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# Predictors of prostate carcinoma in PSA gray zone patients with PI-RADS score of 3

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**Abstract**

Our aim was to evaluate the predictors of prostate cancer and clinically significant prostate cancer in patients with prostate-specific antigen (PSA) level between 4-10 ng/ml who had pre-biopsy Prostate Imaging–Reporting and Data System (PI-RADS) score of 3. The study analyzed data from 94 patients who underwent transrectal prostate biopsy with the PI-RADS score of 3 between January 2019 and December 2023. The detection rates of prostate cancer and clinically significant prostate cancer were calculated. Simple and multiple logistic regression analysis were conducted to evaluate the predictors of prostate cancer and clinically significant prostate cancer. The receiver operating characteristics curve analysis and area under curve values were used to determine the priority of parameters. In our study, the incidence of PI-RADS 3 lesion was 18.5%. The overall prostate cancer detection rate was 38.2% with the clinically significant prostate cancer detection rate was 22.3%. For prostate carcinoma and clinically significant prostate carcinoma logistic regression analysis revealed that free to total prostate-specific antigen (f/t PSA) ratio and age were the independent predictors. Receiver Operating Characteristic curve analysis and area under curve revealed that f/t PSA ratio had the highest value (0.770) followed by prostate volume (PV) (0,751) for clinically significant prostate cancer. Prostate-specific antigen density (PSAD) had the third highest area under curve value of 0.739. Although current guidelines recommend not performing biopsy for patients with PSAD<0.10 ng/ml/cc in patients with PI-RADS score 3, our clinically significant prostate cancer detection rate was 13% with this level. Therefore, we recommend that each patient should be evaluated individually with PI-RADS score 3. For deciding on biopsy, not only PSAD but also f/t PSA and PV should be considered, especially in PSA gray zone patients. However, further studies with more patients are required to validate this recommendation.

**Keywords:** prostate biopsy, PI-RADS, prostate-specific antigen density, prostate cancer

## 1. Introduction

Prostate carcinoma (PCa) is one of the most common cancers in men (1), and prostate biopsy, which is invasive and may lead to complications, including sepsis (2), is the only method for pathological diagnosis.

Traditionally ultrasonography-guided transrectal prostate biopsy (TRUS-PB) has been criticized for missing clinically significant prostate carcinoma (csPCa) which is defined as Gleason grade ≥2, while detecting clinically insignificant prostate carcinoma (cisPCa) defined as Gleason grade ≤ 1 (3), primarily due to the low sensitivity and specificity of prostate-specific antigen (PSA) and suspicious digital rectal examination (DRE), which triggers the biopsy procedure (4).

A new imaging technique, multiparametric prostate magnetic resonance imaging (mpMRI), which has been recommended by current urology guidelines for all biopsy candidate patients (5), has emerged as the new standard for biopsy decisions, because it has a high sensitivity for csPCa (6). Prostate Imaging–Reporting and Data System (PI-RADS) scoring was introduced to specify more consistent and adjusted mpMRI results, especially for csPCa (7). The system uses a scoring system starting from 1 to 5, with scores of 1 and 2 indicating a low and very low risk of csPCa, while scores of 4 and 5 indicate a high or very high risk of csPCa, respectively (8). However, a PI-RADS score of 3 indicates an 'intermediate' or 'equivocal' risk for csPCa. There are specific recommendations in the urology guidelines for patients with PRADS scores < 3 and > 3, but there are no specific recommendations for patients with a score of 3. Some authors recommend immediate biopsy(targeted or combined with systematic biopsy) (9), while others suggest follow-up without a biopsy but mpMRI and PSA (10). However, targeted biopsy is unavailable in every center, including our hospital. According to our urology department principle, we recommend that every patient with a PI-RADS 3 lesion should be referred to advanced centers in other cities for targeted biopsy. Nevertheless, only some patients can undergo this procedure, and some prefer a biopsy at our hospital.

In addition, mpMRI results vary depending on the radiologist who evaluates them. Although the PI-RADS classification was designed to reduce mpMRI inter-observer variability, this inter-observer variability can reach up to 54% (11). For this reason, the first option may be to seek the opinion of a second radiologist, who is experienced in evaluating mpMRI, before the biopsy decision since 51% of unnecessary biopsies could be avoided, and 34.5% of men with low suspicion for csPCa could safely skip prostate biopsy (12).

The objective of the present study was to conduct a comparative analysis of our standard systematic 12-core

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TRUS-PB pathology results in patients having a PI-RADS score of 3 with the available literature. The study also aimed to identify the predictors for PCa and csPCa in PI-RADS 3 lesion patients.

## 2. Materials and methods

### 2.1. Study design and patients

This retrospective single-center study included PSA grey-zone patients with PI-RADS 3 lesions who underwent TRUS-PB at our tertiary referral hospital from January 2019 to December 2023.

We thoroughly reviewed the electronic media database of 628 patients who underwent diagnostic pre-biopsy mpMRI and TRUS-PB at our institution. Our biopsy criteria included a PSA level≥ 4 ng/ml and any hardness or suspicious nodule on DRE, as well as lesions on mpMRI findings, suspicious previous pathology results, and staging purposes.

The study inclusion criteria were patients in the PSA gray zone with a pre-biopsy PI-RADS score of 3 who underwent TRUS-PB. Of the 686 patients who underwent mpMRI, 327 were eliminated from the study because they had PI-RADS scores< 3, 232 patients were eliminated from the study because their PI-RADS scores were> 3, and 127 patients left with a PI-RADS score of 3. Of these 127 patients, five were eliminated because they were previously diagnosed with PCa, and 14 patients were eliminated because their PSA values were not between 4-10 ng/ml. Fourteen patients whose pathology reports showed atypical small acinar proliferation (ASAP) (12 patients) and high-grade prostatic intraepithelial neoplasia (HG-PIN) (2 patients) were also eliminated from the study, and the remaining 94 patients were included in the study.

### 2.2. Procedure

All systematic TRUS-PB procedures were performed by the same 25-year experienced urology doctor (CB) in the same outpatient biopsy room in our department, while the patients were in the left lateral decubital position and under local anesthesia. The same ultrasonography device (Aloka ProSound 5500SV) and an automatic single-use 18-gauche biopsy gun were used in all biopsies.

mpMRI imaging procedures were performed in our hospital with a 1.5 T (Magnetom Essenza by Siemens) device and multiplanar T2-weighted imaging, diffusion-weighted imaging, and dynamic contrast-enhanced MRI phases without spectrometry. The mpMRI was evaluated by different radiologists who agreed with our hospital at another center.

All pathologic evaluations of biopsy specimens were performed and reported by experienced pathology doctors working in our hospital.

### 2.3. Demographic and clinical variables with groups

The biopsy pathology results were used for categorization of the patients into three groups. The benign prostatic hyperplasia (BPH) group consisted of 58 patients with BPH (53 patients) and prostatic intraepithelial neoplasia (PIN) (5 patients). The remaining 36 patients were diagnosed with PCa. The PCa patients were divided into csPCa (21 patients) and cisPCa (15 patients) groups according to the International Society of Urological Pathology [ISUP] grading (3). All parameters of the patients, including age, PSA, prostate volume (PV), PSA density (PSAD), free to total PSA ratio (f/t PSA), DRE results, biopsy core numbers, and whether it was a primary or repeat biopsy, were examined. Logistic regression analysis was performed for independent predictors of PCa and csPCa, while Receiver Operating Characteristic (ROC) curve analysis was conducted to determine the effectiveness and priority of the parameters.

Although it was not our study's primary aim, we also classified the patients into three groups based on the zones where PI-RADS 3 lesions were observed. Group 1 had lesions in the peripheral zone (PZ) only, Group 2 in the transitional zone (TZ) only, and Group 3 in both zones. The pathological results of the patients in each group were compared.

### 2.4. Statistical analysis

SPSS 22.0 and MedCalc 19.7.1 were the statistical analysis software packages used for the study. The correctness of numerical variables for normal distribution was assessed using the Shapiro-Wilk test. To compare variables that were normally distributed among the three groups, ANOVA and least significant difference (LSD) tests were used. Kruskal-Wallis and Dunn's tests were employed to compare non-distributed variables among the three groups. The chi-squared test was used to explore the relationships between categorical variables. Logistic regression analyses were conducted to examine the predictive parameters of PCa and csPCa. ROC curve analysis and Area Under the Curve (AUC) values were used to prioritize the parameters for both PCa and csPCa. Hazard ratios and 95% confidence intervals were calculated, and p-values < 0.05 were considered statistically significant.

## 3. Results

We reviewed 686 patients who underwent pre-biopsy mpMRI. The PI-RADS score distribution was as follows: 327 patients (47.6%) had PI-RADS score< 3, while 232 patients (33.8%) had PI-RADS score> 3. The incidence of PI-RADS score 3 was 18.5% with the 127 patients, and 94 of them were included into the study.

Table 1 summarizes the clinical data of the remaining 94 patients according to pathological groups. The BPH group consisted of 58 patients (61.7%): 53 patients with BPH, and 5 patients with PIN. Of the patients with PCa pathology, 36 patients (38.2%) were divided into the csPCa group with 21 patients (22.3%) and the cisPCa group with 15 patients (15.9%). The 81 (86.1%) patients had their first biopsy, and 13 (13.8%) had a previous negative biopsy (PNB).

The csPCa and cisPCa group had higher age, PSAD, abnormal DRE ratio and higher primer biopsy ratio but lower f/t PSA, smaller PV and lower rate of PNB than the BPH group. Only one patient with PNB had csPCa while the remaining 12

patients had BPH pathology.

**Table 1.** Demographics and classification of patients based on pathology results with PI-RADs Score 3 that underwent transrectal prostate biopsy

| Parameters | BPH | cisPCa | csPCa | p<0,05 |
|---|---|---|---|---|
| No of patients n,(Row%) | 58 (61.7) | 15 (16.0) | 21 (22.3) | |
| Age years m,(IQR) | 63 (59 -68 ) | 69 (63 -72 ) | 68 (64 -73 ) | 0.023‡ |
| PSA ng/ml m,(IQR) | 6.3 (4.7 -8.2 ) | 5.4 (4.9 -7.4 ) | 6.1 (5.4 -8.1 ) | 0.734ǁ |
| f PSA ng/ml m,(IQR) | 1.4 (1 -2.1 ) | 1.2 (1 -1.5 ) | 1 (0.8 -1.2 ) | 0.006*ǁ |
| PV ml m, (IQR) | 65.5 (55 -85 ) | 46 (44 -64 ) | 39 (31 -65 ) | 0.001*ǁ |
| PSAD ng/ml/ml m,(IQR) | 0.09 (0.06 -0.12 ) | 0.12 (0.07 -0.18 ) | 0.15 (0.09 -0.19 ) | 0.004*ǁ |
| f/t PSA ratio m,(IQR) | 0.25 (0.17 -0.33 ) | 0.23 (0.14 -0.26 ) | 0.16 (0.12 -0.2 ) | 0.001*ǁ |
| No. of biopsy cores m, (IQR) | 12 (12 -12 ) | 12 (12 -12 ) | 12 (12 -12 ) | 0.342ǁ |
| Primer biopsy n.(%) | 46 (79.3 ) | 15 (100 ) | 20 (95.2 ) | 0.015*† |
| PNB n, (%) | 12 (20.7 ) | 0 (0 ) | 1 (4.8 ) | |
| DRE normal n,(%) | 40 (69 ) | 8 (53.3 ) | 10 (47.6 ) | 0.174† |
| DRE abnormal n,(%) | 18 (31 ) | 7 (46.7 ) | 11 (52.4 ) | |

*p<0,05, †chi-square test, ‡ANOVA and LSD test, ǁKruskal Wallis and Dunn test BPH: benign prostate hyperplasia cisPCa: clinically insignificant prostate carcinoma csPCa: clinically significant prostate carcinoma DRE: digital rectal examination f/t PSA: free total PSA ratio IQR: interquartile range m: median PI-RADS: Prostate Imaging–Reporting and Data System PNB: previous negative biopsy PSA: prostate specific antigen PSAD: prostate specific antigen density PV: prostate volume

The study's findings reveal that age, PV, PSAD, f/t PSA, and primer biopsy were identified as significant predictors of PCa in univariate analysis. However, the multivariate analysis indicated that only age and f/t PSA were independent predictors of PCa. The same analysis for csPCa demonstrated that age, PV, PSAD, and f/t PSA were predictive factors in the univariate analysis. In contrast, age and f/t PSA remained independent predictive factors in the multivariate analysis, as shown in Table 2.

**Table 2.** Univariate and multivariate analysis for the predictive parameters of PCa and csPCa

| Parameters | Univariate OR (95% CI) | P<0.05 | Multivariate OR(95% CI) | p<0.05 |
|---|---|---|---|---|
| For PCa | | | | |
| Age | 1.09 (1.02-1.17) | **0.008*** | 1.19 (1.09 -1.30 ) | **0.001*** |
| PV | 0.97 (0.96-0.99) | **0.005*** | 0.98 (0.96 -1.00 ) | 0.108 |
| PSAD† | 2.57 (1.28-5.18) | **0.008*** | 0.77 (0.25 -2.34 ) | 0.644 |
| f/t PSA† | 0.39 (0.22-0.69) | **0.001*** | 0.24 (0.10 -0.61 ) | **0.003*** |
| Anormal DRE | 2.22 (0.94-5.24) | 0.068 | 1.89 (0.60 -5.97 ) | 0.281 |
| Primer Biopsy | 9.13 (1.13-73.58) | **0.038*** | 8.14 (0.89 -74.76 ) | 0.064 |
| No of biopsy core | 0.74 (0.36-1.51) | 0.407 | 0.51 (0.15 -1.73 ) | 0.282 |
| Parameters | Univariate OR (95% CI) | P<0.05 | Multivariate OR(95% CI) | P<0.05 |
| For csPCa | | | | |
| Age | 1.10 (1.01-1.19) | **0.024*** | 1.2 (1.07 -1.35 ) | **0.002*** |
| PV | 0.97 (0.94-0.99) | **0.006*** | 0.98 (0.95 -1.01 ) | 0.283 |
| PSAD† | 3.27 (1.44-7.50) | **0.005*** | 0.98 (0.26 -3.61 ) | 0.971 |
| f/t PSA† | 0.30 (0.14-0.62) | **0.001*** | 0.21 (0.07 -0.67 ) | **0.008*** |
| Anormal DRE | 2.44 (0.88-6.79) | 0.086 | 1.99 (0.49 -8.13 ) | 0.340 |
| Primer Biopsy | 5.21 (0.64-42.88) | 0.124 | 4.06 (0.42 -38.95 ) | 0.224 |
| No of biopsy core | 0.96 (0.47-1.95) | 0.911 | 0.66 (0.19 -2.27 ) | 0.511 |

† Multiplied by 10 CI: confidence interval DRE: digital rectal examination f PSA: free prostate specific antigen f/t PSA: free total PSA ratio OR: odds ratio PCa: prostate carcinoma PSA: prostate specific antigen PSAD: prostate specific antigen density PNB: previous negative biopsy

The ROC curve analysis for PCa demonstrated that PV had the highest AUC value (0.723). This was followed by f/t PSA (0.705) and PSAD (0.681) (Fig. 1, Table 3). For csPCa, f/t PSA had the highest AUC value (0,770), followed by PV (0.751) and PSAD (0.739) (Fig. 2, Table 3). The cutoff values of the parameters together with sensitivity and specificity for both PCa and csPCa are shown in Table 4.

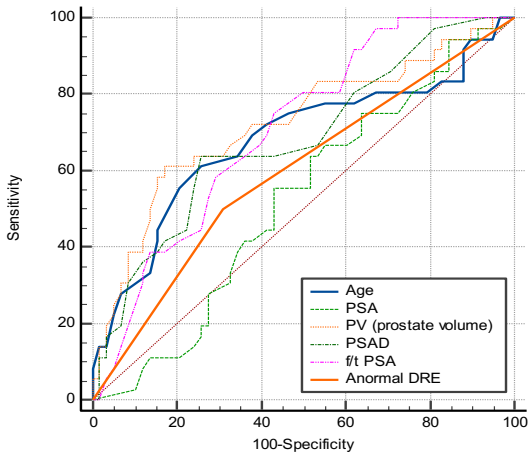


**Fig. 1.** ROC curve analysis and AUC values of parameters for PCa

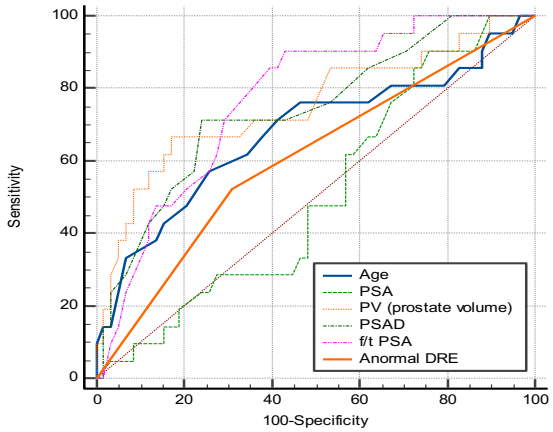


**Fig. 2.** ROC curve analysis and AUC values of parameters for cs

**Table 3.** AUC values of parameters for PCa and csPCa according to ROC curve analysis in PSA grey zone patients with PI-RADS score of 3

| Variables for PCa | AUC | SE [a] | 95% CI [b] |
|---|---|---|---|
| Age | 0.680 | 0.0611 | 0.576 to 0.772 |
| PSA | 0.521 | 0.0605 | 0.416 to 0.625 |
| PV | 0.723 | 0.0567 | 0.621 to 0.810 |
| PSAD | 0.681 | 0.0574 | 0.577 to 0.773 |
| f/t PSA | 0.705 | 0.0531 | 0.602 to 0.795 |
| Abnormal DRE | 0.595 | 0.0522 | 0.489 to 0.695 |
| **Variables for csPCA** | **AUC** | **SE[a]** | **95% CI[b]** |
| Age | 0.677 | 0.0764 | 0.562 to 0.777 |
| PSA | 0.505 | 0.0706 | 0.390 to 0.620 |
| PV | 0.751 | 0.0693 | 0.641 to 0.842 |
| PSAD | 0.739 | 0.0648 | 0.628 to 0.832 |
| f/t PSA | 0.770 | 0.0559 | 0.661 to 0.857 |
| Abnormal DRE | 0.607 | 0.0637 | 0.490 to 0.715 |

[a]Hanley & McNeil, 1982[b] Binomial exact AUC: area under curve CI: confidence interval 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 ROC curve: receiver operating characteristic curve SE: standard error

We also classified patients according to the lesion locations in the peripheral zone (PZ) and transitional zones (TZ). There were no statistically significant differences between the groups according to the pathological results. However, the highest csPCa rate (29.1%) was observed in patients with PI-RADS 3 lesions in both the zones. Patients with only PZ PI-RADS 3 lesions had a csPCa rate of 26%, and patients with only TZ PI-RADS 3 lesions had a csPCa rate of 17.3%.

**Table 4.** Cutoff values with sensitivity and specificity of parameters for PCa and csPCa calculated by Youden J index in PSA grey zone patients with PI-RADS score of 3

| Variables for PCa | Cutoff value | Sensitivity | 95% CI | Specificity | 95% CI |
|---|---|---|---|---|---|
| Age, years | > 67 | 61.11 | 43.5- 76.9 | 74.14 | 61.0- 84.7 |
| PSA, ng/ml | > 6.1 | 55.56 | 38.1- 72.1 | 56.90 | 43.2 - 69.8 |
| PV, cc | ≤ 49 | 61.11 | 43.5- 76.9 | 82.76 | 70.6- 91.4 |
| PSAD, ng/ml/cc | > 0.11 | 63.89 | 46.2- 79.2 | 74.14 | 61.0- 84.7 |
| f/t PSA | ≤ 0.23 | 75.00 | 57.8- 87.9 | 56.90 | 43.2- 69.8 |
| Abnormal DRE | > 0 | 50.00 | 32.9- 67.1 | 68.97 | 55.5- 80.5 |
| **Variables for csPCa** | **Cutoff value** | **Sensitivity** | **95% CI** | **Specificity** | **95% CI** |
| Age, years | > 67 | 57.14 | 34.0 - 78.2 | 74.14 | 61.0 - 84.7 |
| PSA, ng/ml | > 6.7 | 28.57 | 11.3 - 52.2 | 55.17 | 41.5 - 68.3 |
| PV, cc | ≤ 49 | 66.67 | 43.0 - 85.4 | 82.76 | 70.6 - 91.4 |
| PSAD, ng/ml/cc | > 0.12 | 71.43 | 47.8 - 88.7 | 75.86 | 62.8 - 86.1 |
| f/t PSA | ≤ 0.23 | 90.48 | 69.6 - 98.8 | 56.90 | 43.2 - 69.8 |
| Abnormal DRE | > 0 | 52.38 | 29.8 - 74.3 | 68.97 | 55.5 - 80.5 |

CI: confidence interval csPCa: clinically significant prostate carcinoma DRE: digital rectal examination f/t PSA: free total PI-RADS: Prostate Imaging–Reporting and Data System PSA ratio PCa: prostate carcinoma PSA: prostate specific antigen PSAD: prostate specific antigen density PV: prostate volume

## 4. Discussion

In our study, PI-RADS 3 scores were detected in 18.5% of patients with mpMRI. PCa and csPCa detection rates were 38.2% and 22.3% respectively. Although these results were consistent with the literature, there were significant differences between PCa and csPCa detection rates in patients with PI-RADS 3 scores in different studies.

In two meta-analyses, the incidence of PI-RADS 3 lesions was 22-32% (13) and 17.3% (14). The same meta-analyses also calculated csPCa rate of 16-21% and 18.5% respectively (13, 14). In another meta-analysis by Oerther et al., the prevalence of PCa in PI-RADS 3 lesions was 27%, whereas the incidence of csPCa was16% (15). In a study by Zhang et al., where transrectal ultrasound-guided saturation biopsy of 24 cores was

applied to patients with a PI-RADS score of 3, the detection rates of PCa and csPCa were 37.2% and 23.4% respectively, which were quite similar to our results (16). However, in three other studies, these rates were lower than those reported in other studies. In these three studies, csPCa detection rates were 11% (targeted and systematic biopsy) (17), 4.2% (targeted and systematic biopsy) (18), and 2.1% (targeted biopsy only) (19). The different rates of PI-RADS 3 lesions and the PCa and csPCa detection rates in PIRADS 3 lesions may depend on the experience of the radiologist reading the mpMRI, the experience of the doctor performing the biopsy, which Gleason grade is used to define csPCa, the difference in the evaluation of nodules in the transitional zone between versions V2.0 and V2.1, and the type of biopsy (systematic, targeted or combined).

Logistic regression analysis in the present study demonstrated that only age and f/t PSA were independent predictors of PCa and csPCa. Our study population included patients only in the PSA gray zone (4-10 ng/ml), and f/t PSA is most valuable in this range, which may explain our results (20). Older age is a well-known risk factor for PCa development (21). In similar studies, Sheridan et al. also defined age > 70 years, PV ≤ 36 cc, and abnormal DRE as predictors of csPCa (22), while Yang et al. have shown that age and PSAD are two independent predictive factors (23). Meanwhile, according to Kim et al., PSAD ≥ 0.20 ng/ml/cc was found to be the sole independent predictive factor for csPCa in PIRADS 3 patients (24).

In the present study, f/t PSA had the highest AUC value (0.770) followed by PV (0.751) and PSAD (0.739). Although all these traditional clinical parameters, such as age, PSA, PV, f/t PSA, and DRE, were used to decide on a biopsy in patients with PI-RADS 3, PSAD is the most discussed in the literature, including guidelines (5,25-26). The EAU guidelines classify biopsy recommendations according to the PSAD levels in PI-RADS 3 patients. The PSAD $\geq$ 0.20 ng/ml/ml level is advised for ‘’perform biopsy’’ while PSAD < 0.10 ng/ml/ml level is advised for ‘’no biopsy’’ since only 4% of patients have csPCa (5,25). Similarly, Görtz et al. demonstrated that when PSAD < 0.10 ng/ml/ml was accepted as a cutoff level, csPCa was not detected in 97.6% (42/43) of patients (26). However, in our study, we detected 28.2% (13/46) PCa and 13% (6/46) csPCa when we accepted PSAD < 0.10 ng/ml/ml as a reference. Furthermore, a study by Hansen et al. found even higher rates of csPCa (18%) when using a PSAD cutoff value of < 0.10 ng/ml/ml (27). And when we take our study’s PSAD cutoff value of > 0.12 ng/ml/ml according to Youden J index, our csPCa detection rate would be 44.1% (15/34).

The most crucial difference that distinguishes our study from studies in the literature is that our cancer detection rates were obtained only by systematic prostate biopsy, and this is another controversial issue in PI-RADS 3 lesions since it is not clear whether the type of biopsy was performed in PI-RADS 3 patients. In their study by Maggi et al. demonstrated that there was no statistical difference between PCa and csPCa detection rates of biopsies performed with targeted and systematic biopsies (23.5% vs. 23.9% and 11.4% vs. 12.3%, respectively). However, they reached the highest PCa and csPCa results with combined biopsy (14). In contrast, Hansen suggested that in PI-RADS 4-5 lesions, systematic biopsy missed 11%, and targeted biopsy missed 9% of csPCa. Conversely, in PI-RADS 3 lesions, targeted biopsy missed 56% (14/25) of csPCa cases, while systematic biopsy missed only 4% (1/25). The authors declared that while combined biopsy is required for csPCa in PI-RADS 4 and 5 lesions, systematic biopsy alone might be sufficient for PI-RADS 3 lesions (27). Similarly, Araújo et al. also suggested that systematic biopsy should always be performed if csPCa is suspected, while targeted biopsy could be omitted in PI-RADS 3 lesions (28).

Our study also classified PI-RADS 3 lesions into groups according to the zones in which lesions were located and calculated PCa and csPCa detection rates. The highest number of patients were in the group with PI-RADS 3 lesions located only in TZ (TZ = 46 patients, PZ = 24 patients). This may be because the differentiation of BPH nodules from real lesions in the TZ is more challenging than that in PZ lesions. Consistent with the literature, the lowest csPCa rates were found in the TZ group (13); however, no statistically significant difference was detected.

This study has several limitations. First, it was conducted retrospectively in a single center, and the sample size of 94 patients may be considered a limitation. The second limitation of the study was that the study's pathology results were determined solely by TRUS-PB since targeted biopsies were not performed, and the entire prostate tissues were not examined. Third, our study enrolled patients starting from 2019, so both PI-RADS versions (2.0 and 2.1) were employed to assess the suspicious lesions.

In conclusion, csPCa detection rate in our study was 22.3% in PI-RADS 3 lesions, although no targeted biopsies were performed. Age and the f/t PSA ratio were the only independent predictive factors for PCa and csPCa. Moreover, only one patient (7.6%) with PNB had csPCa. On the basis of these results, we recommend evaluating each patient individually. Targeted or combined with systematic biopsy may be the first option for biopsy-naïve patients. However, for deciding on biopsy, not only PSAD but also f/t PSA and PV should be considered, especially in PSA gray zone patients.

**Conflict of interest**

The authors declared no conflict of interest.

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None to declare.

**Authors' contributions**

Concept: CB, KE, UB. Design: CB, KE, UB. Data Collection or Processing: CB, KE, UB, MCC, MDD, FY. Analysis or Interpretation: CB, KE, UB, MCC, MDD, FY. Literature Search: CB, KE, UB, MCC, MDD, FY. Writing: CB, KE, UB, MCC, MDD, FY

**Ethical Statement**

The research studies involving human participants have been conducted according to the ethical standards established by the institutional and national research committees based on the 1964 Helsinki Declaration. The study's retrospective nature and all procedures being part of routine care led to the local Ethics Committee of the University Karabuk waiving ethical approval for the study. The study has been assigned the number 2024/1636 on 11/02/2024.

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