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RESEARCH

Predictive parameters of prostate carcinoma in negative multiparametric prostate magnetic resonance imaging patients

Negatif multiparametrik prostat manyetik rezonans görüntülemesi olan hastalarda prostat kanseri belirteçleri

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Abstract

Purpose: The aim of this study was to evaluate the predictors of prostate cancer and clinically significant prostate cancer in prostate-specific antigen grey zone patients with pre-biopsy negative multiparametric prostate magnetic resonance imaging.

Materials and Methods: The study analyzed data from 227 patients with negative pre-biopsy multiparametric prostate magnetic resonance imaging results. The detection rates of prostate cancer and clinically significant prostate cancer were calculated, and simple and multiple logistic regression were used to evaluate the predictors of prostate cancer and clinically significant prostate cancer.

Results: The overall prostate cancer rate was 18.9% and the clinically significant prostate cancer detection rate was 8.8%. Multivariate analysis revealed that prostate-specific antigen density and abnormal digital rectal examination were the independent predictive factors for prostate carcinoma, while age and abnormal digital rectal examination were the independent predictive factors for clinically significant prostate carcinoma. Prostate-specific antigen density with the cutoff value of > 0,12 ng/ml/cc had the highest area under curve values for clinically significant prostate carcinoma followed by prostate volume with a cutoff value of ≤ 46 cc.

Conclusion: Based on the findings of the study, the cutoff value of prostate-specific antigen density of > 0,12 ng/ml/cc and prostate volume ≤ 46 cc might be considered for biopsy decision in grey zone patients regardless of multiparametric prostate magnetic resonance results. However, further studies with larger cohorts are required to validate these recommendations.

Keywords:.Prostate biopsy, prostate volume, prostate-specific antigen density, prostate cancer

Öz

Amaç: Biyopsi öncesi negatif multiparametrik prostat manyetik rezonans görüntülemesi (mpMRI) olan ve prostat spesifik antijen (PSA) değeri 4-10 ng/ml olan hastalarda prostat kanseri ve klinik olarak anlamlı prostat kanserinin belirleyicilerini değerlendirilmesi amaçlanmıştır..

Gereç ve Yöntem: Çalışma, biyopsi öncesi mpMRI negatif olan 227 hastanın verilerini analiz edildi. Bu 227 hastanın patoloji raporları incelenerek hangi oranda prostat kanseri ve klinik anlamlı prostat kanseri saptandığı hesaplandı. Tek değişkenli ve çift değişkenli analizlerle hangi faktörlerin (yaş, PSA düzeyi, prostat hacmi, PSA yoğunluğu, serbest /total PSA oranı, primer biyopsi ile önceki negatif biyopsi ve parmakla rektal muayene sonuçları) prostat kanseri ve klinik anlamlı prostat kanseri için risk oluşturduğu ölçüldü.

Bulgular: Prostat kanser oranı ve klinik olarak anlamlı prostat kanseri tespit oranı sırasıyla %18,9 ve %8,8 idi. Çok değişkenli analiz, prostat kanseri için PSA yoğunluğu ve şüpheli dijital rektal muayene sonuçlarının, klinik anlamlı prostat kanseri için ise yaş ve şüpheli dijital rektal muayene sonuçlarının risk olduğunu ortaya çıkardı. Hem prostat kanseri hem de klinik anlamlı prostat kanseri için PSA yoğunluğu ve prostat hacmi en yüksek AUC değerine sahipti. Klinik anlamlı prostat kanseri için PSA yoğunluğu eşik değeri> 0.12 ng/ml/cc iken prostat hacmi eşik değeri ≤ 46 cc olarak ölçüldü.

Sonuç: Çalışmanın bulgularına göre bu grup hastalarda biyopsi kararı verebilmek için PSA yoğunluğu (> 0,12 ng/ml/ml) ve prostat hacminin (≤ 46 cc) dikkatle değerlendirilmesi önerilebilir. Bu bulguların daha yüksek hacimli çalışmalarla desteklenmesine ihtiyaç vardır.

Anahtar kelimeler: Prostat biyopsisi, prostat hacmi, prostat spesifik antijen yoğunluğu, prostat kanseri

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INTRODUCTION

According to the latest guidelines, multiparametric prostate magnetic resonance imaging (mpMRI) should be routinely offered to all patients who are candidates for prostate biopsy[1]. This advanced imaging technology has changed the diagnostic pathway for prostate carcinoma (PCa), and its regular implementation can significantly enhance the accuracy of clinically significant PCa (csPCa) diagnosis while decreasing unnecessary biopsies[2-4].

The mpMRI results are interpreted and categorized using the Prostate Imaging-Reporting and Data System (PI-RADS)[5]. While current urology guidelines recommend targeted and systematic biopsies for patients with suspicious lesions on mpMRI, scored as PI-RADS ≥ 3[1], there is a lack of clear recommendations for patients with no visible lesions on mpMRI, classified as PI-RADS ≤ 2, often referred to as negative mpMRI[1,2]. Pre-biopsy negative mpMRI accounts for 27–44% of all prostate biopsy candidates[6-8], and studies have shown that patients with negative pre-biopsy mpMRI may have PCa and csPCa, with rates of up to 26% and 18%, respectively[3,8,9]. Additionally, biopsy pathology results are less precise than those obtained from radical prostatectomy (RP) specimens, and research has demonstrated that up to 30% of biopsy pathology results may be upgraded[10]. Therefore, it is essential to make a biopsy decision in this group, and traditional parameters are used to make this decision. These parameters mainly include age, prostate-specific antigen (PSA), prostate volume (PV), free PSA (fPSA), free-to-total PSA ratio (f/t PSA), PSA density (PSAD), and digital rectal examination (DRE). In studies with negative mpMRI patients, Haack et al.[11] identified age, PV, PSA, and fPSA as independent predictors of PCa, while Panebianco et al.[12] found that age, PSA, and PSAD were independent predictors of csPCa in a multivariable analysis. Liang et al.[13], in their study involving patients with negative bi-parametric prostate MRI, suggested that those with PSAD ≥ 0.15 ng/ml/cc, a suspicious DRE, and no prior history of prostate biopsy should undergo a biopsy. However, Schoots et al.[14] stated that biopsy could be considered only for patients with PSAD ≥ 0.20 ng/ml/cc in negative mpMRI patients.

The present study aimed to identify predictive parameters for PCa and csPCa in PSA gray-zone patients with negative mpMRI results who underwent systematic ultrasonography-guided transrectal prostate biopsy (TRUS-PB) and evaluate their priority. Our main goal was to prevent unnecessary biopsies in patients with pre-biopsy negative mpMRI by determining the risk groups based on clinical parameters.

MATERIALS AND METHODS

Sample

We retrospectively reviewed our prospectively maintained database of 628 patients who underwent diagnostic pre-biopsy mpMRI and TRUS-PB at the urology department of the Karabuk Training and Research Hospital from January 2019 to December 2023. The ethics committee of Karabuk University approved the study (reference number 2024/1641) on February 11, 2024. Informed consent was obtained from all the participants.

The data for the study, including PSA, fPSA, PV, DRE, mpMRI reports, and pathology results, were electronically available in our hospital database. However, data for each patient undergoing prostate biopsy at our clinic were meticulously recorded separately, and we followed the patients prospectively. In addition to clinical information, details such as the prophylactic antibiotic used during the biopsy, type of anesthesia administered, visual pain scale scoring, and body mass index were routinely documented for each biopsy patient. Patients were thoroughly informed about potential complications and requested to return for a follow-up visit one week after the procedure.

Our biopsy indications were a PSA level ≥ 4 ng/ml, abnormal DRE, prior biopsy outcomes showing suspicion of PCa, or for staging purposes. Over the past five years, suspicious mpMRI results have been added to our biopsy indications. The study included patients with PSA values between 4-10 ng/ml, PI-RADS score < 3, and no prior diagnosis of PCa. Patients with biopsy results indicating high-grade prostatic intraepithelial neoplasia (HGPIN) or atypical small acinar proliferation (ASAP) were also eliminated. Of the 628 patients initially considered, 94 were eliminated because their PSA values were outside the 4-10 ng/ml range. Additionally, 268 patients were eliminated because their PI-RADS scores were > 2. Eight more patients were eliminated because previous biopsies showed PCa, leaving a total of 258 patients. Among these, 29 were

eliminated due to pathology results showing ASAP, and two more were eliminated because of HGPIN. Ultimately, 227 patients met all criteria and were included in the study.

Procedure

The TRUS-PB procedure involved obtaining 10–12 cores in the same biopsy room under local anesthesia. All biopsies were performed by the same urology doctor with 25 years of experience (CB) using the same ultrasonography device (Aloka ProSound 5500SV) and a disposable automatic biopsy gun (18 gauge-24 cm) while the patient was in the left decubitus position. We employed the Magnetom Essenza by Siemens, a 1.5 Tesla machine with T2-weighted, diffusion-weighted, and dynamic contrast-enhanced imaging. Spectroscopy was not performed. The mpMRI results were assessed by experienced radiologists who agreed with our hospital.

PV was calculated using the ellipsoid formula (0.52 × width × depth × height) based on measurements obtained from the mpMRI images. Serum PSA and fPSA levels were specifically obtained from patients prior to undergoing procedures, including DRE or catheterization, and were promptly analyzed within 4-6 hours in our hospital's laboratory. PSA results from external facilities were not considered.

Pathological assessments were performed at the pathology department of our hospital. Based on the pathology results, the patients were categorized into the benign prostatic hyperplasia (BPH) and PCa groups. Patients with pathological results showing ASAP or HGPIN were not included in the study. Patients with prostatic intraepithelial neoplasia (PIN) (13 patients) and BPH (171 patients) were classified into the BPH group (184 patients). Patients with a Gleason score ≥ 6 were assigned to the PCa group (43 patients). In comparison, GS ≥ 7 denoted the csPCa group (20 patients), while GS < 7 represented clinically insignificant PCa group (cisPCa) (23 patients), according to the International Society of Urological Pathology (ISUP) grading[15]. We computed the median and interquartile range (IQR) for age, PSA level, PV, f/t PSA ratio, number of biopsy cores, PSAD, and number and percentage of DRE for each group. We also assessed whether the biopsy was primary or repeated. Subsequently, we analyzed age, PSA level, PV, f/t PSA ratio, PSAD, DRE results, and biopsy type to identify the potential predictors of PCa and csPCa.

Statistical analysis

The power analysis of the study determined that a minimum 42 to 63 patients with negative mpMRI results were required to detect a statistically significant area under the curve (AUC) value of 0.660 for PSA between those with and without PCa[13]. This calculation assumed a group size ratio of 1 to 1.5 ($\alpha = 0.05$, $1\text{-}\beta = 0.80$) and was performed using MedCalc version 20.115. For statistical analysis, analysis of variance (ANOVA) was used for normally distributed parameters. Non-normally distributed variables were analyzed using Kruskal–Wallis and Dunn tests. The chi-squared test was used to examine the relationships between categorical variables. Univariate and multivariate logistic regression analyses used to identify the independent predictors of PCa and csPCa. Variables included age, PV, PSAD, f/t PSA, abnormal DRE, primer biopsy, PNB, and a number of cores. Receiver operating characteristic (ROC) curve analysis and AUC values were used to determine the priority of parameters, such as age, PSA, PV, f/t PSA, PSAD, and abnormal DRE for both PCa and csPCa. This analysis was performed using SPSS version 22.0 for Windows. We calculated hazard ratios and 95% confidence intervals, considering p-values less than 0.05 as significant.

RESULTS

Patients' data according to the pathological groups are summarized in Table 1. Among the 227 patients included in the study, the pathology results were distributed as follows: 7% (13/227) for patients with PIN, 75.3% (171/227) for BPH, 18.9% (43/227) for PCa, 8.8% (20/227) for csPCa, and 10.1% (23/227), for cisPCa. The BPH group consisted of 171patients with BPH and 13 patients with PIN, totaling 184 patients (81.1%). The PCa group including 43 patients (18.9%) was divided into csPCa group (20 patients, 8.8%) and cisPCa group (23 patients, 10.1%). Of the included patients, 194 (85.4%) underwent a primary biopsy while 33(14.5%) had a previous negative biopsy (PNB).

No statistically significant differences were observed between the groups in terms of age, PSA levels, and number of biopsy cores. When comparing cisPCa and csPCa, no significant differences were found in parameters such as fPSA, PV, f/t PSA, PSAD, and DRE results. However, statistically significant differences in these parameters were observed

between the cisPCa and csPCa groups compared to the BPH group. Patients with PCa and csPCa exhibited higher PSAD levels but lower fPSA, PV, f/t PSA, PNB, and abnormal DRE results than those in the BPH group. A detailed comparison of parameters according to pathology results is provided in Supplementary Material 1.

The results of univariate analysis suggested that PV, PSAD, f/t PSA, and abnormal DRE were predictors of PCa. However, multivariate analysis indicated that only PSAD and abnormal DRE were significant risk factors. For csPCa, univariate analysis showed that PV, PSAD, f/t PSA, and abnormal DRE were all predictive factors, while multivariate analysis suggested that only age and abnormal DRE were independent risk factors (Table 2).

This study also aimed to assess the priority of the parameters in detecting both PCa (Figure 1) and csPCa (Figure 2) using ROC curve analysis. In detecting PCa, PSAD and PV demonstrated the highest AUC value of 0.786, followed by f/t PSA, with an AUC of 0.711. For the detection of csPCa, PSAD revealed the highest AUC value of 0.802, followed by PV (AUC = 0.795), and abnormal DRE (AUC = 0.725).

The PSAD cutoff value for detecting PCa was determined to be > 0.12 ng/ml/cc, resulting in a sensitivity of 65.12% and specificity of 88.04%. A PV cutoff value of ≤ 53 cc achieved a sensitivity of 74.4% and specificity of 73.9%, while for f/t PSA, cutoff values of ≤ 0.15 showed a sensitivity of 44.1% and specificity of 93.48%.

For csPCa, the determined PSAD cutoff value (> 0.12 ng/ml/cc) achieved a sensitivity of 70.0% and specificity of 88.04%. Similarly, a PV cutoff value of ≤ 46 cc yielded a sensitivity of 70.0% and specificity of 82.0%, while for f/t PSA, a cutoff value of ≤ 0.15 showed a sensitivity of 50.0% and specificity of 93.48% (Table 3).

Table 1-Demographic characteristics and patient classification by pathology results for PSA grey zone patients with PI-RAD scores of 1 and 2 who underwent transrectal prostate biopsy.

Parameters	BPH	cisPCa	csPCa	p
No of patients n,(%)	184 (81.1)	23 (10.1)	20 (8.8)	
Age years m,(IQR)	64.5 (59 -68)	65 (58 -69)	67.5 (62 -71)	0.182†
PSA ng/ml m,(IQR)	5.6 (4.6 -7.35)	5.9 (5.2 -7.3)	5.75 (5.05 -6.9)	0.831ǂǂ
f PSA ng/ml m,(IQR)	1.4 (1.1 -1.8)	1 (0.8 -1.7)	1.1 (0.7 -1.4)	0.001*ǂǂ
PV ml m, (IQR)	66 (53 -90)	45 (28 -55)	38.5 (27 -56.5)	0.001*ǂǂ
PSAD ng/ml/cc m,(IQR)	0.09 (0.06 -0.11)	0.14 (0.1 -0.22)	0.14 (0.11 -0.2)	0.001*ǂǂ
f/t PSA ratio m,(IQR)	0.25 (0.2 -0.31)	0.18 (0.13 -0.25)	0.17 (0.13 -0.26)	0.001*ǂǂ
No. of biopsy cores m, (IQR)	12 (12 -12)	12 (12 -12)	12 (12 -12)	0.053ǂǂ
Primer biopsy n.(%)	153 (83.2)	23 (100.0)	18 (90.0)	0.015*‡
PNB n, (%)	31 (16.8)	0 (0)	2 (10.0)	
DRE normal n,(%)	138 (75.0)	9 (39.19)	6 (30.0)	0.001*‡
DRE abnormal n,(%)	46 (25.0)	14 (60.9)	14 (70.0)	

†ANOVA test ǂǂ Kruskal Wallis and Dunn tests, ‡Chi-square test

BPH: benign prostate hyperplasia cisPCa: clinically insignificant prostate carcinoma csPCa: clinically significant prostate carcinoma DRE: digital rectal examination f/t PSA: free to total PSA ratio PI-RADS: Prostate imaging-reporting and data system IQR: interquartile range m: median PNB: previous negative biopsy PSA: prostate specific antigen PSAD: prostate specific antigen density PV: prostate volume

Table 2- Predictive parameters for prostate cancer and clinically significant prostate cancer through univariate and multivariate analysis in PSA grey zone patients with PI-RAD scores of 1 and 2.

Parameters	Univariate analysis	p < 0.05	Multivariate analysis	p < 0.05
PCa	OR (95% CI)		OR (95% CI)	
Age	1.03(0.98-1.09)	0.257	1.06 (0.99 -1.14)	0.102
PV	0.95(0.93-0.97)	0.001*	0.98 (0.95 -1.01)	0.128
PSAD*10	9.28(4.11-20.98)	0.001*	3.07 (1.08 -8.74)	**0.035***
f/t PSA*10	0.38(0.24-0.62)	0.001*	0.6 (0.36 -1.02)	0.058
Abnormal DRE	5.60(2.75-11.40)	0.001*	5.3 (2.2 -12.78)	**0.001***
Primer biopsy	4.15(0.95-18.08)	0.058	4.86 (0.88 -26.64)	0.069
PNB	0.24(0.05-1.05)	0.058	0.21 (0.04 -1.13)	0.069
No of biopsy core	1.02(0.59-1.76)	0.935	1.55 (0.79 -3.04)	0.200
csPCa	OR (95% CI)	p < 0.05	OR (95% CI)	p < 0.05
Age	1.08(0.99-1.16)	0.070	1.14 [1.02 -1.27]	**0.018***
PV	0.95(0.92-0.97)	0.001*	0.98 [0.94 -1.01]	0.202
PSAD*10	9.60 (3.49-26.42)	0.001*	2.48 [0.71 -8.66]	0.156
f/t PSA*10	0.30(0.15-0.60)	0.001*	0.42 [0.16 -1.13]	0.086
Abnormal DRE	7.00(2.54-19.28)	0.001*	9.88 [2.48 -39.4]	**0.001***
Primer biopsy	1.82(0.40-8.26)	0.436	1.65 [0.27 -10.27]	0.589
PNB	0.55(0.12-2.49)	0.436	0.6 [0.1 -3.76]	0.589
No of biopsy core	0.52(0.25-1.09)	0.084	0.7 [0.26 -1.86]	0.472

*PSAD and f/t PSA multiplied by ten

CI: confidence interval csPCa: clinically significant prostate carcinoma DRE: digital rectal examination f PSA: free prostate specific antigen f/t PSA: free total PSA ratio OR: odds ratio PCa: prostate carcinoma PI-RADS: Prostate imaging-reporting and data system PSA: prostate specific antigen PSAD: prostate specific antigen density PNB: previous negative biopsy

Table 3. Threshold values, sensitivity, and specificity of various parameters for prostate carcinoma and clinically significant prostate carcinoma in PSA grey zone patients with PI-RADS Scores of 1 and 2.

Parameters for PCa	Cutoff value	Sensitivity	95% CI	Specificity	95% CI
Age (years)	>63	65.12	49.1- 79.0	47.28	39.9- 54.8
PSA (ng/ml)	>5.1	76.74	61.4- 88.2	35.33	28.4- 42.7
PV (cc)	≤53	74.42	58.8-86.5	73.91	66.9-80.1
PSAD(ng/ml/cc)	>0.12	65.12	49.1-79.0	88.04	82.5-92.4
f/t PSA (ratio)	≤0.15	44.19	29.1-60.1	93.48	88.9-96.6
Abnormal DRE	>0	65.12	49.1-79.0	75.00	68.1-81.1
Primer biopsy	>0	95.35	84.2-99.4	16.85	11.7-23.1
Parameters for csPCa	Cutoff value	Sensitivity	95%CI	Specificity	95%CI
Age (years)	>67	50.00	27.2-72.8	72.28	65.2-78.6
PSA (ng/ml)	>5.6	60.00	36.1-80.9	51.09	43.6-58.5
PV (cc)	≤ 46	70.00	45.7-88.1	82.07	75.7- 87.3
PSAD(ng/ml/cc)	>0.12	70.00	45.7-88.1	88.04	82.5-92.4
f/t PSA (ratio)	≤0.15	50.00	27.2-72.8	93.48	88.9-96.6
Abnormal DRE	>0	70.00	45.7-88.1	75.00	68.1-81.1
Primer biopsy	>0	90.00	68.3-98.8	16.85	11.7-23.1

csPCa: clinically significant prostate carcinoma DRE: digital rectal examination f/t PSA: free total PSA ratio PCa: prostate carcinoma PI-RADS: Prostate imaging-reporting and data system PSA: prostate specific antigen PSAD: prostate specific antigen density PV: prostate volume

The study also analyzed the impact of primer biopsy with PNB, revealing that only 6% (2/33) of PNB patients had csPCa, while 9.3% (18/194) of primer biopsy patients had csPCa. However, no statistically significant differences were observed between the groups. ROC curve analysis of primer biopsies for PCa and csPCa is provided in Supplementary Material 2.

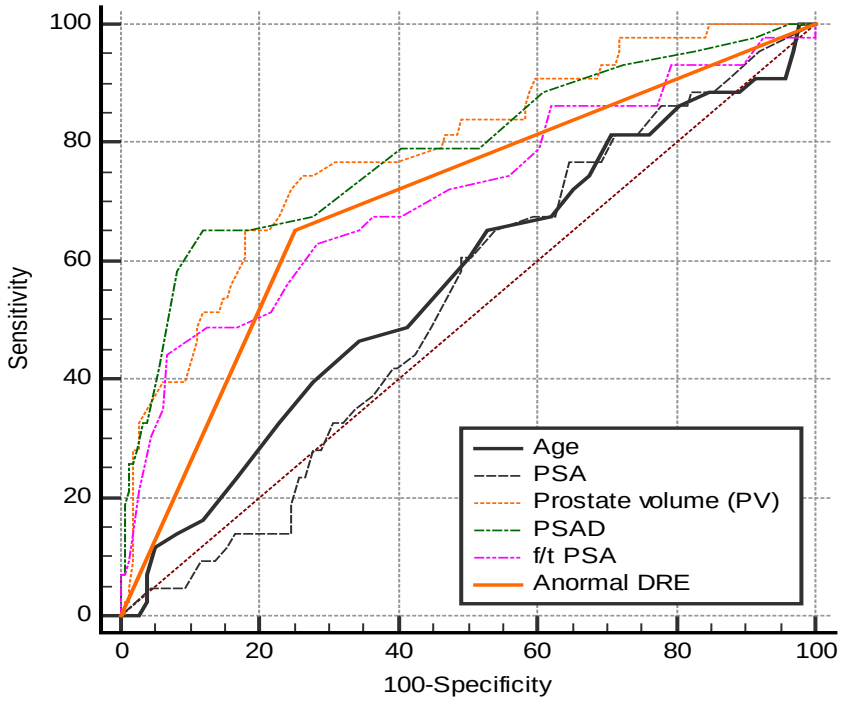

Figure 1-ROC curve analysis and corresponding AUC values of various parameters for prostate carcinoma in PSA grey zone patients with PI-RAD scores of 1 and 2.

Variable	AUC	SE [a]	95% CI [b]
Age	0.565	0.0497	0.498 to 0.630
PSA	0.530	0.0456	0.463 to 0.596
PV	0.786	0.0397	0.726 to 0.837
PSAD	0.786	0.0434	0.727 to 0.838
f/t PSA	0.711	0.0488	0.647 to 0.769
Abnormal DRE	0.701	0.0462	0.636 to 0.759

[a]Hanley & McNeil, 1982 [b]Binomial exact
AUC: area under curve DRE: digital rectal examination f/t PSA: free total PSA ratio
PI-RADS: Prostate imaging-reporting and data system PSA: prostate specific antigen PSAD: prostate specific antigen density PV: prostate volume ROC curve: receiver operating characteristic curve

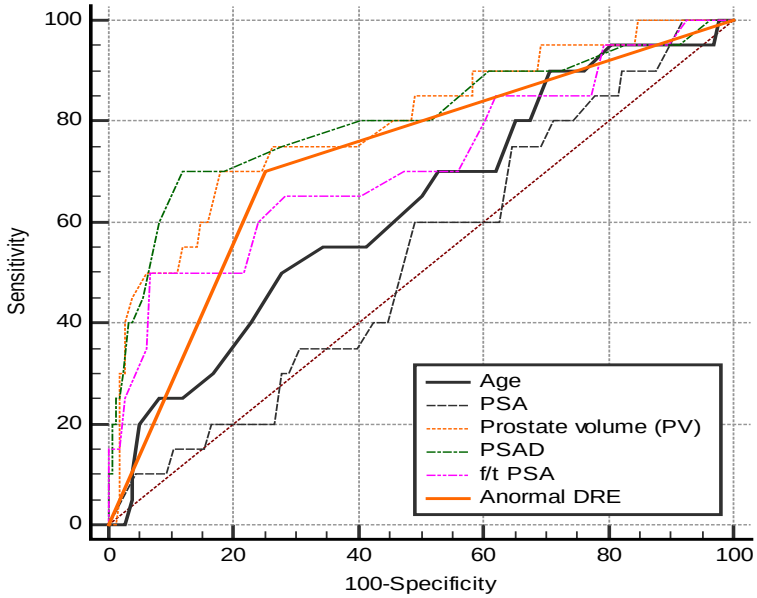

Figure 2. ROC curve analysis and corresponding AUC values of various parameters for clinically significant prostate carcinoma in PSA grey zone patients with PI-RAD scores of 1 and 2.

Variable	AUC	SE [a]	95% CI [b]
Age	0.629	0.0663	0.559 to 0.696
PSA	0.530	0.0647	0.459 to 0.600
PV	0.795	0.0581	0.733 to 0.848
PSAD	0.802	0.0633	0.741 to 0.855
f/t PSA	0.714	0.0697	0.647 to 0.775
Abnormal DRE	0.725	0.0622	0.658 to 0.785

[a]Hanley & McNeil, 1982 [b] Binomial exact
AUC: area under curve DRE: digital rectal examination f/t PSA: free total PSA ratio
PI-RADS: Prostate imaging-reporting and data system PSA: prostate specific antigen PSAD: prostate specific antigen density PV: prostate volume ROC curve: receiver operating characteristic curve

DISCUSSION

Our study aimed to identify predictive parameters for PCa and csPCa among patients with negative pre-biopsy mpMRI results. Multivariate analysis revealed that PSAD and abnormal DRE were independent predictive factors for PCa, whereas age and abnormal DRE were the independent predictive factors for csPCa. PSAD and PV had the highest AUC values for PCa in ROC curve analysis. Similarly, PSAD had the highest AUC value for csPCa, followed by PV.

In our study, the overall detection rate of PCa was 18.9%, with csPCa detected in 8.8% of cases, which is consistent with findings in the existing literature. However, in studies in which RP pathology results were used as a reference, patients with negative mpMRI results tended to have a higher incidence of confirmed csPCa. For instance, Johnson et al. reported csPCa rates of up to 34% in patients with negative mpMRI results when analyzing the whole-mount pathology of prostate glands[16]. Similarly, Stabie et al. observed that csPCa was detected outside of the index lesion on mpMRI at a rate of 30%[17]. Furthermore, in a study of 1042 men undergoing template prostate biopsy, the incidence of csPCa increased from 12% to 28% in patients with negative mpMRI when RP pathology results were used as a reference[18]. Thus, patient selection for biopsy becomes crucial in cases with negative mpMRI results, wherein PSAD emerges as a widely utilized parameter for patient stratification. PSAD is

prominently featured in the European Association of Urology (EAU) guidelines, offering a framework for risk assessment and subsequent biopsy recommendations[1,14]. According to EAU guidelines, the recommendation for the low-risk group (< 0.10 ng/ml/cc) is to "skip a biopsy", while for the low-intermediate-risk group (0.10–0.15 ng/ml/cc) and intermediate-high-risk group (0.15–0.20 ng/ml/cc), "no biopsy" is advised. However, for high-risk groups (≥ 0.20 ng/ml/cc), "consider biopsy" is recommended. Adhering to these guidelines, our study revealed potential instances of undetected cases, with 7.5% (9/119) of PCa and 3.3% (4/119) of csPCa in the low-risk group, which was considered an acceptable risk. In the low-intermediate-risk group, these rates increased to 22.9% (20/87) for PCa and 9.1% (8/87) for csPCa. In the intermediate-high-risk group, we would have failed to detect 42.8% (3 out of 7) of PCa cases and an equal percentage of csPCa cases, below acceptable thresholds. In the present study, the detection rates of PCa and csPCa in the high-risk group (≥ 0.20 ng/ml/cc) were 78.5% (11/14) and 35.7% (5/14), respectively. Similarly, Nordström et al. also categorized PSAD into three groups and discovered that the highest rate of GS ≥ 7 was associated with the rate of 46.2% when PSAD > 0.2 ng/ml/cc (95% CI 42.4–50.0). They reported that each 0.01 increase in PSAD increased the likelihood of GS ≥ 7 cancer 6-fold (OR 1.06; 95% CI 1.05–1.07). The authors also found that the correlation between PCa and PSAD was limited to tumors with a GS ≥ 7, suggesting that PSA passage into the circulation increases in high-grade tumors[19].

Furthermore, a meta-analysis by Pagniez et al. investigated indicative parameters for csPCa in patients with negative mpMRI results, revealing PSAD as the strongest predictor[20]. Similarly, Buisset et al. observed that PSAD ≥ 0.15 ng/ml/cc, along with factors such as a family history of PCa and clinical stage ≥ T2a, predicted csPCa in patients with negative mpMRI results[21]. Moreover, Oishi et al. recommended prostate biopsy in mpMRI negative patients who had a PSAD > 0.15 ng/ml/cc if they had no prior biopsy history[22].

The f/t PSA ranked third in terms of the AUC value for PCa and fourth for csPCa. Compared with other parameters, there are limited studies in the literature on f/t PSA in patients with negative mpMRI. In one of them, Artiles et al. recommended biopsy for patients with f/t PSA < 0.2 who had negative mpMRI[23]. In contrast, the present study demonstrated that the cutoff value of f/t PSA was ≤ 0.15 for both PCa and csPCa.

In the present study, PV in conjunction with PSAD, exhibited the highest AUC value for detecting PCa and the second-highest AUC value for detecting csPCa. The inverse correlation between PV and PCa has been previously established in a meta-analysis by Moolupuri et al.[24]. Additionally, Articles et al., in their study involving saturation biopsy in patients with negative mpMRI, identified a smaller PV as an independent risk factor for csPCa. They reported that a PV > 50 cc significantly predicted the absence of csPCa on saturation biopsy (OR 0.11, 95% CI 0.01–0.94, p=0.04)[23]. The cutoff values for PV in the present study were ≤ 53 cc for PCa and ≤ 46 cc for csPCa. Compared with PV > 50cc as a reference, our findings revealed PCa in 9.3% (15/165) of patients and csPCa in only 3.8% (6/160) of patients, which is consistent with the existing literature.

Although a high PSA level triggers the initiation of biopsy procedures, the present study found that PSA had the lowest AUC value compared to the other parameters for both PCa and csPCa. PSA has long been criticized for its low sensitivity and specificity, with PSA > 4.0 ng/ml having an approximate sensitivity of only 20% and specificity of 60–70%[25]. Moreover, PSA levels within the range of 4-10 ng/ml have shown PCa detection rates ranging from approximately 22.0 to 43.5%[26,27]. Notably, more than 20% of men diagnosed with PCa exhibit PSA levels of < 4 ng/ml[28]. In a comprehensive meta-analysis, PSA level and DRE demonstrated low positive predictive values for detecting PCa, approximately 25.1% and 17.8%, respectively[29]. In contrast, in our study, abnormal DRE was the only parameter identified as a predictive risk factor for both PCa and csPCa in the multivariate analysis, and it had the third highest AUC value for csPCa detection. In addition, in our cohort, 90.1% of patients (138/153) with normal DRE results were diagnosed with BPH. We attribute these high rates to the consistent performance of DRE by a single urologist with 25 years of experience who also conducted all biopsies.

In our multivariate analysis, age also emerged as a predictive risk factor for PCa with a cutoff age of > 63 years, showing a sensitivity of 65.1% and specificity of 47.2%. Similarly, for csPCa, the cutoff age was > 67 years, with a sensitivity of 50.0% and specificity of 72.2%. Furthermore, we evaluated the impact of primer biopsy with PNB. We found that

only 6% of PNB patients had csPCa, compared to 9.3% of primer biopsy patients, indicating no statistically significant difference.

Our study has several limitations. First, it was conducted at a single center and had a retrospective design, with a relatively small patient sample. Second, we relied solely on the biopsy pathology results, which may be upgraded upon pathological examination of radical prostatectomy specimens. The strength of our study was that although it was a retrospective study in nature, we have taken great care in updating the data of patients who underwent biopsy in our clinic. Furthermore, all PV measurements, DRE, and biopsies were performed by a single qualified doctor, ensuring consistency in the study standards.

In conclusion, the decision to perform biopsy in patients with suspected prostate cancer who have negative mpMRI results remains a controversial issue in urology. The radiologist's experience in interpreting mpMRI is crucial in this context. In addition to the PSAD value recommended in the EAU guidelines, factors such as age, PV, and f/t PSA ratio might also be considered in the biopsy decision-making process. However, it is more appropriate to evaluate each patient individually rather than generalize. According to the results of our study, we might recommend considering a biopsy for patients in the PSA grey zone who are over 67 years old, have a PV of ≤ 46 cc, a PSAD of > 0.12 ng/ml/cc, and an f/t PSA ratio of ≤ 0.15, regardless of MRI results. Nevertheless, further studies with larger cohorts are needed to validate this recommendation.

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