



Prostate-specific Antigen Density and Clinically Significant Prostate Cancer: Impact of Prostatic Volume in PI-RADS 3 Lesions; High Volume Single-center Analysis

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Abstract

Objective: Prostate-specific antigen density (PSAd) has gained traction as a superior diagnostic marker, compared with PSA alone, for predicting clinically significant prostate cancer (csPCa). However, prostate gland volume may affect the diagnostic accuracy of PSAd. To evaluate how prostate volume influences the diagnostic performance of PSAd for detecting csPCa in patients with Prostate Imaging Reporting and Data System (PI-RADS) 3 lesions.

Materials and Methods: We retrospectively analyzed 576 patients with PI-RADS 3 lesions who underwent PSA testing, multiparametric magnetic resonance imaging (MRI), and cognitive- and fusion-guided transrectal prostate biopsies between 2017 and 2025. PSAd was calculated as serum PSA divided by MRI-measured prostate volume. Patients were stratified into three groups according to prostate volume: ≤ 30 mL, 31-50 mL, and ≥ 51 mL. csPCa was defined as International Society of Urological Pathology grade ≥ 2 . Diagnostic performance of PSAd was assessed using receiver operating characteristic (ROC) curve analysis with volume-specific cut-offs.

Results: The overall csPCa detection rate was significantly higher in patients with prostates ≤ 30 mL ($p < 0.001$). Across all volume groups, csPCa detection remained $< 5\%$ when PSAd < 0.10 ng/mL/mL. For glands ≤ 30 mL, csPCa rates rose sharply above this threshold. ROC analysis revealed that small prostates had a slightly higher diagnostic accuracy [area under the curve (AUC) 0.668] compared with intermediate (AUC 0.599) and large (AUC 0.633) glands. Optimal PSAd cut-offs were narrowly distributed (0.1058-0.1531), but diagnostic sensitivity varied with volume.

Conclusion: The findings indicate that the diagnostic performance of PSAd in predicting csPCa is influenced by prostate volume. Instead of proposing definitive universal cut-off values, our results suggest that lower PSAd thresholds may be considered in patients with larger prostate volumes, particularly in borderline cases such as PI-RADS 3 lesions. Incorporating prostate volume into PSAd interpretation may improve risk stratification and contribute to more individualized biopsy decision-making.

Keywords: Multiparametric magnetic resonance imaging, PI-RADS, prostate cancer, PSA density, PSMA

Introduction

Prostate cancer (PCa) remains one of the most prevalent malignancies affecting men globally, with significant implications for both morbidity and mortality. Current diagnostic pathways often begin with serum prostate-specific antigen (PSA) testing and digital rectal examination, followed by multiparametric

magnetic resonance imaging (mpMRI) and biopsy when indicated (1,2). Despite its utility, serum PSA is influenced by various benign conditions, particularly benign prostatic hyperplasia, thereby reducing its specificity for detecting clinically significant PCa (csPCa).

To overcome this limitation, PSA density (PSAd), defined as the ratio of serum PSA to prostate volume, has been proposed as a

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more refined marker for csPCa. PSAd has demonstrated higher predictive value for csPCa compared to PSA alone, particularly in cases where MRI findings are equivocal, such as Prostate Imaging Reporting and Data System (PI-RADS) 3 lesions (3-6). Guidelines such as those from the European Association of Urology (EAU) and National Institute for Health and Care Excellence recently suggest the integration of PSAd into clinical decision-making, especially for PI-RADS 3 lesions (7).

PSAd is used to aid decision-making in cases of indeterminate PI-RADS 3 lesions on MRI. In patients with PI-RADS 3 lesions and a PSAd below 0.10 ng/mL/mL, biopsy may be deferred due to the low risk of csPCa (4,8), whereas biopsy is recommended when PSAd is 0.10 ng/mL/mL or higher (7). However, the use of fixed PSAd thresholds may not account for differences in prostate size. Larger prostates typically produce higher PSA levels because of increased benign prostatic tissue, thereby potentially obscuring the contribution of malignant foci. Conversely, smaller glands may yield elevated PSAd values for relatively insignificant cancers. Despite its increasing use in biopsy decision-making, there are limited studies investigating how prostate volume alters the diagnostic performance of PSAd (9).

This study aims to evaluate, within a high-volume, single-center cohort of 576 PI-RADS 3 lesions, the influence of prostate volume on PSAd for detecting csPCa. In our study, by examining PSAd thresholds across stratified prostate volume groups, we hope to determine whether volume-adjusted interpretations could improve diagnostic accuracy and more effectively guide biopsy strategies.

Materials and Methods

Patients and Methods

This retrospective study was conducted in 576 patients with PI-RADS 3 lesions who underwent transrectal ultrasonography (TRUS)-guided biopsies for suspected PCa at our tertiary institution between January 2017 and January 2025. Written informed consent was obtained from all patients before TRUS-guided biopsies. All procedures were performed in accordance with the 1964 Declaration of Helsinki and its later amendments. The study was approved by our Institutional Ethics Committee of Ankara University (decision no: 106-596-25, date: 12.08.2025).

All patients were biopsy-naive and had a clinical suspicion of PCa based on either elevated PSA levels or abnormal findings on digital rectal examination. After serum PSA testing, mpMRI, and transrectal ultrasound-guided cognitive (E.Ö.) and fusion-targeted prostate biopsy (N.H.) within the diagnostic pathway. Patients presenting with PSA levels above 40 ng/mL were excluded because these levels are commonly associated with advanced or metastatic PCa and may bias the analysis of localized disease.

All patients were scanned on a 3T MRI scanner within three months before the biopsy. For image assessment, all mpMRI examinations performed before 2019 were re-reviewed by an experienced abdominal radiologist (D.K.Ö., with 10 years of expertise in prostate MRI) according to the PI-RADS v2.1 criteria. All PI-RADS 3 lesions identified after 2019 were reassessed. Total

prostate volume was calculated on MRI using the ellipsoid formula (10), and divided into three groups according to volumes ≤ 30 mL, 31-50 mL, and ≥ 51 mL. Biopsy specimens were evaluated according to the International Society of Urological Pathology (ISUP) modified Gleason system (11). csPCa is defined on histopathology as a Gleason score $\geq 3+4$ (\geq ISUP grade 2), per-lesion basis. PSAd was calculated as PSA divided by prostate volume. Diagnostic performance was analyzed at thresholds of <0.10 , 0.10-0.14, 0.15-0.19 and ≥ 0.20 ng/mL/mL.

MR Image Acquisition Technique

mpMRI images were obtained using a 3.0 Tesla MR system (Verio; Siemens Medical Solutions, Erlangen, Germany). A standard body-matrix coil was used to receive signals from the patients' prostates. The MRI scanning procedure incorporated three-directional (3D) (sagittal, coronal, and axial) T2 turbo spin-echo (TSE) imaging; axial diffusion-weighted imaging sequences performed at three b-values (0, 1000, and 2000 mm^2/s) using echo-planar technology; and an axial TSE T2-weighted sequence encompassing pelvic lymph nodes to the level of the aortic bifurcation. After injecting gadolinium contrast medium (0.2 mL/kg) into the vein at 2.5 mL/s, followed by 15 mL of saline, dynamic contrast-enhanced images were obtained in the axial plane using a fat-suppressed 3D T1 VIBE protocol.

TRUS Biopsy Procedure

TRUS was using GE P5 or LOGIQ S8 ultrasound scanners (GE Healthcare, Milwaukee, Wisconsin) equipped with a biplanar convex/convex transrectal probe (BE9CS). The biopsies were performed via the transrectal route using a fully automatic core biopsy device with an 18-gauge, 25 cm tru-cut needle (Geotek). The T2W axial images were loaded onto the ultrasound machine, and after fusing selected images with real-time TRUS images, a fusion biopsy was performed with at least three samples taken from the target lesion (N.H.). Subsequently, a 12-core systematic biopsy was performed. Prior to cognitive biopsy, the locations of suspicious lesions were reviewed by the operator (E.Ö.), and three additional cores from the region of the index lesion were taken using cognitive TRUS guidance. All biopsy procedures were performed by the two operators, each with more than 10 years of experience in TRUS-guided prostate biopsy. All biopsy specimens were labelled according to the site of the prostate that was biopsied and were sent for histopathologic evaluation.

Statistical Analysis

Statistical analyses were performed using SPSS® Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Patient characteristics were reported using descriptive statistics. Descriptive statistics were expressed as medians and interquartile ranges for variables that were not normally distributed. The chi-square and Fisher's exact tests were used to compare categorical variables between groups. The diagnostic performance of PSAd was assessed across prostate volume groups using the area under the receiver operating characteristic (ROC) curve (AUC). Optimal cut-off points were determined such that sensitivity and specificity were balanced. A p-value of less than 0.05 at the 95% confidence level was considered to indicate statistical significance.

Results

The cohort consisted of 576 patients. Patient characteristics for those with PI-RADS 3 lesions who underwent biopsy are shown in Table 1. The median age was 64 years, the median PSA was 6.5 ng/mL, and the median PSA_d was 0.11 ng/mL/mL. The median prostate volume was 65 mL, and the maximum prostate volume was 255 mL. Among all patients with PI-RADS 3 lesions, those with a prostate volume ≤ 30 mL had a significantly higher rate of csPCa compared to those with volumes of 31-50 mL and ≥ 51 mL ($p < 0.001$).

For PSA_d values below 0.10 ng/mL/mL, the rate of csPCa remained under 5% across all prostate volume groups. Among patients with prostate volumes ≤ 30 mL, csPCa rates were consistently higher at all PSA_d levels above 0.10 ng/mL/mL compared to other volume groups, with a statistically significant

difference observed in the 0.10-0.14 ng/mL/mL range ($p = 0.009$) (Table 2). Among patients with prostate volume ≤ 30 mL, no csPCa was detected when PSA_d was < 0.10 ng/mL/mL, while detection rates were 30.8% for 0.10-0.14, 27.3% for 0.15-0.19, and 44.3% for ≥ 0.20 ng/mL/mL. For those with prostate volume of 31-50 mL, the corresponding rates were 4.9%, 8.3%, 11.8%, and 17.4%, while in patients with prostate volume ≥ 51 mL, the rates were 3.3%, 5.7%, 4%, and 17.6%, respectively (Table 2).

PSA_d showed varying diagnostic accuracy across prostate volume groups. In glands ≤ 30 mL, the AUC was 0.668 with an optimal cut-off of 0.1441 ng/mL/mL. For prostates measuring 31-50 mL, the AUC was 0.599 and the cut-off was 0.1531 ng/mL/mL. In glands ≥ 51 mL, diagnostic performance remained moderate with an AUC of 0.633 and a lower optimal cut-off of 0.1058 ng/mL/mL (Table 3) (Figure 1).

Parameters	Overall cohort (n=576)
Age, median (IQR)	64 (59-70)
PSA (ng/mL), median (IQR)	6.5 (4.87-8.6)
Prostate MRI volume (mL) median (IQR)	65 (50-88)
PSA density (ng/mL ²), median (IQR)	0.11 (0.07-0.13)
PSA density, n (%)	
<0.10	258 (44.8%)
0.10-0.14	190 (33.1%)
0.15-0.19	70 (12.1%)
≥ 0.20	58 (10.1%)
Biopsy procedure,	
Cognitive-targeted (n=223)	223 (38.7%)
Fusion-targeted (n=353)	353 (61.3%)
Biopsy results, n (%)	
Benign	455 (79%)
ISUP grade 1	73 (12.7%)
ISUP grade ≥ 2	48 (8.3%)

PSA: Prostate-specific antigen, MRI: Magnetic resonance imaging, PI-RADS: Prostate Imaging Reporting and Data System, ISUP: International Society of Urological Pathology, IQR: Interquartile range

Parameters (n=576)	Prostate volume			P-value*
	≤ 30 mL (n=46; 8%)	31-50 mL (n=170; 29.5%)	≥ 51 mL (n=360; 62.5%)	
csPCa detection rates				
PI-RADS 3 overall, (n=576)	15/46 (32.6%)	16/170 (9.4%)	17/360 (4.7%)	<0.001
PSA density <0.10 (n=258)	-/4 (-)	2/41 (4.9%)	7/213 (3.3%)	0.816
PSA density 0.10-0.14 (n=190)	4/13 (30.8%)	6/72 (8.3%)	6/105 (5.7%)	0.009
PSA density 0.15-0.19 (n=70)	3/11 (27.3%)	4/34 (11.8%)	1/25 (4%)	0.129
PSA density ≥ 0.20 (n=58)	8/18 (44.3%)	4/23 (17.4%)	3/17 (17.6%)	0.106

*: Chi-square and Fisher's exact tests, PI-RADS: Prostate Imaging Reporting and Data System, PSA: Prostate-specific antigen, csPCa: Clinically significant prostate cancer

Prostate volume	AUC	%95 CI	Optimal PSA _d cut-off (ng/mL/mL)
≤ 30 mL	0.668	0.504-0.831	0.1441
31-50 mL	0.599	0.440-0.757	0.1531
≥ 51 mL	0.633	0.497-0.769	0.1058

PSA: Prostate-specific antigen, AUC: Area under the curve, PSA_d: PSA density, CI: Confidence interval

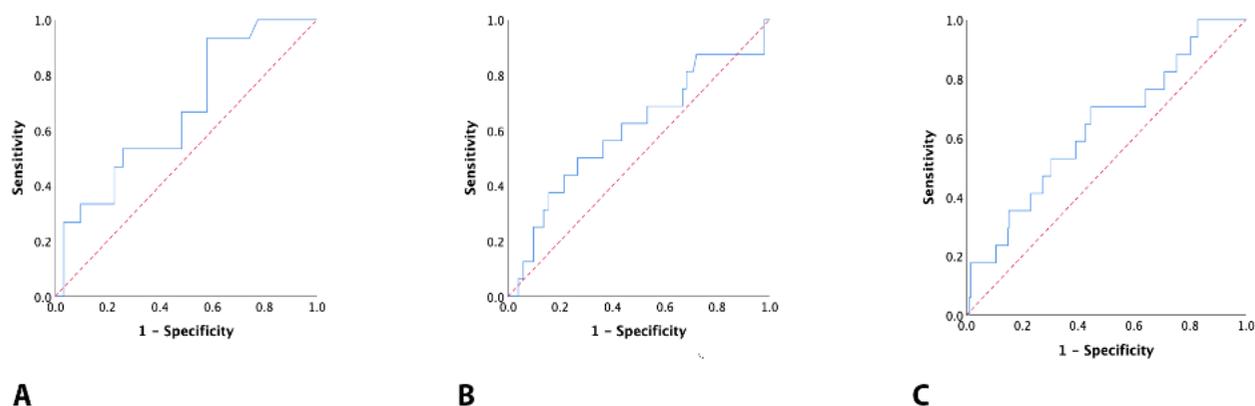


Figure 1. Receiver operating characteristic curves demonstrating the diagnostic performance of prostate-specific antigen (PSA) density for clinically significant prostate cancer across three prostate volume groups: (A) ≤ 30 mL, (B) 31-50 mL, and (C) ≥ 51 mL. Area under the curve values and optimal cut-off points were calculated separately for each group. The discriminative ability of PSA density varied by gland size, highlighting volume-dependent thresholds

Discussion

MRI alone has inherent limitations due to variability in interpretation among readers and between centers (1,12,13). This limitation becomes particularly critical for PI-RADS 3 “gray zone” lesions, where reported rates of csPCa diagnosis range widely from 3% to 50% (14,15). Such a broad range reflects the heterogeneity of biopsy outcomes within this lesion category, underscoring the challenge in clinical decision-making for PI-RADS 3 findings. Since PSAd is calculated using MRI and PSA values, both routinely obtained in the diagnostic workup for suspected PCa, it provides a straightforward, cost-effective metric that has been widely adopted in clinical settings. Much research has focused on identifying optimal PSAd thresholds to enhance sensitivity among patients with negative MRI findings or to improve specificity when MRI results are equivocal. Tools such as the risk-adapted biopsy decision model proposed by Schoots and Padhani (4) exemplify this approach. Furthermore, regardless of prostate volume stratification, PSAd has been demonstrated to outperform PSA alone as a predictor of csPCa (5,16).

According to the 2025 EAU guidelines, a risk-adapted strategy based on PSAd is proposed to guide biopsy decisions for PI-RADS-detected lesions. In this framework, a csPCa detection rate of $<5\%$ is considered very low risk, 5-10% is considered low risk, and 10-20% is considered intermediate risk. The minimum csPCa risk threshold for recommending biopsy is set at $\geq 10\%$. For PI-RADS 3 lesions, this risk corresponds to a PSAd of ≥ 0.10 ng/mL/mL, with biopsy strongly recommended at PSAd ≥ 0.20 ng/mL/mL. Consistent with earlier reports, Koparal et al. (17) demonstrated that a PSAd value greater than 0.20 ng/mL/mL serves as an independent predictor of csPCa in patients with PI-RADS 3 lesions. In our cohort, which included a substantial number of PI-RADS 3 lesions biopsied by two experienced operators, csPCa detection rates remained below 5% across all prostate volume groups when PSAd was <0.10 , confirming the very low-risk category defined by the EAU. These findings support omitting biopsy for PI-RADS 3 lesions with PSAd <0.10 , regardless of prostate size.

Univariate analysis showed that starting from a PSAd threshold of 0.10 ng/mL/mL, csPCa detection rates increased across all prostate volume groups, with the most pronounced rise observed in prostates ≤ 30 mL. ROC curve analysis also supported this volume-dependent diagnostic variability. While csPCa detection rates increased with rising PSAd across all prostate volume groups, ROC analysis revealed that the discriminative power of PSAd was not uniform. Despite relatively similar optimal cut-off values, the AUC was highest in the ≤ 30 mL group, indicating superior diagnostic performance in small prostates. In contrast, PSAd had a lower AUC in intermediate and large prostates, suggesting reduced discriminative accuracy in these groups. Although the AUC was lower in large prostate groups (≥ 50 mL), setting a lower PSAd cut-off value may be beneficial for detecting csPCa in this group.

These findings suggest that applying a uniform PSAd threshold may lead to underdiagnosis of csPCa in men with large prostate volumes and unnecessary biopsies in those with small volumes. While some studies have proposed lower PSAd thresholds for large prostates to preserve sensitivity, our results support this approach. Additionally, the ability to detect csPCa at lower PSAd levels in small prostates suggests that PSAd is a more sensitive biomarker in this subgroup. Although PSAd was associated with increasing csPCa risk across all volume categories, its discriminatory power appeared to be stronger in smaller glands. Therefore, adapting PSAd thresholds according to prostate volume may improve the accuracy of clinical decision-making.

A study that evaluated PSAd in detail found that among patients with PSAd between 0.09 and 0.19 ng/mL/mL, those with a prostate volume of less than 33 mL had higher detection rates of csPCa (5). In a recent publication, Robinson et al. (18) assessed how PSAd cut-off values might vary according to prostate volume when sensitivity is held constant. They identified cut-off values of 0.21 ng/mL/mL for small prostates and 0.11 ng/mL/mL for large prostates. However, they reported that smaller prostate volumes were associated with higher sensitivity in detecting csPCa. They emphasized that these cut-off values were not intended as direct clinical recommendations, but rather to

illustrate the extent to which PSA_d thresholds may need to be adjusted based on prostate volume.

Our study confirms that the diagnostic performance of PSA_d in PI-RADS 3 lesions is affected by prostate size. Larger glands may dilute the PSA contribution from cancer, reducing PSA_d sensitivity. However, the optimal PSA_d cut-off values we identified ranged narrowly from 0.10 to 0.15 ng/mL/mL across volume groups; csPCa detection rates were notably higher in patients with smaller prostates, even at similar PSA_d levels. This highlights the potential for enhanced diagnostic sensitivity in small prostate volumes and suggests that using a uniform PSA_d threshold may not be equally effective for all prostate sizes. Moreover, the clinical relevance of prostate volume extends beyond this specific context. In some situations, such as when patients present with a PSA_d value below 0.10 ng/mL/mL and PI-RADS 1-2 findings on mpMRI, a prostate biopsy is usually not recommended. Determining whether repeat biopsy should be performed in patients with initially negative biopsy results but persistently suspicious PI-RADS scores remains challenging in clinical practice. To enhance diagnostic precision and reduce the risk of overlooking csPCa, several complementary parameters have been explored. For example, Şahin et al. (19) reported that lesion density defined as the length of the mpMRI-detected lesion adjusted for prostate volume served as an independent predictor of csPCa. These findings highlight that prostate volume meaningfully influences both lesion density and PSA_d (19).

Study Limitations

This study has several limitations. First, the retrospective design represents the main limitation and may have introduced selection bias regarding which patients with PI-RADS 3 lesions proceeded to biopsy. Another important consideration is the timing of mpMRI in relation to prostate biopsy. During the early phase of the study period (2017-2019), mpMRI was not routinely performed before the initial biopsy; therefore, biopsy-naïve patients who underwent mpMRI during that interval were also included in the analysis. At our institution, however, mpMRI was already being used prior to the first biopsy in selected patients presenting with elevated PSA levels or abnormal findings on digital rectal examination. As these patients generally had higher PSA values and suspicious clinical findings, their inclusion may have contributed to selection bias. Although the study included a relatively large cohort, all data were derived from a single academic tertiary referral center, which may limit the generalizability of the results. On the other hand, all MRI examinations were jointly reassessed by two experienced radiologists, enhancing the reliability of the radiological evaluation. Overall, our findings may provide a useful basis for future research aimed at further investigating and validating the relationship between prostate volume, PSA_d, and the detection of csPCa in patients with PI-RADS 3 lesions.

Conclusion

Our results imply that prostatic volume affects PSA_d's diagnostic efficacy in predicting csPCa. Our study encourages the use of lower PSA_d thresholds in individuals with larger prostate

volumes, especially in borderline cases such as PI-RADS 3 lesions, rather than suggesting clear new cut-off values. In this patient group with diagnostic uncertainty, our volume-adjusted interpretation may enhance risk classification and facilitate tailored biopsy decisions.

Ethics

Ethics Committee Approval: The study was approved by our Institutional Ethics Committee of Ankara University (decision no: İ06-596-25, date: 12.08.2025).

Informed Consent: Written informed consent was obtained from all patients before TRUS-guided biopsies.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: E.S., S.B., Concept: Ç.A., E.S., S.B., Design: D.K.Ö., Data Collection or Processing: A.F.Ö., A.M., S.E., Analysis or Interpretation: D.K.Ö., E.Ö., N.H., Ç.G., Literature Search: Ç.A., M.A.İ., M.C.K., Writing: Ç.A., E.Ö., N.H.

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Data Availability Statement

The data sets generated and/or analyzed during the current study are not publicly available but can be obtained from the corresponding author upon reasonable request.

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