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PROSTATE SPECIFIC ANTIGEN DENSITY AS A PREDICTOR FOR PROSTATE CANCER IN CASES WITH PROSTATE SPECIFIC ANTIGEN LEVELS GREATER THAN 4NG/ML

Urology

Dr Sumit Kumar Panda	Associate Professor, Urology
Dr Deepak Kumar Kisku	Associate Professor, General Surgery
Dr Shyamjit K Suresh*	3rd Year PG Resident, General Surgery *Corresponding Author
Prof. (Dr.) Sudhir Kumar Panigrahi	Professor, General Surgery
Prof. (Dr.) Rajat Kumar Patra	Professor, General Surgery
Dr Nagasurya Poojitha Alapati	3rd Year PG Resident, General Surgery

ABSTRACT

Prostate cancer remains a significant global health concern, with early detection essential for improved patient outcomes. While prostate-specific antigen (PSA) testing is widely used for screening, its specificity is limited, particularly for PSA levels exceeding 4 ng/mL. Prostate- specific antigen density (PSAD), which adjusts PSA values according to prostate volume, potentially offers greater diagnostic accuracy. This study aimed to evaluate the predictive value of PSAD in prostate cancer diagnosis and investigate its correlation with patient age, tumor aggressiveness, Gleason grade, and PIRADS scoring. A cross-sectional analytical study involving 229 men aged between 40 and 79 years with PSA levels above 4 ng/mL was conducted from March 2023 to February 2025. Participants underwent transrectal ultrasound (TRUS)-guided prostate biopsies, and the data were analyzed using IBM SPSS v26.0. The findings revealed significantly higher median PSAD values in prostate cancer patients (localized cancer: 0.39; metastatic cancer: 1.62) compared to those with benign conditions (BEP: 0.14; prostatitis: 0.21; p=0.001). PSAD demonstrated strong positive correlations with higher Gleason grades (Group 1: 0.18; Group 5: 1.0) and PIRADS scores (score 2: 0.14; score 5: 0.89; p=0.001), while no significant association with patient age was observed (p=0.88). In conclusion, PSAD is a reliable, age-independent biomarker that enhances specificity in prostate cancer detection, predicts tumor aggressiveness, and informs clinical decision-making, particularly when combined with MRI findings. Routine incorporation of PSAD into diagnostic protocols could significantly reduce unnecessary biopsies and improve patient management.

KEYWORDS

Prostate Cancer, PSA Density, Gleason Grade, PIRADS Score, TRUS Biopsy

INTRODUCTION

Prostate cancer remains one of the most prevalent malignancies in men, contributing significantly to cancer-related morbidity and mortality worldwide. Early detection is critical for improving outcomes. Serum prostate-specific antigen (PSA), a glycoprotein secreted by prostate epithelial cells, is widely used as a non-invasive screening tool. However, elevated PSA levels are not specific to cancer and can also occur in benign prostatic enlargement (BEP), prostatitis, and other non-malignant conditions, particularly in men with PSA levels >4 ng/mL. [1,2]

To improve specificity, prostate-specific antigen density (PSAD)—the ratio of PSA to prostate volume measured by transrectal ultrasound (TRUS)—has been introduced. PSAD accounts for prostate size, offering better discrimination between benign and malignant conditions, especially within the diagnostic "gray zone" (PSA 4–10 ng/mL). A PSAD value ≥0.15 ng/mL/cm³ has been associated with a higher likelihood of prostate cancer and is widely used as a threshold for recommending biopsy. [3,4]

PSAD offers advantages over PSA alone by addressing variability in prostate volume. Cancerous tissues produce more PSA per unit volume than benign tissues, leading to disproportionately elevated PSA levels in malignancy. In contrast, BEP typically causes a proportional PSA rise relative to gland size. [5,6] PSAD also has prognostic value, correlating with Gleason scores and tumor aggressiveness. [7,8]

Incorporating PSAD with multiparametric MRI (mpMRI) and clinical risk factors enhances diagnostic accuracy and informs management decisions, reducing unnecessary biopsies and overtreatment. [9,10] Despite operator-dependent limitations in TRUS-based volume estimation, PSAD remains a practical, cost-effective tool in routine clinical use. [11,12]

OBJECTIVES

This study aimed to determine the proportion of biopsy-confirmed prostate cancer in patients with PSA >4 ng/mL and PSAD >0.2 ng/mL/cm³ presenting with lower urinary tract symptoms. It also evaluated the association between PSAD levels and age, cancer versus benign diagnosis, tumor aggressiveness, and histopathological subtypes.

MATERIALS AND METHODS

This descriptive cross-sectional analytical study was conducted from March 2023 to February 2025 at the Departments of General Surgery and Urology, Kalinga Institute of Medical Sciences (KIMS), Bhubaneswar, to evaluate the role of prostate-specific antigen density (PSAD) in predicting prostate cancer in patients with PSA >4 ng/mL.

Inclusion and Exclusion Criteria: Men aged >50 years presenting with lower urinary tract symptoms (LUTS), PSA >4 ng/mL, and undergoing TRUS-guided biopsy were included. Exclusion criteria were bleeding disorder, acute prostatitis, prior prostate surgery, age >80 years, frailty with multiple co-morbidities and serum PSA < 4ngm/mL.

Sampling and Sample Size: Consecutive sampling was employed. Patients were grouped by PSA levels: 4.1–10, 10.1–20, 20.1–50, 50.1–100, and >100 ng/mL. The sample size was calculated as 250 based on standard prevalence estimation.

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Study Parameters: Collected data included PSA level, prostate

volume (via TRUS), PSAD, PI-RADS score (if MRI was done), and biopsy histopathology including Gleason grading.

Procedure: TRUS-guided 12-core prostate biopsies were performed using an 18G needle after antibiotic prophylaxis. Systematic sampling was done from both lobes.

Data Collection and Analysis: Data were recorded using a structured proforma. Statistical analysis was performed using IBM SPSS v26.0. Descriptive statistics were used for quantitative variables; Chi-square, t-tests, and ANOVA for comparisons. Sensitivity, specificity, and predictive values of PSAD were calculated. Significance was set at $p<0.05$.

Ethical Approval: Ethical clearance was obtained from the institutional ethics committee. Informed consent was taken from all participants, and confidentiality was maintained throughout the study.

RESULTS

A total of 229 patients aged 40–79 years were included. The majority were aged 70–79 (53.3%), followed by 60–69 (33.2%). PSA levels ranged from 4 to 157 ng/mL, with the largest group (40.2%) falling in the 4–10 ng/mL range. PSA levels between 10.1–20 ng/mL and 20.1–50 ng/mL accounted for 22.7% and 19.2% respectively, while higher PSA ranges (>50 ng/mL) represented 17.9% of patients.

Prostate volume (PV) ranged from 25 to 183 cc. Most patients had mild (37.1%) or moderate (38.0%) enlargement. Marked prostatomegaly (>80 cc) was seen in 22.7%; only 2.2% had normal-sized prostates (<30 cc).

PSA density (PSAD) showed a median value of 0.21 ng/mL/cc. About 43.2% had PSAD >0.25, indicating high suspicion for malignancy. PSAD 0.15–0.25 was seen in 25.3%, and 31.4% had PSAD <0.15.

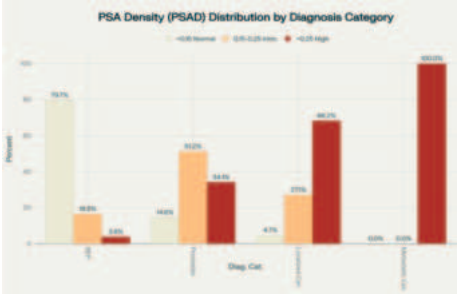
Table 1 Demographic and Diagnostic Distributions in Prostate Cancer Study

Among 94 biopsy-confirmed cancer patients, the most common Gleason Grade Group was Group 5 (42.6%), followed by Groups 4 (19.1%), 2 and 3 (each 13.8%). Only 10.6% had low-grade (Group 1) disease. Most cases were thus high-grade malignancies.

PI-RADS scores were available for cancer-positive cases (n=94). PIRADS 4 and 5 were predominant (45.7% and 42.6%, respectively), consistent with high suspicion of clinically significant cancer. Only 1 patient had a PIRADS 2 lesion that turned out to be malignant.

PSAD significantly differed by diagnosis category. Median PSAD was 0.14 in BEP, 0.21 in prostatitis, 0.39 in localized cancer, and 1.62 in metastatic cases. All metastatic cases had PSAD >0.25. A significant association was found between high PSAD and prostate cancer diagnosis ($p<0.001$).

Table 2 PSAD Distribution by Diagnosis Category

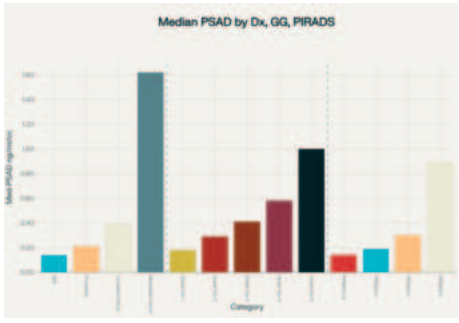


PSAD values did not significantly differ across age groups (p=0.88), indicating age had minimal influence on PSA density once prostate volume was accounted for.

A clear correlation was observed between PSAD and tumor aggressiveness. Median PSAD increased with Gleason Grade: Group 1 (~0.18), Group 2 (~0.29), Group 3 (~0.41), Group 4 (~0.58), and Group 5 (~1.0). This trend was statistically significant ($p<0.001$).

Similarly, PSAD rose with increasing PIRADS score: median PSAD for PIRADS 2 (~0.14), PIRADS 3 (~0.19), PIRADS 4 (~0.30), and PIRADS 5 (~0.89), again with strong statistical significance ($p<0.001$).

Table 3 Comparison of Median PSA Density (PSAD) Values Across Diagnosis Categories, Gleason Grade Groups, and PIRADS MRI Scores



DISCUSSION

This study confirms PSA density (PSAD) as a valuable biomarker for distinguishing between benign and malignant prostate conditions and for predicting tumor aggressiveness. PSAD was significantly higher in patients with prostate cancer, especially those with metastatic disease ($p < 0.001$), while showing no significant association with age ($p = 0.88$), reinforcing its reliability across age groups.

Patients with benign prostatic enlargement (BEP) and prostatitis showed low median PSAD values (~0.14 and ~0.21 ng/mL/cc, respectively), mostly within or just above the normal range. In contrast, localized prostate cancer cases had a median PSAD of ~0.39, and metastatic cancer cases showed markedly elevated PSAD (~1.62), with all exceeding 0.25. The stepwise rise in PSAD from benign to localized to metastatic disease underlines its role in risk stratification. Notably, 100% of metastatic cases had PSAD >0.25, making it a strong predictor of advanced disease.

Importantly, PSAD was unaffected by age. Median values were consistent across all age groups, indicating that PSA-to-volume ratio remains stable despite age-related prostate enlargement. This supports uniform application of PSAD thresholds without age adjustment, simplifying interpretation in clinical settings.

There was a clear correlation between PSAD and tumor grade. Median PSAD increased with rising Gleason Grade Group—from ~0.18 in Group 1 to ~1.0 in Group 5—demonstrating its association with tumor burden and aggressiveness. Higher PSAD may reflect increased PSA output per tumor volume or more extensive disease. Clinically, elevated PSAD in biopsy- proven cases should prompt consideration of higher-grade or larger-volume disease and guide further management.

PSAD also showed a strong relationship with PIRADS scores. Higher PIRADS scores (4 and 5) were associated with significantly higher PSAD (median ~0.30 and ~0.89, respectively), while PIRADS 1–2 scores corresponded with low PSAD (~0.14). This alignment reinforces the utility of combining MRI findings with PSAD for better diagnostic accuracy. In PIRADS 3 lesions, PSAD can aid decision-making: high values support biopsy, while low values may justify observation.

Overall, PSAD enhances specificity in prostate cancer diagnosis, especially in the PSA "gray zone" (4–10 ng/mL), reducing unnecessary biopsies and identifying clinically significant cancers. Its correlation with grade, metastasis, and imaging suspicion highlights its diagnostic and prognostic utility.

In conclusion, PSAD is a robust, age-independent, cost-effective marker. It correlates with malignancy, tumor aggressiveness, and radiological suspicion, and improves clinical decision-making when combined with MRI. Its incorporation into routine prostate cancer evaluation is strongly supported by these findings.

CONCLUSION

This study demonstrates that PSA density (PSAD) is a reliable and clinically valuable predictor of prostate cancer presence and aggressiveness in men with elevated PSA levels. PSAD was significantly higher in patients with prostate cancer, especially in metastatic cases ($p < 0.001$), and showed strong correlation with higher Gleason grades and PIRADS scores. Notably, PSAD remained unaffected by patient age, supporting its consistent applicability across age groups.

Clinically, PSAD enhances decision-making by improving the specificity of PSA testing. It can help identify patients who may safely avoid biopsy despite moderately raised PSA and, conversely, flag those at higher risk who require further evaluation. When combined with MRI, PSAD improves diagnostic accuracy—high PSAD with PIRADS 4–5 lesions strongly indicates significant cancer, while low PSAD in equivocal cases may support surveillance.

Incorporating PSAD into routine prostate cancer evaluation aids in distinguishing benign from malignant conditions, guides biopsy decisions, and helps predict tumor aggressiveness. This study supports its broader use in diagnostic pathways to enable more personalized, accurate, and efficient prostate cancer care.

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