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Determination of the PSA Cut-off Value to Predict the Clinically Significant Prostate Cancer in Patients with Positive Multiparametric MRI: A Population-based Study

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Abstract

Objective: In this study, we investigated the correlation between prostate imaging reporting and data scoring system (PIRADS) grades of patients' prostate lesions detected by multiparametric prostate magnetic resonance imaging (MpMRI) and prostate specific antigen (PSA) values obtained before prostate biopsy and its role in predicting clinically significant cancer in prostatectomy specimens.

Materials and Methods: Patients who underwent biopsy and were diagnosed with prostate cancer (PCa) because of positive or negative MpMRI were evaluated. Histopathological factors were recorded, and the relationship between the PIRADS grading system and PSA values was analyzed in patients who underwent radical prostatectomy and preoperative MpMRI. PSA cut-off values predicting clinically significant PCa (CSPCa) in MpMRI were calculated.

Results: A total of 1,319 patients were included in the study. MR-fusion biopsy was performed in 58% of the patients, and malignant histopathology was detected in 49% of the patients. While 87% of the patients had CSPCa, 13% had clinically insignificant PCa. The sensitivity and specificity of the PSA 4 ng/mL cut-off value were 88.6% and 15.1% in all patient groups, respectively. In predicting CSPCa, sensitivity was 88.9% and specificity was 18.8% for PSA 4 ng/mL cut-off value in MpMRI-negative patients. If PSA >4 ng/mL in MpMRI-negative patients, there is a >45% PCa detection rate in biopsy, but biopsy is more appropriate for PSA >10 ng/mL for CSPCa. In MpMRI-positive patients, if PSA is >2.5 ng/mL, biopsy provides a >50% PCa and >30% CSPCa diagnosis. If there are PIRADS 5 lesions and PSA is >2.5 ng/mL, biopsy has a >70% PCa and >60% CSPCa detection rate.

Conclusions: It may be appropriate to consider higher PSA cut-off values (PSA >10 ng/mL) to make a biopsy decision in patients with negative MpMRI, whereas it may be possible to detect CSPCa at lower PSA values in patients with positive MpMRI findings and high PIRADS grade.

Keywords: Multiparametric magnetic resonance imaging, prostate specific antigen, prostate cancer, prostate biopsy

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Introduction

Prostate cancer (PCa) is the second most common cancer in men and is responsible for approximately 15% of all male cancers (1). Risk calculators, urine-based tests, and sophisticated imaging methods for PCa diagnosis have been developed in recent years (2,3,4,5). However, none of these devices can replace a suspected digital rectal examination and/or elevated prostate specific antigen (PSA) level for prostate biopsy at the level of guideline recommendation (6). Although there is no definite threshold value for the PSA test, which has revolutionized the diagnosis of PCa, higher values predict higher rates of cancer and clinically significant cancer (7,8,9).

Multiparametric prostate magnetic resonance imaging (MpMRI), which is a breakthrough in PCa imaging, should be performed before prostate biopsy (6). In particular, it is correlated with radical prostatectomy specimens that MpMRI has high sensitivity in detecting and localizing ISUP grade 2 cancers (10). Prostate ımaging reporting and data scoring system (PIRADS) version 2 is a system created for the international interpretation and reporting of lesions in MpMRI (11). The correlation of the PIRADS scoring system with the histopathology of prostatectomy specimens has been investigated, and we demonstrated that high PIRADS scores may be a poor prognostic criterion in our previous multicenter study (12). PCa risk continues in the case of negative MpMRI findings. In this case, the importance of PSA and digital rectal examination, which are classical diagnostic tools, is increasing. Calculation of a PSA cut-off value that can differentiate PCa from clinically significant cancer in MpMRI-negative patients may provide clinical benefit and prevent unnecessary biopsies. There are very limited data in the literature on PSA values predicting MpMRI findings and clinically significant prostate cancer (CSPCa) diagnosis. Some retrospective series conducted with a limited number of patients focused specifically on PSA values in the gray zone (4-10 ng/mL) and evaluated its correlation with high-risk cancers (13,14).

Although there is no clear threshold value and it is not a disease-specific marker, PSA is the first test to be used in PCa suspicion. Therefore, we evaluated the correlation of PSA levels with prostatectomy cancer rates in patients grouped according to PIRADS grades on MpMRI in a population-based multicenter study.

Materials and Methods

The study was conducted retrospectively with the introduction of MpMRI data into the Urologic Cancer Database-Prostate, the Urooncology Association, Turkey. Study data were collected and managed using research electronic data capture (REDCap) electronic data capture tools hosted at our institutions (15,16). REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources. A total of 1,319 patients from 15 different centers were included in the study. The data from each participating center were anonymized and entered into the database. Patients who underwent prostate biopsy and were found to have PCa because of positive or negative MpMRI were evaluated. The PSA cut-off value was investigated for positive MpMRI before biopsy. After the MpMRI findings were positive, clinically significant and clinically insignificant disease were evaluated after radical prostatectomy. The PSA cut-off value for predicting a clinically significant disease in MpMRI-positive patients was investigated.

Diagnosing lesions with clinical significance in disease management, evaluating the extent of the disease at the time of diagnosis, and determining the risk of progression are important goals. Thus, this study aims to prevent unnecessary treatments in patients with a low risk of progression. Patients who underwent 1.5 or 3 tesla MpMRI and radical prostatectomy were included in the study.

We accepted patients with PIRADS 1 and 2 lesions as potential candidates for active surveillance and these lesions as negative, and PIRADS 3-5 lesions as patients who may require active treatment, and we accepted these lesions as positive (17). Clinically significant cancer in radical prostatectomy was defined as a tumor with a volume of >0.2 cm^3, Gleason grade >7, or extracapsular extension, according to the Johns Hopkins-based definition (18). First the primary endpoint of our study was to evaluate the rates of PCa detection in MpMRI -negative and -positive patients and the change in these rates according to PSA values. Therefore, determining the PSA threshold values predicting this distinction by distinguishing clinically significant and clinically insignificant cancers in radical prostatectomy was the secondary endpoint of our study. A flowchart of the study is shown in Figure 1.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The Urooncology Association study protocol number is TUO-PR-19-02.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS, Version 20.0; SPSS, Chicago, III) was used for statistical analysis. ROC curve

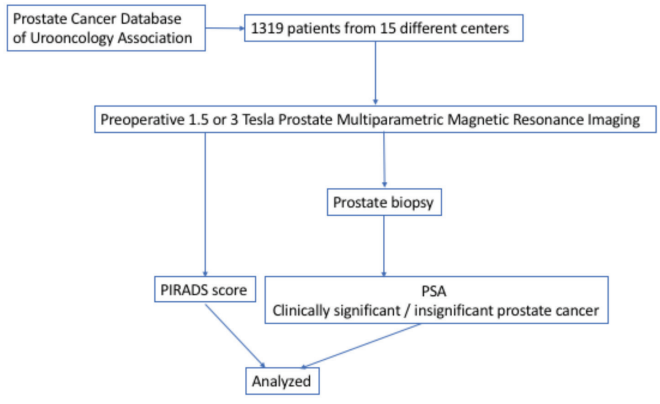

Figure 1. Flowchart of the study

PIRADS: Prostate imaging Reporting and Data Scoring System, PSA: Prostate-specific antigen

analysis was used to predict PSA levels according to preoperative MpMRI findings detecting PCa in biopsy and CSPCa in radical prostetectomy. PSA intervals were evaluated to detect the best predictive PSA cut-off in MpMRI-negative and MpMRI-positive patients for predicting PCa and CSPCa. In parallel, it was also assessed according to the PIRADS lesions in MpMRI-positive patients. Statistical significance was accepted as p-value<0.05 for all analyzes.

Results

A total of 1,319 patients who met the study criteria were included in the study. The mean PSA level was 9.1 ng/mL. Three-tesla MRI was applied to the majority of patients (82% vs. 12%). Approximately three quarters of the patients had PIRADS 4 and 5 lesions on MRI, and more than half of the patients had undergone MR-fusion biopsy. Approximately half of the patients had malignant histopathology on biopsy, and ISUP grades were mostly 1 and 2. Radical prostatectomy was performed in 656 patients, and the histopathology of the prostatectomy specimens was mostly in the ISUP grade 1-3 group, consistent with the biopsy. Surgical margins were positive in approximately one-third of the patients, and extraprostatic spread was in another third. Approximately 1 of 10 patients had lymph node metastasis and seminal vesicle invasion. Most patients had CSPCa (87% vs. 13%). The demographic and clinicalopathological characteristics of the patients are summarized in Table 1.

The sensitivity and specificity of the PSA 4 ng/mL cut-off value were 88.6% and 15.1% in all patient groups [area under the curve (AUC): 565, p<0.001]. In the analysis of 321 patients with negative MpMRI, the sensitivity of the PSA 4 ng/mL cut-off value was 87.7% and the specificity was 19.9% (AUC: 0.575, p=0.02); In the analysis of 998 patients with positive MpMRI, the sensitivity of the PSA 4 ng/mL cut-off value was 88.8% and the specificity was 13.5% (AUC: 0.560, p=0.001). The sensitivity for PSA 4 ng/mL value of those with PIRADS 5 lesions was 93.2% and the specificity was 17.9% (AUC: 0.627, p=0.004). To predict CSPCa, the sensitivity was 88.9% and specificity was 18.8% for the PSA cut-off value of 4 ng/mL in MpMRI-negative patients (AUC: 0.571, p=0.039). The ROC curve of the PSA value for patients with negative MpMRI findings (PIRADS 1-2) is shown in Figure 2. In patients with positive MpMRI, the sensitivity for PSA 4 ng/mL cut-off value was 90% and the specificity was 14% (AUC: 0.583, p<0.001). Figure 3 shows the ROC curve of PSA values for patients with positive MpMRI findings (PIRADS 3-5).

In patients with PIRADS 5 lesions, the sensitivity for PSA cut-off value of 4 ng/mL was 92.5% and the specificity was 17.5% for predicting CSPCa (AUC: 0.607, p=0.018). The relationship between PSA values, MpMRI findings, and PIRADS grades in all patient groups and patients with CSPCa is presented in Table 2.

Discussion

Various serum, urine, and imaging-based diagnostic methods are being developed for the diagnosis of PCa, which is one of the most common cancers in men. However, none of these methods can replace the gold standard diagnosis with biopsy and histopathological examination. Various modifications are being studied and different nomograms are developed to increase the accuracy of these methods and to identify only the necessary biopsies, which is an invasive and complicated procedure. For these modifications, one or more of these items are often used together. Among these, the simple and rapidly accessible PSA serum test and MpMRI, which have been used with increasing frequency in recent years, are two important diagnostic tools. We believe that determining the threshold values that can predict high PIRADS-grade lesions and associated CSPCa for PSA, which is the first diagnostic method used, may prevent overdiagnosis and overtreatment. In this multicenter study, we aimed to investigate the correlation between PIRADS grades of prostate lesions detected by MpMRI and PSA values

Table 1. Demographic and clinicopathological data

Variables		**n=1319**
Age		
PSA		9.1±12.2 (0.5-335.3)
MpMRI (tesla)	**1.5**	162 (12.3)
	3	1089 (82.6)
	N/A	68 (5.2)
Lesion in the MpMRI	**Negative**	321 (24.3)
	Positive	998 (75.7)
PIRADS grade (n=998)	**PIRADS 3**	263 (26.4)
	PIRADS 4	489 (49)
	PIRADS 5	246 (24.6)
Biopsy	**TRUS-Bx**	506 (38.4)
	MR-fusion	770 (58.4)
	Kognitive	43 (3.3)
Biopsy pathology	**Benign**	663 (50.3)
	Malign	656 (49.7)
Biopsy ISUP grade (n=656)	**ISUP 1**	294 (22.3)
	ISUP 2	195 (14.8)
	ISUP 3	81 (6.1)
	ISUP 4	42 (3.2)
	ISUP 5	44 (3.3)
Radical prostatectomy (n=656)		464 (70.7)
Radical prostatectomy ISUP grade (n=464)	**ISUP 1**	110 (23.7)
	ISUP 2	198 (42.7)
	ISUP 3	94 (20.3)
	ISUP 4	23 (5)
	ISUP 5	39 (8.4)
Surgical margin positivity (n=449)		132 (29.4)
Extraprostatic extension (n=450)		126 (28)
The seminal vesicle invasion (n=453)		45 (9.9)
Lymph node metastasis (n=219)		28 (12.8)
Clinically significant/ insignificant prostate cancer (n=464)	**Clinically insignificant**	62 (13.4)
	Clinically significant	402 (86.6)

ISUP: International Society of Urologic Pathologists, MpMRI: Multiparametric magnetic resonance ımaging, N/A: Not available, PIRADS: Prostate imaging reporting and data scoring system, PSA: Prostate-specific antigen

before prostate biopsy and to calculate PSA threshold values for predicting clinically significant cancer in prostatectomy specimens.

A diagnostic model, including MpMRI, has recently been developed to identify clinically significant and clinically insignificant PCa. In this retrospective study of 784 patients, PSA and MpMRI models for diagnostic accuracy were higher for clinically significant and insignificant PCa (19). Unlike our study, PSA derivatives were used in this study, and seminal vesicle and lymph node invasions were included in MpMRI instead of the PIRADS system. In addition, biopsy results were considered the prostate histopathology evaluated in this study. However, similar to our findings, it has been concluded that PSA and MpMRI are predictive factors for cancer aggressiveness. Very few studies in the literature have used the PIRADS system and PSA derivatives for prostate biopsy indication. In a retrospective analysis with a high number of cases reported from Korea, it was concluded that patients with a PIRADS score of ≤2 should not undergo unnecessary biopsy regardless of PSA density (PSAD), and patients with a PIRADS score of 3 should be decided according to the PSAD results (20). In this study, unlike others, biopsy-naïve and previously biopsied patients were evaluated in separate groups, and the results were confirmed in both groups. MpMRI assessments were performed by two different centers. Biopsy histopathology was also based on this study, which included several cases and most of which were clinically significant cancers. In another retrospective series, the PIRADS system and the classical parameters; PSA, prostate volume, and

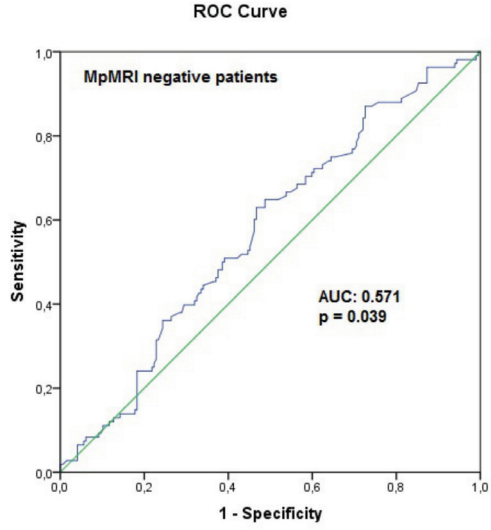

Figure 2. ROC curve analyzes of PSA values in patients with negative MpMRI findings

ROC: Receiver operating characteristics, PSA: Prostate specific antigen, MpMRI: MpMRI: Multiparametric magnetic resonance imaging, AUC: Area under the curve

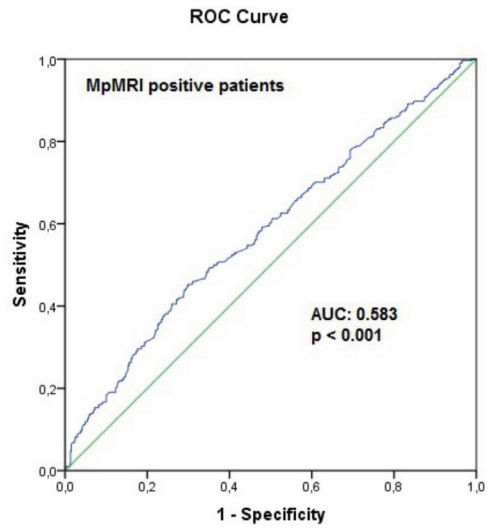

Figure 3. ROC curve analyzes of PSA values in patients with positive MpMRI findings

ROC: Receiver operating characteristics, PSA: Prostate specific antigen, MpMRI: MpMRI: Multiparametric magnetic resonance imaging, AUC: Area under the curve

Table 2. Relationship between PSA values, MpMRI findings, and PIRADS grades

	PCa (n)	PCa rates according to PSA levels (ng/mL)					p-value
		<2.5	2.5-3.99	4-9.99	10-19.99	>20	
MpMRI negative (n=321)	155	4 (33.3)	10 (30)	89 (46.8)	48 (60.8)	4 (40)	0.019
MpMRI positive (n=998)	501	8 (29.6)	48 (52.7)	302 (47.9)	95 (51.9)	48 (71.6)	0.001
PIRADS 3 (n=263)	73	2 (20)	11 (47.8)	45 (25.9)	14 (30.4)	1 (10)	0.138
PIRADS 4 (n=489)	238	4 (40)	26 (49.1)	162 (49.4)	35 (44.3)	11 (57.9)	0.805
PIRADS 5 (n=246)	190	2 (28.6)	11 (73.3)	95 (74.2)	46 (79.3)	36 (94.7)	0.002
	Clinically significant PCa (n)						
MpMRI negative (n=305)	108	2 (18.2)	8 (27.6)	61 (33.9)	34 (45.3)	3 (30)	0.054
MpMRI positive (n=822)	294	4 (19)	26 (35.1)	169 (32.9)	67 (41.9)	28 (57.1)	0.001
PIRADS 3 (n=237)	37	1 (10)	4 (23.5)	21 (13.2)	10 (23.8)	1 (10)	0.402
PIRADS 4 (n=402)	137	2 (20)	14 (31.8)	91 (34.6)	21 (30.9)	9 (52.9)	0.404
PIRADS 5 (n=183)	120	1 (16.7)	8 (61.5)	57 (62)	36 (72)	18 (81.8)	0.033

MpMRI: Multiparametric magnetic resonance imaging, PCa: Prostate cancer, PIRADS: Prostate imaging reporting and data scoring system, PSA: Prostate specific antigen

PSAD's predictive capacity for biopsy results were evaluated (21). Approximately half of the patients in this series were benign and the other half had a clinically significant cancer histopathology. In the multivariate analysis, it was concluded that the combination of PIRADS and PSAD would aid in decision making for prostate biopsy. It has been shown that PIRADS <3 and PSAD <0.15 ng/mL/mL can prevent unnecessary biopsies. Contrary to our study, the inclusion of benign histopathology may be the reason why PSA was not detected as a predictive factor in the logistic regression analysis

In another study describing factors predicting CSPCa in patients with PSA values in the gray zone (4-10 ng/mL), prostate volume, PSA density, and MpMRI were the independent factors that could define clinically significant cancer (22). tPSA appeared as a significant factor only in the univariate analysis. The small number of clinically important cancers in the gray zone (n=28) was an important limitation of this study. Most patients in our study had CSPCa. Most of this study group consisted of benign cases, and there were very few cancer cases (n=56). As a result, it is possible to expect a low mean PSA value and a limited role in distinguishing clinically important cancers. A noninvasive test that can predict a clinically insignificant or significant PCa diagnosis and reduce unnecessary biopsies is required. This requirement is a priority for patients with PSA levels in the gray zone. In another study including 104 patients in the gray zone, the PIRADS system had a high diagnostic performance in predicting CSPCa when PSA density-free PSA% was added (23). The PIRADS system, PSA, and PSAD were found to be independent predictors of PCa and CSPCa (24). Identification of the high-risk group is improved using a PIRADS system combined with PSA and PSAD. A detection rate of 96.1% was detected for high-risk PCa and 93.0% for CSPCa, and 6.1% for PCa and 2.2% for CSPCa for the low-risk group. We conclude that PIRADS v2 can be used as a reliable and independent predictor of PCa and CSPCa. The combination of the PI-RADS v2 score with PSA and PSAD can aid in the prediction and diagnosis of PCa and CSPCa and prevent unnecessary biopsies. An important aspect of the study that differentiated it from ours and others was that it divided the patients into groups as normal, gray zone, and high according to their PSA values, and differentiated clinically significant and insignificant cancer within each group separately. However, in this study, the cut-off value determined instead of PSA was the PIRADS score.

Four hundred ninety one patients were included in a study investigating the factors that would aid clinical decision-making to avoid unnecessary prostate scanning in patients with PIRADS v2 ≤3. In patients with a PIRADS score of 3, PSA and its derivatives appeared to be important factors for distinguishing clinically significant cancer, but in patients with a score ≤3, only age, PSAD, and the PIRADS system were predictive factors (25). These results reflected the results of a single center and lacked external validation. In addition, it was based on biopsy histopathology data instead of radical prostatectomy results. A nomogram that includes all these factors will differentiate clinically important cancer; therefore, studies should focus on this issue. As this study shows, the distinctive feature of PSA becomes more prominent in prostates with high PIRADS scores, which supports the results of our study.

Study Limitations

Its retrospective nature was the main limitation. One major limitation was the absence of centralization. PSA values were obtained from different laboratories, MpMRI images from different devices, and interpretations from different experts. Another limitation was that prostatectomy operations were performed in different centers by different surgeons using different methods. In addition, our study lacked new biomarkers, such as the 4 K score and PCA3. However, it is undeniable fact that this study reflects the real-life scenario better. However, being a multicenter study makes centralization and homogenization difficult. The fact that our study used PSA and MpMRI, two widely used and easily accessible devices in the diagnosis of PCA, stands out as a factor that facilitates its reproducibility and adaptation to clinical use. Another strength of our study was that prostatectomy histopathology was used as a reference instead of biopsy histopathology used in many studies.

Conclusion

In light of these results, it may be appropriate to base a biopsy decision on higher PSA values in MpMRI-negative patients, while it may be possible to detect CSPCa at lower PSA values in patients with MpMRI-positive and high PIRADS grades. Our study is a pioneering study in terms of suggesting a PSA cut-off value to distinguish clinically insignificant-significant cancer and prevent unnecessary biopsies by combining the historical diagnosis and screening tool of PSA with MpMRI PIRADS findings. Certainly, alternative prospective, multicenter studies are needed on this subject. Thus, it is possible to provide more consistent data by better demonstrating the correlation of PSA and its derivatives with the PIRADS system and their role in detecting clinically significant cancer.

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Contribution: There is not any contributors who may not be listed as authors.

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Ethics

Ethics Committee Approval: The study is structured as a database report and therefore, ethical committee approval was not sought.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.K., S.Ç., F.N., S.S., H.Ö., B.A., G.A., L.T., V.İ., B.Ş., S.E., Concept: F.K., S.Ç., Design: F.K., S.Ç., F.N., S.S., H.Ö., B.A., G.A., L.T., V.İ., B.Ş., S.E., Data Collection or Processing: F.K., S.Ç., F.N., S.S., H.Ö., B.A., G.A., L.T., V.İ., B.Ş.,

S.E., Analysis or Interpretation: F.K., S.Ç., B.Ş., Literature Search: F.K., S.Ç., Writing: F.K.

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