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ROLE OF SERUM PROSTATE-SPECIFIC ANTIGEN AND PROSTATE SIZE IN THE DIAGNOSIS OF PROSTATE CANCER: A PROSPECTIVE OBSERVATIONAL STUDY

General Surgery

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ABSTRACT

Background Serum prostate-specific antigen (PSA) is sensitive but poorly specific for prostate cancer, particularly in the 4–10 ng/mL "gray zone," because benign prostatic hyperplasia also elevates PSA. Correcting PSA for gland size (PSA density, PSAD) may improve diagnostic accuracy. **Objectives**To evaluate the role of serum PSA and prostate size (volume and PSAD) in predicting histo- pathologically confirmed prostate cancer, and to compare their diagnostic performance.**Materials and Methods** A prospective observational study of 30 consecutive men with raised PSA and/or abnormal digital rectal examination (DRE) over 14 months. Serum PSA was measured, prostate volume estimated by ultrasound using the prolate ellipsoid formula, and PSAD calculated. Diagnosis was confirmed by TRUS-guided 12-core biopsy with ISUP grading. Sensitivity, specificity, predictive values and ROC analysis were computed.**Results** Cancer was detected in 11/30 men (36.7%). Cancer cases had higher PSA (16.6 ± 12.3 vs 6.7 ± 2.6 ng/mL; p=0.0022), smaller glands (39.6 ± 6.3 vs 53.5 ± 14.1 cc; p=0.0039) and higher PSAD (0.392 ± 0.225 vs 0.121 ± 0.020 ng/mL/cc; p<0.001). At the 0.15 ng/mL/cc threshold, PSAD achieved 90.9% sensitivity and 89.5% specificity (AUC 0.986), outperforming PSA ≥4.0 ng/mL (100% / 10.5%) and total PSA alone (AUC 0.842). **Conclusion** PSA is a highly sensitive but non-specific screening marker; incorporating prostate size as PSAD substantially improves specificity and overall diagnostic accuracy, and may reduce unnecessary biopsies, especially in the diagnostic gray zone.

KEYWORDS

Prostate-specific Antigen; Psa Density; Prostate Volume; Prostate Cancer; Ultrasound; Isup Grade Group.

INTRODUCTION

Prostate cancer is among the most common malignancies in men worldwide. Global estimates for 2022 placed it as the fourth most commonly diagnosed cancer overall and the second most common cancer in men, with close to 1.47 million new cases reported in that year. In India, although historically uncommon, the age-adjusted incidence has risen progressively and prostate cancer now ranks among the leading cancers in men in several urban registries, a trend attributed to an ageing population, increasing PSA testing and improved diagnostic infrastructure.

Serum prostate-specific antigen (PSA), a serine protease produced almost exclusively by prostatic epithelial cells, transformed prostate cancer detection after its introduction as a screening test. However, PSA is organ-specific rather than cancer-specific: it is elevated not only in malignancy but also in benign prostatic hyperplasia (BPH), prostatitis and after instrumentation. Consequently, the conventional cut-off of 4.0 ng/mL is highly sensitive but suffers from low specificity, and a substantial proportion of biopsies performed for PSA in the 4–10 ng/mL "diagnostic gray zone" are negative.

Because much of the PSA elevation in older men is driven by an enlarging benign gland, several PSA derivatives have been proposed to improve specificity. Of these, PSA density (PSAD) — the ratio of serum PSA to prostate volume measured by ultrasound — directly accounts for gland size. A PSAD threshold of 0.15 ng/mL/cc is widely used to stratify the risk of clinically significant cancer. Prostate volume itself is therefore not merely a confounder but a clinically usable variable that contextualises any given PSA value.

Against this background, the present prospective observational study evaluates the individual and combined roles of serum PSA and prostate size (volume and PSAD) in predicting histopathologically confirmed prostate cancer in men undergoing TRUS-guided biopsy, and directly compares their diagnostic performance.

MATERIALS AND METHODS

Study Design

A hospital-based prospective observational study was conducted in the Department of Surgery , [Index Medical College], over a period of 14 months ([November/2024] to [December/2025]). All consecutive eligible patients presenting to the outpatient and inpatient services during this period were enrolled after written informed consent.

Written informed consent was obtained from all participants or their legally acceptable representatives.

Study Population

Inclusion Criteria:

Inclusion criteria
Male patients ≥ 50 years of age (or ≥ 45 years with a positive family history)
Serum PSA ≥ 4.0 ng/mL and/or abnormal/suspicious digital rectal examination (DRE)
Lower urinary tract symptoms warranting evaluation
Fit to undergo TRUS-guided prostate biopsy
Provided written informed consent

Exclusion Criteria:

Exclusion criteria
Prior diagnosis or treatment of prostate cancer
Previous prostate surgery (TURP/open prostatectomy) or radiotherapy
Acute urinary tract infection, acute prostatitis or recent catheterisation/instrumentation (within 4 weeks)
5-alpha-reductase inhibitor use within 6 months (alters PSA)
Bleeding diathesis or unfit for biopsy; refusal of consent

Sample Size Calculation

A total of **30 patients** who satisfied the eligibility criteria within the study period were enrolled sampling .The sample size for a diagnostic-accuracy study this is typically based on an expected sensitivity/specificity of the index test (e.g., PSAD), an anticipated cancer prevalence, and a desired precision .

Outcome Measures and Assessments

Clinical evaluation and DRE. All patients underwent history, examination and DRE; findings were recorded as normal or suspicious (nodule, induration, asymmetry).

Serum PSA. Venous blood was drawn before DRE/instrumentation and total serum PSA measured. Standard interpretive categories are shown in Table 2.

Prostate volume and PSAD. Prostate volume was estimated by Ultrasound, volume . PSA density was calculated as serum PSA divided by prostate volume (ng/mL/cc); a threshold of 0.15 ng/mL/cc was used.

Biopsy and histopathology. TRUS-guided systematic 12-core needle biopsy was performed under antibiotic cover. Specimens were reported by a pathologist, and malignant cases were assigned a Gleason score and ISUP grade group (Table 3).

Reference values and grading (standard tables)

Serum total PSA	Interpretation	Age-specific upper limit (Oesterling)
< 4.0 ng/mL	Conventional normal range (cancer not fully excluded)	40–49 yr: ≤ 2.5
4.0 – 10.0 ng/mL	Diagnostic "gray zone" – PSA derivatives most useful	50–59 yr: ≤ 3.5
> 10.0 ng/mL	High probability of malignancy	60–69 yr: ≤ 4.5
PSA density ≥ 0.15 ng/mL/cc	Increased likelihood of clinically significant cancer	70–79 yr: ≤ 6.5
ISUP Grade Group	**Gleason score**	**Description**
1	≤ 6 (3+3)	Only individual discrete well-formed
2	3+4 = 7	Predominantly well-formed glands with lesser poorly-formed/fused component
3	4+3 = 7	Predominantly poorly-formed/fused glands with lesser well-formed component
4	8 (4+4, 3+5, 5+3)	Only poorly-formed/fused glands, or with lesser cribriform/solid
5	9–10 (4+5, 5+4, 5+5)	Lacks gland formation, with or without necrosis

OBSERVATIONS AND RESULTS

Thirty men were enrolled over the study period. Prostate cancer was confirmed in 11 patients (36.7%) and benign pathology (BPH ± prostatitis) in 19 patients (63.3%). Baseline characteristics by final diagnosis are shown in Table 4.

Variable	Cancer (n=11)	Benign (n=19)	p-value
Age (years), mean ± SD	71.5 ± 4.0	64.7 ± 4.9	0.002
Serum PSA (ng/mL), mean ± SD	16.6 ± 12.3	6.7 ± 2.6	0.0022
Serum PSA (ng/mL), median	12.0	6.0	–
Prostate volume (cc), mean ± SD	39.6 ± 6.3	53.5 ± 14.1	0.0039
PSA density (ng/mL/cc), mean ± SD	0.392 ± 0.225	0.121 ± 0.020	< 0.001

Cancer cases were significantly older, had higher PSA, smaller prostate glands and markedly higher PSA density than men with benign disease. The smaller gland size in cancer patients despite higher PSA underlies the discriminatory value of PSA density.

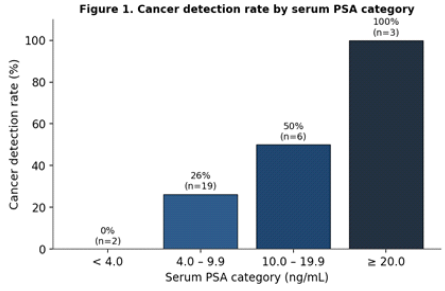

Figure 1. Cancer detection rate increases progressively with serum PSA category.

PSA category (ng/mL)	n	Cancers	Detection rate (%)
< 4.0	2	0	0.0
4.0 – 9.9	19	5	26.3
10.0 – 19.9	6	3	50.0
≥ 20.0	3	3	100.0
Prostate volume (cc)	**n**	**Cancers**	**Detection rate (%)**
< 30	0	0	0.0
30 – 49	19	10	52.6
50 – 69	8	1	12.5
≥ 70	3	0	0.0

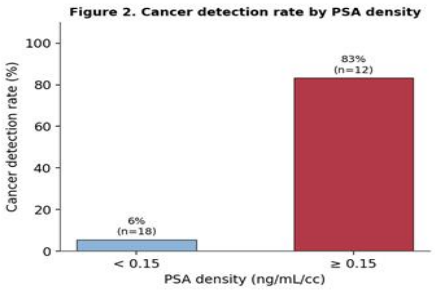

Figure 2. Cancer detection rate by PSA density at the 0.15 ng/mL/cc threshold.

PSA density (ng/mL/cc)	n	Cancers	Detection rate (%)
< 0.15	18	1	5.6
≥ 0.15	12	10	83.3

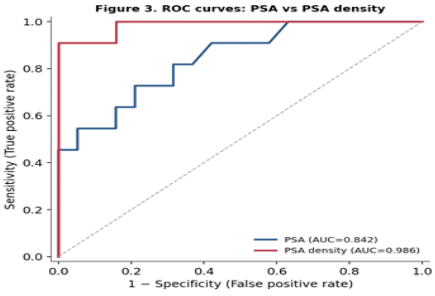

Figure 3. ROC curves. PSA density (AUC 0.986) discriminated cancer better than total PSA (AUC 0.842).

Index test	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Acc (%)
Serum PSA ≥ 4.0 ng/mL	100.0	10.5	39.3	100.0	43.3
Serum PSA ≥ 10.0 ng/mL	54.5	84.2	66.7	76.2	73.3
PSA density ≥ 0.15 ng/mL/cc	90.9	89.5	83.3	94.4	90.0
Suspicious DRE	72.7	89.5	80.0	85.0	83.3

Serum PSA ≥ 4.0 ng/mL was the most sensitive test (100%) but the least specific (10.5%), confirming its limited ability to avoid negative biopsies. Raising the threshold to ≥ 10.0 ng/mL improved specificity (84.2%) at the cost of sensitivity (54.5%). PSA density ≥ 0.15 ng/mL/cc gave the best overall balance — sensitivity 90.9%, specificity 89.5%, accuracy 90% — and the highest AUC.

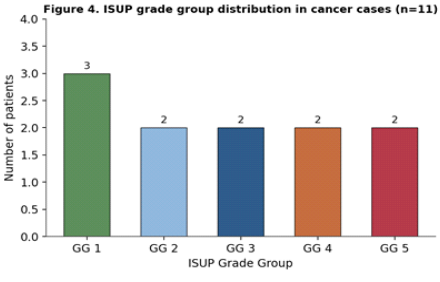

Figure 4. ISUP grade-group distribution among the confirmed cancers.

ISUP Grade Group	Gleason score	n	% of cancers
1	3+3=6	3	27.3
2	3+4=7	2	18.2
3	4+3=7	2	18.2

4	4+4=8 / 3+5 / 5+3	2	18.2
5	4+5=9, 5+4=9, 5+5=10	2	18.2

CORRELATION

PSA density correlated strongly with ISUP grade group among cancer cases (Spearman $\rho = 0.982$, $p < 0.001$), indicating that higher PSAD values were associated with higher-grade, more clinically significant disease. Serum PSA showed only a weak, non-significant correlation with prostate volume in this cohort ($\rho = 0.271$, $p = 0.147$).

DISCUSSION

This prospective study reaffirms a long-standing clinical observation: serum PSA is a sensitive but non-specific marker for prostate cancer, and accounting for prostate size markedly improves its diagnostic performance. In our cohort, PSA ≥ 4.0 ng/mL identified every cancer but generated a large number of negative biopsies, whereas PSA density at the 0.15 ng/mL/cc threshold preserved high sensitivity while substantially improving specificity and accuracy.

These findings are consistent with the foundational work of Catalona and colleagues, who established serum PSA as a practical screening test, and with Benson and colleagues, who introduced PSA density specifically to distinguish benign prostatic enlargement from cancer and demonstrated its superiority over absolute PSA in the intermediate range. The persistence of low specificity at the 4.0 ng/mL cut-off also mirrors evidence that a meaningful proportion of cancers occur below this value and that no single PSA threshold cleanly separates benign from malignant disease.

The mechanistic explanation is straightforward. Benign prostatic hyperplasia increases serum PSA in proportion to gland volume; for a given PSA, a smaller gland implies a higher PSA output per unit tissue and therefore greater suspicion of malignancy. In our data, cancers arose in significantly smaller glands yet exhibited higher PSA, producing the clear separation in PSA density seen between groups. The strong correlation between PSAD and ISUP grade group further suggests that PSAD reflects not merely the presence of cancer but its biological aggressiveness, supporting its contemporary use in risk stratification and active-surveillance decisions.

Clinically, incorporating prostate size into PSA interpretation — as PSAD — can reduce unnecessary biopsies in men with gray-zone PSA and large benign glands, while still flagging high-risk disease. This is particularly relevant in resource-constrained settings where avoiding low-yield invasive procedures has clear value.

Limitations

- Single-centre study with a small sample size, limiting statistical power and the precision of the diagnostic estimates (wide confidence intervals).
- Selection bias is inherent, as only men referred for biopsy were studied; the spectrum of disease may differ from the general population (verification/work-up bias).
- Prostate volume by ultrasound is operator-dependent; multiparametric MRI and PI-RADS were not incorporated.
- Short follow-up precludes assessment of clinical outcomes; the reference standard (systematic biopsy) may itself miss some cancers.

CONCLUSION

Serum PSA is a valuable, highly sensitive first-line marker for prostate cancer but lacks specificity, especially in the 4–10 ng/mL gray zone where benign enlargement contributes to elevation. Integrating prostate size through PSA density significantly improves specificity, overall diagnostic accuracy and correlation with tumour grade. PSA density is therefore a simple, inexpensive and clinically useful adjunct that can refine the decision to biopsy and help avoid unnecessary procedures. Larger, multicentre studies incorporating MRI are warranted to confirm optimal thresholds.

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