 PROSTATE CANCER PREDİCTABİLİTY

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ABSTRACT

Introduction

Many men with non-clinically significant PCa (N-CSPCa) will not progress to become symptomatic within their lifetime. If we can predict clinically significant PCa (CSPCa), we can prevent patients from unnecessary biopsies, overdiagnoses, and overtreatment. The purpose of this study was to determine whether PSAD and f/t PSA can predict CSPCa (Gleason [?] 7) in patients diagnosed with prostate cancer on biopsy with a PSA level of 2.5-10 ng/ml or not.

Materials and Methods

78 patients who underwent TRUSG-guided prostate biopsy with PSA 2.5-10.0 in our clinic between March 2017 - August 2020 and whose pathology result was reported as prostate adenocarcinoma, were retrospectively evaluated. In addition to the demographic content of the patients, PSA, free PSA, prostate size (with TRUSG), rectal examination findings and prostate biopsy pathology results were recorded. Clinically significant prostate cancer was defined as a Gleason score 7.

Results

The mean age of the patients was 66.9 ± 8.4, PSA value was 6.9 ± 1.8, free / total PSA ratio was 18 ± 8.1%, and PSA density 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 ROC curve (AUC) of the PSAD for predicting CSPCa was 0.719 with a 95% Cl (0.604–0.835), and the standard errors were 0.062 and 0.059, respectively. When PSAD cutoff was 0.130 for predicting CSPCa, sensitivity and specificity were 75% and 63%, respectively.

Conclusion

PSAD can be used for predicting CSPCa, but f/t PSA can not. PSAD is not a strong stand-alone tool with 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.

Key words: prostate-specific antigen; clinically significant prostate cancer

MAIN TEXT

Introduction

Prostate cancer (PCa) is the second most common cancer in men. An estimated 1.1 million cases were diagnosed worldwide with PCa in 2012, accounting for 15% of the cancers diagnosed in men (1). For several years, the combination of the prostate-specific antigen (PSA) and digital rectal examination (DRE) has been used to diagnose PCa early. Catalona et al. suggested using a total PSA cutoff value of 4 ng/ml in order to recommend a prostate biopsy for diagnosing PCa (2). However, more than 20% of men diagnosed with PCa have PSA levels lower than 4 ng/ml and early detection in these patients could be expected to 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 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 become symptomatic within their lifetime (6,7). If we can predict clinically significant PCa (CSPCa), we can prevent patients from unnecessary biopsies, overdiagnoses, and overtreatment. Some studies have shown that PSA, PSAD, f/t PSA can predict a Gleason score and CSPCa at the PSA level of 4-10 ng/dl (8,9). The purpose of this study was to determine whether PSAD and f/t PSA can predict CSPCa (Gleason [?] 7) in patients diagnosed with prostate cancer on biopsy with a PSA level of 2.5-10 ng/ml or not.

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 and adenocarcinoma of the prostate on TRUS biopsies. We excluded patients who had PSA levels < 2.5 or >10 and patients who have 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 pathology reports were recorded. Our primary endpoint was to assess the associations of PSAD and f/t PSA with CSPCa. CSPCa was defined as Gleason [?]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 International Society of Urological Pathology (ISUP) grading for Gleason subgroups (10) (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 of the data was carried out using the IBM Statistical Package for Social Sciences (SPSS) 20 program on the computer. The suitability of the variables to normal distribution was examined with the Shapiro Wilk Test. The Mann-Whitney U test was used to compare continuous outcome variables in two groups; one-way analysis of variance (ANOVA) 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 was used in groups that did not show normal distribution for multiple comparison. The significance level was accepted as $p < 0.05$. Two receiver operating characteristic (ROC) curves were drawn to obtain the best PSA and PSA density cutoff value for CSPCa.

Approval was obtained from the Ethical Board of Trabzon Kanuni Training and Research Hospital for this retrospective study.

Results

The mean age of the patients was 66.9 +- 8.4 (44-88), PSA was 6.92 +- 1.85 (2.69-9.91), free PSA was 1.20 +- 0.52 (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 46 patients (59%) in grade group 1, 21 patients (26.9%) in grade group 2, seven patients (9%) in grade group 3, four patients (5.1%) in grade group 4, and zero patients in grade group 5. Thirty-two patients (41%) had 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% Cl (0.549–0.793), 0.719 with a 95% Cl (0.604–0.835), and the standard errors were 0.062 and 0.059, respectively. When PSA cutoff was 6.29 for predicting CSPCa, sensitivity and specificity were 78.1% and 50%, respectively. When PSAD cutoff was 0.130 for predicting CSPCa, 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 through 1990s, PSA has evolved into an invaluable tool for detecting, staging, and monitoring prostate cancer in men. For several years, an abnormal DRE, elevated PSA, or both were used to diagnose PCa. Today, most prostate cancers are diagnosed as clinically nonpalpable (stage T1c) disease with PSA levels between 2.5 and 10 ng/mL (11). PSA screening for PCa leads to a small reduction in disease-specific mortality over 10 years but does not affect overall mortality (12). Today, attention has turned from the detection of any PCa to a focus on detecting CSPCa, often interpreted as a Gleason score [?]7 cancer (11). PSAD and f/t PSA are well-known for PCa detection, especially in PSA levels $<$ 10 ng/ml (3,5). The aim of our study is to determine f/t PSA and PSAD's value in predicting CSPCa.

Recent studies have shown that PSAD is associated with CSPCa. In Omri et al.'s study found that PSAD is correlated with CSPCa (based on radical prostatectomy pathology reports) in small ($<$ 50 cc) and medium (50-75cc) size prostates and level of PSAD is directly associated with the ISUP grade groups (13). In Liu et al.'s study, univariate and multivariate logistic regression analyses demonstrated that PSAD predicted CSPCa (based on prostate biopsy pathology reports) in the PSA level of 4-10 ng/ml (9). 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). On the other hand, 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. There was no correlation 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 thought that there was not a correlation between PSAD and CSPCa for large prostates like Omri et al. said. But we are not sure that size is $>$ 75 cc because all ISUP grade groups mean prostate volume were $<$75 cc in our study.

Ceylan et al. said that there is 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 (8). Unlike that, there was no clinical significance between f/t PSA and CSPCa in our study. Unlike PSA values, there was no clinical significance between free PSA and CSPCa. The mean free PSA was not different 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).

PSAD is beneficial, available, cost-effective, and can be used as a tool for predicting CSPCa. In the MRI era for PCa, PSAD can be combined with MRI for superior predictive ability to detect CSPCa (14,15). PSAD can also be used for predicting N-CSPCa. Therefore, PSAD may be used to identify better candidates for active surveillance in the future, as Yun-Sok Ha et al. stated. They found that adopting a lower PSAD threshold of 0.085 decreased the risk of advanced disease to 17.5–21.7% (16). In our study, the PSAD cutoff was 0.130 for predicting CSPCa (sensitivity 75% and specificity 63%).

The first limitation of our study is the limited patient population. The second limitation is that we used

prostate biopsy reports for deciding clinically significant PCa, such as Liu J et al.'s and Ceylan et al.'s studies. However, the latest pathology can upgrade in radical prostatectomy specimens. It may be that some of our N-CSPCa patients had CSPCa in reality. In Corcoran et al.'s study, 418 of 1312 patients had an upgrade in Gleason score. Of the 1312 patients, 363 had upgraded Gleason 6 to >6. This study found that PSAD was also a predictor of upgrade of biopsy Gleason 6 (17). We could not use radical prostatectomy pathology reports for deciding CSPCa because some of our patients chose active surveillance or radiation therapy in our center, while others lost follow-up or chose focal therapy alternatives in other centers.

Conclusion

According to the results of this study, PSAD can be used for predicting CSPCa, but f/t PSA can not. PSAD is not a strong stand-alone tool with 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.

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Conflict of Interests

The authors declare that there are no conflict of interests.

Author Contributions

Concept **FB, HRA** ; Data collection **FB, AOG, HZA** ; Data analysis and interpretation **FB, AOG,HZA** ; Drafting the article**FB** ; Critical revision of the article **HRA** ; Final approval of the version to be published **FB**

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Tables

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

(abb. 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]	6.5±1.8	0.010[Aa]
Free PSA	1.2±0.5	1.2±0.5	0.780[a]
PSA density	0.2±0.07[A]	0.1±0.07	0.001[Aa]
Free / total PSA ratio	16.1±7	19.1±8.6	0.084[a]
Prostate volume	47.9±16.4	57.6±20.6[A]	0.030[Ab]

(abb. 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)**	**ISU**
PSA	6.9±1.9	6.5±1.8	7.4±1.8	7.3
Free PSA	1.2±0.5	1.2±0.5	1.2±0.6	1.2
PSA density	0.2±0.08	0.1±0.08	0.2±0.07	0.1
Free / total PSA ratio	18±8.1	19.4±8.6	16.1±7.6	16.
Prostate volume	53.6±19.5	57.6±20.6	45.0±16.3	61.

(abb. ISUP: International Society of Urological Pathology, PSA: prostate-specific antigen)

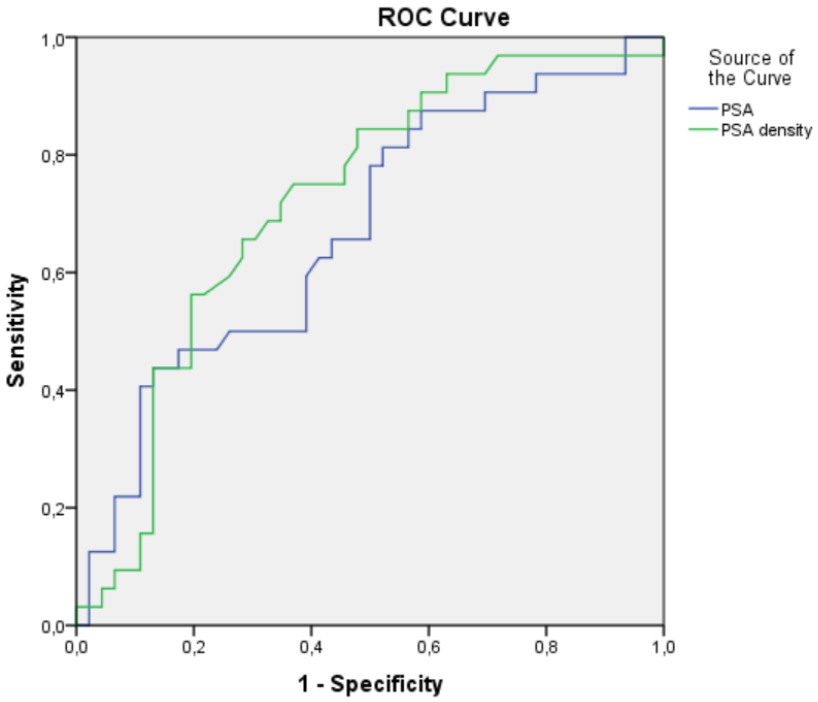
[A]Represents a statistically significant difference (P <0.05).

[a] One-Way ANOVA

[b]Kruskal Wallis-H test

Figure

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



(abb. AUC: area under the curve, PSA: prostate-specific antigen ,ROC: receiver operating characteristics, PCa: prostate cancer)