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# *Combining Multiparametric MRI and PSA Density for Improved Diagnostic Accuracy in Prostate Cancer*

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## Abstract

**Objective:** The objective of this research was to investigate the combined use of multiparametric magnetic resonance imaging (Mp-MRI) and prostate-specific antigen density (PSAD) to increase diagnostic accuracy in detecting prostate cancer (PCa) and to reduce unnecessary biopsies.
**Materials and Methods:** This retrospective analysis included 399 patients who underwent prostate biopsy at Ankara City Hospital between 2021 and 2022, primarily due to clinical indications suggestive of PCa. The patient cohort was categorized into distinct groups according to their PSAD, with a defined threshold of 0.15 ng/mL/cc, and their respective prostate imaging reporting and data system (PI-RADS) scores; subsequently, the diagnostic performance metrics, including sensitivity, specificity, and predictive values for determining Pca, were meticulously evaluated across different combinations of PI-RADS classifications and PSAD levels.
**Results:** Among the 399 patients, 37.6% had PCa and 16.8% had clinically significant PCa (csPca). Patients who exhibited PI-RADS scores of 3 or higher combined with a PSAD score of at least 0.15 ng/mL/cc exhibited the greatest positive predictive value, achieving 74.1% for overall PCa and 39.3% for csPca. The integration of PI-RADS assessment with PSAD thresholds notably enhanced diagnostic accuracy, leading to improved detection rates of clinically significant cases while concurrently minimizing the frequency of unnecessary biopsy procedures.
**Conclusion:** The simultaneous application of Mp-MRI and PSAD enhances the precision of Pca diagnosis and serves as a valuable tool for reducing the need for unnecessary biopsies, especially in patients with PI-RADS scores of 3 or above accompanied by elevated PSAD levels.
**Keywords:** Mp-MRI, PI-RADS, PSAD, prostate cancer

## Introduction

Prostate cancer (PCa) accounts for 15% of all cancers and is the most frequently diagnosed malignancy in men (1). One in eight men is at risk of developing PCa during their lifetime (2). PCa is mostly asymptomatic in the early stages, except for a few cases, which results in a higher number of undiagnosed cases compared with those diagnosed. Autopsy studies have found a PCa prevalence of 3-8% in men under the age of 30 (2), with this rate increasing approximately 1.7-fold each year (3). After the age of 79, the prevalence of tyrosine phthalate increases dramatically, reaching 48-71%. PCa is diagnosed in only 2% of patients aged below 50 years. Therefore, routine PCa screening is recommended for men aged >50 years worldwide (3).

Epidemiological data on PCa have varied over time due to etiological factors and The utilization of prostate-specific antigen (PSA) testing. Since the late 1980s, PSA levels, along with digital rectal examination (DRE), have been used for PCa screening (4). However, serum PSA levels are specific to the prostate but not to cancer itself. Thus, they can vary due to factors like age, ethnicity, and prostate volume, even in healthy men. Furthermore, PSA levels can also be elevated in non-malignant conditions, including infections, benign prostatic hyperplasia, physical trauma, and following transurethral procedures (5). These factors can lead to unnecessary decisions for transrectal ultrasound-guided biopsy based on elevated PSA levels (6). Hence, additional tests were introduced to assess PSA levels in diagnosing and monitoring PCa.

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Originally, a PSA limit value of 4.0 ng/mL was introduced as a criterion for the detection of PCa (7). At this threshold, PSA sensitivity and specificity were 20% and specificity 60% (7). Lowering the PSA threshold resulted in reduced specificity but decreased sensitivity. Therefore, no standard PSA threshold has been determined (8). The primary goal of PCa screening is to detect aggressive and potentially fatal tumors early. Effective screening should aim to reduce the mortality of PCa. Based on this understanding, it is clear that lower PSA levels should be considered as thresholds, although, as outlined in the guidelines of the European Association of Urology, more data are required to support this recommendation. However, biopsy is now widely accepted as necessary for PSA levels exceeding 25 ng/mL. Several adjustments to serum PSA measurements have been investigated to improve the clarity of PSA in the early detection of PCa (7).

In current urological practice, PSA, PSA density (PSAD), and DRE are used together to assess patients before deciding on a biopsy (8). Additionally, multiparametric magnetic resonance imaging (Mp-MRI) has been utilized since the 1980s to assess the anatomical structures of the prostate gland and surrounding tissues (9). With advances in MRI technology, the test reliability of Mp-MRI for detecting PCa has increased (10). PSAD, which is determined by severing the serum PSA level by the prostate volume gained through transrectal ultrasound, aids in distinguishing malignant tumors from benign prostatic enlargement, particularly in cases where PSA values ranged from 4 to 10 ng/mL (11). PSAD has been shown to be twice as discriminative as PSA alone, offering higher specificity and sensitivity (12).

In recent years, the use of Mp-MRI has become more widespread, especially after the development of the T2- weighted multiparametric prostate MRI protocol, which includes dynamic contrast-enhanced sequences that provide both anatomical and functional imaging (13).

The present study aimed to assess the combined specificity and sensitivity of Mp-MRI and PSAD for diagnosing PCa and preventing unnecessary prostate biopsies.

## Materials and Methods

Our study adopted a retrospective design, initiated after obtaining approval from the Ankara City Hospital Ethics Committee (approval number: E1-22-3002, date: 02.11.2022). A total of 399 patients who underwent clinical evaluation for Pca and underwent prostate biopsy between 2021 and 2022 at Ankara City Hospital were retrospectively evaluated. The exclusion criteria were: patients without tissue diagnosis within six months of Mp-MRI, patients who had undergone previous transurethral resection, patients without PSA levels measured within 1 month before or after Mp-MRI, and patients whose Mp-MRI was performed without contrast due to renal dysfunction, as well as those with nodules, firmness, or fixation identified during DRE. For patients who underwent biopsy, serum PSA, DRE, prostate size, and PSAD were recorded. The patients were between 42 and 84 years old, with an average age of 64.3±6.9 years.

PSA levels and prostate volumes, measured using transrectal ultrasound, were noted, and PSAD was determined using the following formula: total PSA prostate size. The cutoff value for PSAD was 0.15 ng/mL/cc. Patients were grouped into two categories according to PSAD: Group 1 included those with a PSAD of 0.15, and Group 2 included those with a PSAD of 0.15. The patients' Mp-MRI results were obtained from both external centers and our own institution and classified according to the prostate imaging reporting and data system (PI-RADS) into PI-RADS scores of 1, 2, 3, 4, and 5.

Regardless of the PSAD grouping, patients were divided into two groups based on their PI-RADS scores: patients with PI-RADS scores less than 3, and those with PI-RADS scores of 3 or higher. The total and free PSA values were recorded for all patients.

For the patients included in our study, systematic 12-core biopsies were performed, and in some cases, additional targeted biopsies were performed. Prostate biopsy was performed in the left lateral decubitus orientation, with DRE findings recorded prior to the procedure. Prostate dimensions were measured, and the prostate size was calculated using the ellipsoid formula (transverse diameter × anteroposterior diameter × craniocaudal diameter × $\pi/2$), and the results were recorded. Patients diagnosed with PCa were classified according to the ISUP classification system. Patients with ISUP grade ≥2 were classified as having clinically significant PCa (csPCa).

### Statistical Analysis

Data coding and statistical evaluations were conducted using SPSS 22 software (IBM SPSS Statistics, IBM Corporation, Chicago, IL). The Shapiro-Wilk test was applied to examine the normality of data distribution. Depending on the distribution pattern, data were expressed either as mean ± standard deviation (SD) or as median (range: minimum-maximum). Univariate analysis was performed to identify potential risk factors associated with PCa. Patients were stratified into four groups according to their PI-RADS scores and PSAD levels. For each group, the sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) were calculated. A p-value 0.05 was considered statistically significant.

## Results

The average age of the 399 patients enrolled in the study was 64.3±6.9 years, with a median PSA value of

6.9 ng/mL (range: 1.1-49). PCa was detected in 150 patients (37.6%), and csPca was detected in 67 patients (16.8%). The detection rate of PCa was 11.2% in the PI-RADS <3 group, and 52.3% in the PI-RADS ≥3 group. In the PSAD <0.15 ng/mL/cc group, 23.6% of patients were identified as having Pca, whereas in the PSAD ≥0.15 ng/mL/cc group, the detection rate was 62.1%.

The patients were categorized into four distinct groups based on the combination of their PI-RADS scores and PSAD levels: PI-RADS <3 with PSAD <0.15 ng/mL/cc, PI-RADS <3 with PSAD ≥0.15 ng/mL/cc, PI-RADS ≥3 with PSAD <0.15 ng/mL/cc, and PI-RADS ≥3 with PSAD ≥0.15 ng/mL/cc. For each group, sensitivity, specificity, NPV, and PPV were determined. The highest PPV for both Pca and csPCa was found in the PI-RADS ≥3 + PSAD ≥0.15

ng/mL/cc group, with a PPV of 74.1% for Pca and 39.3% for csPCa (Table 1).

Univariate logistic regression analysis showed that PI-RADS ≥3 [odds ratio (OR) =8.718; 95% confidence interval (CI) =4.906-15.492; p<0.001], PSAD ≥0.15 ng/mL/cc (OR =5.291; 95% CI =3.397-8.241; p<0.001), and the combination of PI-RADS ≥3 and PSAD ≥0.15 ng/mL/cc (OR =9.398; 95% CI =5.68-15.549; p<0.001) were strong determinants of Pca (Table 2).

The integration of PI-RADS scores and PSAD significantly improved the detection of PCa. In particular, in patients with PI-RADS scores of ≥3 and PSAD values ≥0.15 ng/mL/cc, the PPV for Pca was 74.1%, and for csPca, it was 39.3%. The results revealed that patients with higher PI-RADS scores and PSAD levels should undergo biopsy, which can help reduce unnecessary biopsies. The results demonstrated that combining PI-RADS and PSAD offered more accurate diagnostic outcomes and improved the identification of csPca (Table 3).

## Discussion

The utilization of Mp-MRI to enhance the precision of PCa diagnosis is increasing (14). The main expectation from this imaging modality is to accurately identify patients at risk of malignancy without the need for invasive procedures.

**Table 1. PI-RADS score and prostate-specific antigen levels on multiparametric magnetic resonance imaging**

| | n=399 | PI-RADS <3 (n=143), 35.8% | PI-RADS ≥3 (n=256), 64.2% | PSA <0.15 (n=254), 63.7% |
|---|---|---|---|---|
| Age (years) (mean ± SD) | 64.3±6.9 | 64.5±6.9 | 64.2±6.9 | 64.5±6.9 |
| Digital prostate examination | | | | |
| Symptom no | n (%) 325 (81.5) | 129 (90.2) | 196 (76.6) | 223 (87.8) |
| Symptom yes | n (%) 74 (18.5) | 14 (9.8) | 60 (23.4) | 31 (12.2) |
| PSA (ng/mL) [median (min-max)] | 6.9 (1.1-49) | 5.7 (2.7-40) | 7.5 (1.1-49) | 5.8 (1.1-22.5) |
| Prostate volume (cc) [median (min-max)] | 54 (20-220) | 56 (20-220) | 50.5 (20-210) | 62.5 (25-210) |
| Prostate cancer stage, n (%) | 150 (37.6) | 16 (11.2) | 134 (52.3) | 60 (23.6) |
| ISUP stage 1 | 83 | 12 | 71 | 38 |
| ISUP stage 2 | 28 | 1 | 27 | 12 |
| ISUP stage 3 | 13 | 1 | 12 | 5 |
| ISUP stage 4 | 19 | 2 | 17 | 4 |
| ISUP stage 5 | 7 | 0 | 7 | 1 |
| csPCa, n (%) | 67 (16.8) | 4 (2.8) | 63 (24.6) | 22 (8.7) |

SD: Standard deviation, PSA: Prostate-specific antigen, PSAD: Prostate-specific antigen density, PI-RADS: Prostate imaging reporting and data system, ISUP: International Society of Urological Pathology, csPCa: Clinically significant prostate cancer

**Table 2. Evaluation of the relationship between PI-RADS score, prostate-specific antigen density, and prostate cancer detection using univariate and multivariate regression analyses**

| Parameter | OR (%95 CI) | p-value | OR (%95 CI) | p-value |
|---|---|---|---|---|
| PI-RADS ≥3 | 8.718 (4.906-15.492) | **<0.001** | 7.777 (4.272-14.158) | **<0.001** |
| PSAD ≥0.15 ng/mL/cc | 5.291 (3.397-8.241) | **<0.001** | 4.674 (2.891-7.557) | **<0.001** |
| PI-RADS ≥3 + PSAD ≥0.15 ng/mL/cc | 9.398 (5.68-15.549) | **<0.001** | 1.727 (0.517-5.775) | 0.375 |

CI: Confidence interval, PSAD: Prostate specific antigen density, PI-RADS: Prostate imaging-reporting and data system. Bold p-values indicate clinical significance

**Table 3. Effectiveness of the PI-RADS score and prostate-specific antigen density combination in the diagnosis of prostate cancer**

| Combinations of PI-RADS score and PSAD | Sensitivity (%) | | Specifity (%) | | Negative predictive value (%) | | Positive predictive value (%) | |
|---|---|---|---|---|---|---|---|---|
| | PCa | csPCa | PCa | csPCa | PCa | csPCa | PCa | csPCa |
| **PI-RADS <3 + PSAD <0.15 ng/mL/cc, n=110** | 6% | 4.5% | 59.4% | 67.8% | 51.2% | 77.9% | 8.2% | 2.7% |
| **PI-RADS <3 + PSAD ≥0.15 ng/mL/cc, n=33** | 4.7% | 1.5% | 89.6% | 90.4% | 60.9% | 82% | 21.2% | 0.3% |
| **PI-RADS ≥3+ PSAD <0.15 ng/mL/cc, n=144** | 34% | 28.4% | 62.6% | 62.3% | 61.2% | 81.2% | 35.4% | 13.2% |
| **PI-RADS ≥3+ PSAD ≥0.15 ng/mL/cc, n=112** | 55.3% | 65.7% | 80.5% | 79.5% | 41.8% | 92% | 74.1% | 39.3% |

PSAD: Prostate-specific antigen density, PI-RADS: PI-RADS: prostate imaging reporting and data system, PCa: Prostate cancer, csPCa: Clinically significant prostate cancer

In a study by Thompson et al., (14) even in healthy controls, PCa was detected at very low PSA levels. The detection rates in individuals with PSA levels ≤0.5 / 0.6-1 / 1.1-2 / 2.1-3 / 3.1-4 ng/mL were found to be 6.6%, 10.1%, 17%, 23.9%, and 26.9%, respectively (15). In a study of 288 patients by Washino et al., (15) the PI-RADS score and PSAD were analyzed in relation to Mp-MRI. CsPca was identified in 76-97% of patients with a PSAD ≥0.15 and PI-RADS score ≥4 or in patients with a PI-RADS rating of 3 and PSAD ≥0.3. In cases in which both the PI-RADS score and PSAD were elevated, biopsies were performed in patients who initially had negative biopsy results, and Pca was later determined in 22% of those patients (16). In our study, 74.1% (n=83) of the 112 patients with a PI-RADS score ≥3 and PSAD ≥0.15 were determined to have Pca, whereas 39.3% (n=44) were identified as having csPca. In contrast, only 8.2% (n=9) of the 110 patients with a PSAD <0.15 and PI-RADS <3 had Pca, with csPca detected in only 2.7% (n=3) (Table 1). The csPca values of the three patients with a PI-RADS score <3 and PSAD <0.15 suggests that more careful consideration is necessary when making biopsy decisions for this group.

To prevent redundant biopsies in the diagnosis of Pca, recent studies have employed a combination of Mp- MRI and PSAD. In a meta-analysis of 3006 patients by Schoots et al., (16) the relationship between Mp- MRI results, PSAD levels, and clinically significant disease was evaluated. The study found that patients with low-risk PSAD and negative Mp-MRI results could avoid biopsies, whereas those with high-risk PSAD still required biopsy. In particular, in patients with PI-RADS 3 lesions, PSAD plays a crucial role in biopsy decision-making. Mp-MRI-positive patients (PI-RADS 4-5) should undergo biopsy, regardless of PSAD risk categories (17). In our study, the PPV of Pca in patients with PI-RADS ≥3 and PSAD ≥0.15 was 74%, whereas that of csPca was 39%. These results indicate that patients with these characteristics should undergo biopsy. In a retrospective study by Luis Rico et al. (17), which included 99 patients who underwent transperineal prostate biopsy between 2015 and 2020, the role of lesion volume and PSAD in determining csPca in patients with PI-RADS 3 lesions was examined. The study concluded that using lesion volume and PSAD together could lead to more accurate biopsy decisions and help avoid unnecessary biopsies. No csPca was identified in the PI-RADS 3a group (lesion volume <0.5 mL), but in the PI-RADS 3b group (lesion volume >0.5 mL), 18% had csPca. In patients with PI-RADS 3b lesions and PSAD >0.15, the rate of csPca increased to 62.5%, whereas no cancer was detected in those with PSAD <0.15, suggesting that biopsies could be prevented in these patients (18).

Felker et al. (18) identified effective factors for predicting csPca in patients with PI-RADS 3 lesions. In their study of 90 patients, PSAD was found to be the most important factor. CsPca was observed in 60% of patients with a PSAD ≥0.15 ng/mL2. Based on this criterion, biopsies would have been performed only in high-risk patients, thereby reducing unnecessary biopsies by 90% (19). A study by Albert et al. (19) indicated that the integration of Mp-MRI and PSAD could accurately identify low-risk patients and prevent unnecessary biopsies. Using PSAD and Mp-MRI results, low-risk patients could be identified who do not require biopsy, whereas high-risk patients could be prioritized for biopsy (20). In our study, the probability of detecting PCa and csPca was higher in patients with a PI-RADS score ≥3 and PSAD >0.15 ng/mL/cm$^3$. Ghafoori et al. (20) found that PSAD improved the effectiveness of PSA in determining Pca in a group of 330 patients who underwent transrectal biopsy, with Pca diagnosed in 121 patients (36.7%) (21). Lotfi et al. (21) showed that PSAD, especially in men with PSA values between 4 and 10 ng/mL, was more important than total PSA levels (22). Bazinet et al. (22) established the most appropriate cut-off value for PSAD of 15% for detecting Pca in men with standard DRE observation and PSA values between 4 and 10 ng/mL (23). Kefi et al. (23) reported that 15% PSAD limit 15% resulted in 44% sensitivity and 76% specificity for detecting cancer (24). Catalona et al. (24) discovered that using a PSAD limit of 15% led to approximately 50% of PCa patients being missed (25). Benson et al. (25) concluded that PSAD was more valuable than PSA alone in determining Pca (26). In our study, the average PSA level among the 399 individuals who underwent biopsy was 6.9 ng/mL. The Pca identification rate was 23.6% in the PSAD <0.15 ng/mL/cc group and 62.1% in the PSAD ≥0.15 ng/mL/cc group. CsPca was detected in 8.7% (n=22) of patients in Group 1 (PSAD <0.15) and 31% (n=45) of patients in Group 2 (PSAD ≥0.15).

### Study Limitations

Although our institution has an Mp-MRI machine, we do not have an Mp-MRI fusion biopsy system, which allowed us to perform cognitive biopsies under transrectal ultrasound guidance. These factors may affect the generalizability and applicability of our findings.

## Conclusion

The findings of our study highlight the importance of PSAD and Mp-MRI in the diagnosis of Pca. The combination of these two parameters helps improve the accuracy of biopsy decisions, preventing unnecessary biopsies and enabling better detection of csPca.

### Ethics

**Ethics Committee Approval:** Our study adopted a retrospective design, initiated after obtaining approval from the Ankara City Hospital Ethics Committee (approval number: E1-22-3002, date: 02.11.2022)..

**Informed Consent:** Retrospective study.

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**Publication:** The results of the study were not published in full or in part in form of abstracts.

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

### Footnotes

#### Authorship Contributions

Surgical and Medical Practices: F.Ç., C.S.G., S.Ş., Concept: C.Ö., C.S.G., Y.K., S.S., Design: C.Ö., S.B., B.K.A., S.Ş., Data Collection or Processing: S.B., B.K.A., S.Ş., Analysis or Interpretation: F.Ç., S.S., Literature Search: S.B., S.S., Writing: F.Ç., S.S.

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