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ORIGINAL RESEARCH

Diagnostic Value of FPSAD and PI-RADS v2.1 for Clinically Significant Prostate Cancer in Patients with tPSA Levels of 4-10 ng/mL

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Objective: To evaluate the incremental diagnostic value of combining free prostate-specific antigen density (FPSAD) with Prostate Imaging Reporting and Data System version 2.1 (PI-RADS v2.1) for clinically significant prostate cancer (csPCa,defined as Gleason score≥3+4) in the diagnostic gray zone (tPSA 4–10 ng/mL).

Methods: : This retrospective study analyzed 137 patients (75 with csPCa and 62 with non-clinically significant prostate cancer (ncsPCa) who underwent transperineal prostate biopsy at Xiangtan Central Hospital between January 2022 and January 2024. PI-RADS v2.1 scores were assigned based on magnetic resonance (MR) imaging, and prostate volume (PV) and FPSAD were calculated. Statistical analyses included chi-square/Fisher's exact tests for categorical variables and independent *t*-tests for continuous variables. Logistic regression identified independent predictors of csPCa, and a nomogram model was developed. Model performance was evaluated using calibration curves and receiver operating characteristic (ROC) analysis.

Results: Significant differences were observed in FPSAD, PI-RADS v2.1 scores, and free PSA (fPSA) between the csPCa and ncsPCa groups ($P < 0.01$). FPSAD (OR = 1.95, 95% CI: 1.22–2.22, $P < 0.01$) and PI-RADS v2.1 scores (OR = 2.41, 95% CI: 1.57–3.70, $P < 0.01$) were independent predictors of csPCa. The combined FPSAD and PI-RADS v2.1 model demonstrated superior diagnostic performance (AUC =0.829) compared to FPSAD alone (AUC = 0.69) or PI-RADS v2.1 alone (AUC = 0.773) ($P < 0.01$), with 91% sensitivity and 32% fewer unnecessary biopsies than PI-RADS≥3 criteria. In PI-RADS 3 subgroup (n=41), FPSAD correctly reclassified 13/18 (72.2%) indeterminate cases.

Conclusion: For Asian men with tPSA 4–10 ng/mL, the FPSAD+PI-RADS algorithm (cutoffs: >0.017 and ≥4) provides 15–20% higher accuracy than either marker alone, while reducing biopsies by 25%. This approach is particularly valuable for PI-RADS 3 cases, where it resolved >65% of diagnostic uncertainties in our cohort.

Keywords: FPSAD, PI-RADS V2.1, csPCa, ncsPCa, diagnostic value, tPSA

Background

PCa is the second most common malignancy among men globally and the second leading cause of cancer-related death.[1] Serum PSA is a crucial marker for PCa screening and plays a significant role in guiding prostate biopsy. However, the diagnostic value of PSA for PCa has certain limitations, particularly in patients with PSA levels between 4–10 ng/mL. In this range, the detection rate of PCa is only 20%-40%,[2] leading to a significant number of patients undergoing invasive biopsy procedures. Furthermore, with the increasing use of serum PSA as a routine screening test for prostate issues, the number of patients presenting with initial PSA levels between 4–10 ng/mL is growing. However, the prostate cancer biopsy positivity rate in this group is relatively low, requiring further exploration by urologists.

The diagnostic challenge of prostate-specific antigen (PSA) testing is particularly evident in the intermediate range of 4–10 ng/mL, where its specificity for detecting clinically significant prostate cancer (csPCa) remains suboptimal. Importantly, serum PSA levels can be elevated in various non-malignant conditions that must be considered in clinical interpretation. Benign prostatic hyperplasia (BPH) frequently causes PSA elevation through mechanical compression of prostatic ducts and subsequent epithelial disruption. Prostatitis represents another common confounding factor, where inflammatory processes increase vascular permeability and PSA release into circulation. Additional benign conditions

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associated with PSA elevation include urinary tract infections (reported in 25–40% of cases), prostate trauma or manipulation (eg, catheterization, biopsy), and vigorous physical activity. These non-cancerous factors are particularly problematic in the diagnostic gray zone, where they contribute to the limited specificity of PSA testing.[3] This clinical reality underscores the critical need for more specific biomarkers to complement traditional PSA testing.

To enhance the accuracy of PSA-based prediction for PCa biopsy diagnosis, several indices have emerged, including PI-RADS scores, tPSA, fPSA,f/tPSA, and PV. Studies have shown that selecting patients for prostate biopsy based on these indices can improve the positivity rate of prostate biopsy to a certain extent.[4,5] The Prostate Imaging Reporting and Data System (PI-RADS), with its high soft tissue resolution and non-invasive nature, has been widely applied in the localization, characterization, and prognostic assessment of prostate cancer (PCa). PI-RADS v2.1, in particular, has shown high sensitivity and specificity in prostate cancer (PCa).[4] However, a PI-RADS score of 3 shows considerable variability in its diagnostic value for both PCa and csPCa. Previous studies have demonstrated that combining PI-RADS v2.0 with other factors improves the diagnostic accuracy for csPCa,[6] though the results are inconsistent due to variations in study methodologies. This study aims to further validate the diagnostic efficacy of combining PI-RADS v2.1 with other parameters for PCa diagnosis.Previous studies have reported that PSAD is a predictive marker for detecting csPCa, and PSAD has been found to have superior predictive value for PCa.[7] However, research on FPSAD for diagnosing PCa is relatively limited both domestically and internationally. This study aims to evaluate the diagnostic efficacy of FPSAD, PI-RADS V2.1 scores, and their combined application in diagnosing PCa by analyzing clinical data of patients with PSA levels between 4–10 ng/mL who underwent prostate biopsy at Xiangtan Central Hospital.

Materials and Methods

This retrospective study included 75 patients with PCa and 62 patients with BPH who underwent transperineal prostate biopsy at Xiangtan Central Hospital, a tertiary hospital with the strongest comprehensive strength in Xiangtan City, from January 2022 to January 2024. The Department of Urology at Xiangtan Central Hospital is a provincial and municipal-level clinical key specialty.

Inclusion Criteria

The study included individuals who underwent transperineal prostate biopsy at our hospital, with total prostate-specific antigen (tPSA) levels ranging from 4–10 ng/mL. Only those with complete clinical data were considered for inclusion.

Exclusion Criteria

Exclusion was based on the presence of inflammatory conditions such as pneumonia, urinary tract infections, or prostatitis. Additionally, individuals with indwelling urinary catheters before biopsy, autoimmune diseases, thrombosis, or abnormal coagulation function were excluded. Those who had previously undergone a prostate biopsy were also excluded.

Biopsy Procedure

All biopsy procedures were performed by two attending urologists with more than five years of experience using a standardized 12-core systematic biopsy protocol. Patients were placed in the lithotomy position and underwent routine disinfection and draping. Transperineal biopsies were obtained using 18-gauge automatic biopsy needles. Each patient received 12 systematic cores (6 per lobe, including 2 cores each from the apex, mid-gland, and base). For MRI-visible suspicious lesions (PI-RADS≥3), two additional targeted biopsy cores were obtained, resulting in a total of 14 cores for patients with identifiable lesions.

Pathological evaluation was conducted independently by two genitourinary pathologists in a blinded manner. Clinically significant prostate cancer (csPCa) was strictly defined as Gleason score ≥3+4 (Grade Group ≥2). Non-clinically significant prostate cancer (ncsPCa) encompassed both benign prostatic hyperplasia (BPH) and Gleason score 6 (Grade Group1) prostate cancer. Cases with pathological discrepancies were resolved through multidisciplinary consensus discussions involving urologists, radiologists, and pathologists to ensure diagnostic accuracy and consistency. This comprehensive approach guaranteed reliable histopathological classification for all study participants.

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MRI Examination and PI-RADS V2.1 Scoring

A GE 3.0T MRI scanner was used for imaging. Basic scanning sequences included axial diffusion-weighted imaging (DWI), T1WI, T2W1, coronal T2W1, and sagittal T2W1. Scanning parameters adhered to PI-RADS V2.1 recommendations. Two experienced senior radiologists independently scored the bpMRI images according to PI-RADS V2.1, blinded to the pathological results and clinical indicators. In case of disagreement, the two senior radiologists discussed until a consensus was reached.

Data Collection

All patients were divided into the BPH group (control group) and the PCa group (observation group) based on the pathological results of the biopsy. General clinical data, including age, BMI, hypertension, diabetes, coronary heart disease, smoking history, and drinking history, were collected. Blood samples were drawn from all patients within one week before prostate biopsy. Early morning fasting venous blood was collected from the antecubital vein (5 mL) in a vacuum blood collection tube, centrifuged at 3500 r/min for 5 minutes at 4°C, and the upper layer serum was extracted for tPSA and fPSA testing. Prostate ultrasound and enhanced MRI were performed before biopsy. The maximum left-right diameter of the prostate was measured in the transverse plane, and the maximum anteroposterior and superior-inferior diameters were measured in the sagittal plane.

FPSAD is calculated by a standardized process: First, serum free PSA concentrations are measured using an automated immunoassay that specifically identifies unbound PSA isoforms. FPSAD is derived by dividing the free PSA value (in ng/mL) by the prostate volume (in mL). This parameter integrates molecular (free PSA concentration) and anatomical (gland volume) determinants to provide greater diagnostic accuracy compared to PSA alone.PV = anteroposterior diameter (cm) x left-right diameter (cm) x superior-inferior diameter (cm) x 0.52; FPSAD = FPSA/PV.

Statistical Analysis

Descriptive statistics and univariate and multivariate logistic regression models were used to evaluate the diagnostic value of FPSAD, PI-RADS V2.1 scores, and their combined application in distinguishing BPH from PCa using SPSS 26.0. Scatter plots, receiver operating characteristic (ROC) curves, area under the curve (AUC) calculations, nomograms, and calibration curves were generated using R (4.3.2). A two-sided P-value of ≤ 0.01 was considered statistically significant.

Quality Control and Ethics

Standardized data collection involved dual independent entry verification. MRI interpretation consistency was maintained through regular consensus meetings, with 20% pathological case review. A professional biostatistician conducted all analyses with independent verification. The study adhered to STARD 2015 guidelines and Helsinki Declaration principles, including IRB approval, written informed consent, and data anonymization for research purposes only.

Results

This study included 137 patients, of whom 75 (54.74%) had PCa and 62 (45.26%) had BPH. The mean BMI was 22.06 kg/m2, the mean total prostate-specific antigen (tPSA) was 6.47 ng/mL, and the mean PV was 62.06 mL. Comorbidities were present in 57 patients (41.61%) with hypertension, 27 (19.71%) with coronary heart disease, 17 (12.41%) with diabetes, and 30 (23.62%) with urinary tract infection.Compared to BPH patients, PCa patients had significantly higher levels of FPSA, PI-RADS score, and FPSAD ($P \leq 0.01$). There were no significant differences between the two groups in terms of hypertension, coronary heart disease, diabetes, age, BMI, urinary tract infection before biopsy, PV, and tPSA (Table 1). The distribution of FPSAD and PI-RADS in the two groups is shown in Figure 1.

Through multivariate logistic regression analysis, we found that PI-RADS V2.1 scores and FPSAD values were associated with the differentiation of csPCa and ncsPCa. Both PI-RADS V2.1 scores and FPSAD were identified as independent risk factors for csPCa ($P \leq 0.01$). A higher PI-RADS V2.1 score was correlated with an increased likelihood

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Table 1 Comparison of Various Indicators Between the csPca Group and the ncsPca Group (No. = 137)

	csPca	ncsPca	*p*
No. of patients (No)	75	62	
Age (years)	71.92±7.35	70.01±7.53	0.16
BMI (kg/m2)	21.89±2.86	22.36±3.50	0.49
Hypertension (No)	28	29	0.26
Coronary Heart Disease (No)	14	13	0.74
Diabetes Mellitus (No)	10	7	0.72
Urinary Tract Infection (No)	18	12	0.51
TPSA(ng/mL)	6.52±1.67	6.41±1.80	0.69
FPSA(ng/mL)	1.25±0.26	1.09±0.14	0.00
PV(mL)	59.98±14.40	64.58±11.38	0.04
PI-RADS [$M(P_{25},P_{75})$]	4 (3, 4)	2 (2, 3)	0.00
FPSAD	0.022±0.007	0.017±0.004	0.00

of csPCa diagnosis (OR=2.41, 95% CI: 1.57–3.70, $P \leq 0.01$), while an elevated FPSAD value also increased the probability of csPCa diagnosis (OR=1.95, 95% CI: 1.22–2.22, $P \leq 0.01$) (Table 2).

The distribution of FPSAD and PI-RADS in the two groups is shown in Figure 1.The integrated FPSAD and PI-RADS v2.1 model showed superior diagnostic performance (Figure 2). At optimal thresholds (FPSAD>0.017 + PI-RADS≥4), the combination achieved significantly higher AUC (0.829 vs 0.773 for PI-RADS alone, P=0.018; vs 0.692 for FPSAD alone, *P*=0.008), with 91% sensitivity and 32% fewer unnecessary biopsies than PI-RADS≥3 criteria. In PI-RADS 3 subgroup (n=41), FPSAD correctly reclassified 13/18 (72.2%) indeterminate cases.

When the PI-RADS V2.1 score reached 3.5, the Youden index peaked at 0.474. Similarly, when the FPSAD value was 0.017, the highest Youden index was 0.325.

Further analysis confirmed that PI-RADS V2.1 scores and FPSAD values are independent predictors for diagnosing csPCa in patients with tPSA levels between 4–10 ng/mL (VIF=1.07). A nomogram was constructed incorporating five variables: FPSAD, age, fPSA, PV, and PI-RADS V2.1 scores to predict clinically significant prostate cancer (csPCa) in patients with tPSA levels of 4–10 ng/mL (Figure 3). Additionally, the calibration curve for the csPCa and ncsPCa groups closely aligned with the standard curve (Figure 4), indicating good agreement between the predicted and actual classifications.

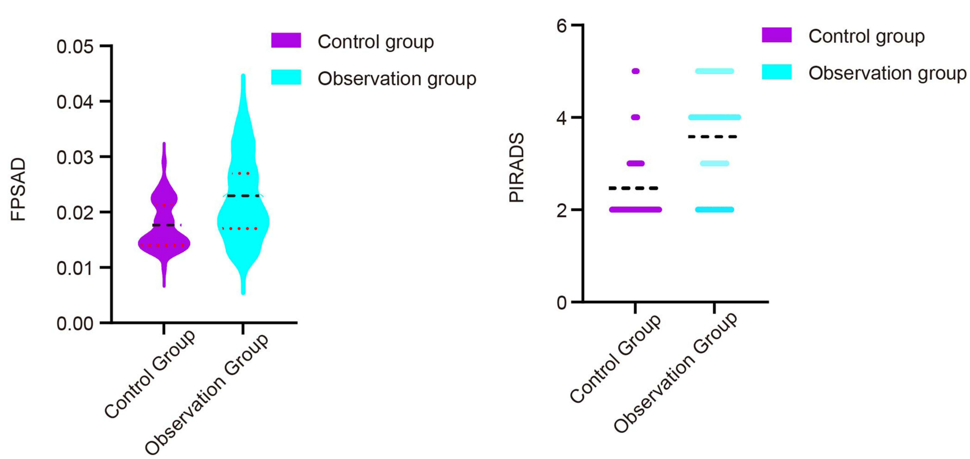

Figure 1 Interactive dot diagram with FPSAD, PI-RADS for csPca and ncsPca plotted on the y axis.

Table 2 The Odds Ratios of PI-RADS v2 Score and FPSAD

	p	OR	95% Confidence Interval	
			Lower Limit	Upper Limit
PI-RADS v2 score	0.00	2.45	1.57	3.70
FPSAD	0.00	1.95	1.22	2.22

Discussion

Prostate cancer is the second most common malignancy among men globally and the second leading cause of cancer-related death, particularly in developed countries.[1] The PSA gray zone, currently accepted clinically, is 4–10 ng/mL,[8] initially proposed based on studies of prostate cancer patients in Western countries. Studies have shown that the incidence of csPCa and ncsPCa is significantly lower in Asian populations compared to Western populations,[9] especially when PSA values are in the 4–10 ng/mL range, leading to less accurate predictions.

Despite the relatively high long-term survival rate for csPCa, late-stage csPCa remains largely incurable even after intensified multi-modal therapy. Therefore, early diagnosis is crucial for csPCa patients. To improve the sensitivity and specificity of csPCa detection in the PSA 4–10 ng/mL range, extensive research has been conducted on PSA, leading to the development of various related biomarkers, including fPSA, f/A-PSA, PI-RADS, p2PSA/fPSA, PV, PSAD, and FPSAD. Similar to PSAD, FPSAD represents the ratio of serum FPSA to PV (FPSA/PV).

Previously, cognition-fused targeted biopsy based on bpMRI has been widely adopted due to its relatively low equipment requirements, simple and rapid operation, low cost, and ease of clinical implementation. However, in 2019, the PI-RADS Steering Committee released PI-RADS version 2.1. Compared to PI-RADS V2, PI-RADS V2.1 introduced minor modifications to simplify MRI interpretation and improve inter-reader consistency.[10] Studies have shown that PI-RADS V2.1 scores ≥ 4 are optimal for diagnosing csPCa.[11] While standalone PI-RADS shows robust performance, combining it with biochemical markers has emerged as a strategy to address diagnostic uncertainties, especially in the tPSA gray zone.Recent studies have further validated the clinical utility of combining biomarkers with imaging for csPCa detection. Similar to our findings, Zhang et al demonstrated that integrating clinical parameters (PSA density, f/tPSA ratio) with biparametric MRI improved AUC to 0.76 in Asian patients with tPSA 4–10 ng/mL, reducing unnecessary

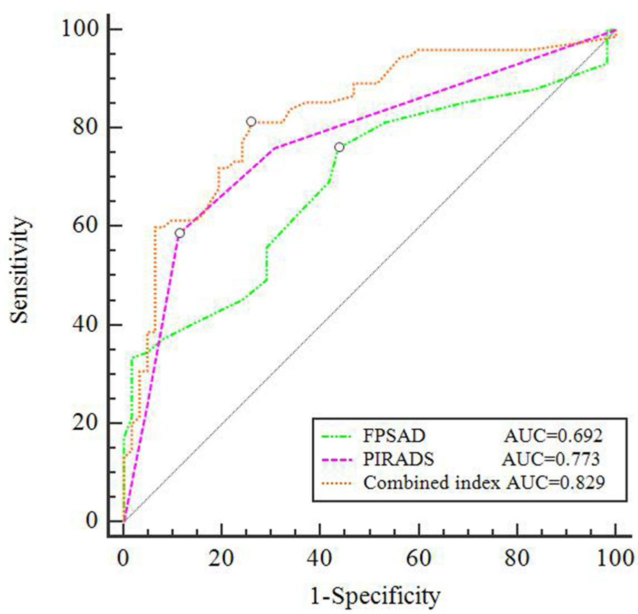

Figure 2 ROC curve plotting 1-speciffcity (x axis) against sensitivity (y axis).
Abbreviation: AUC, Area under the curve.

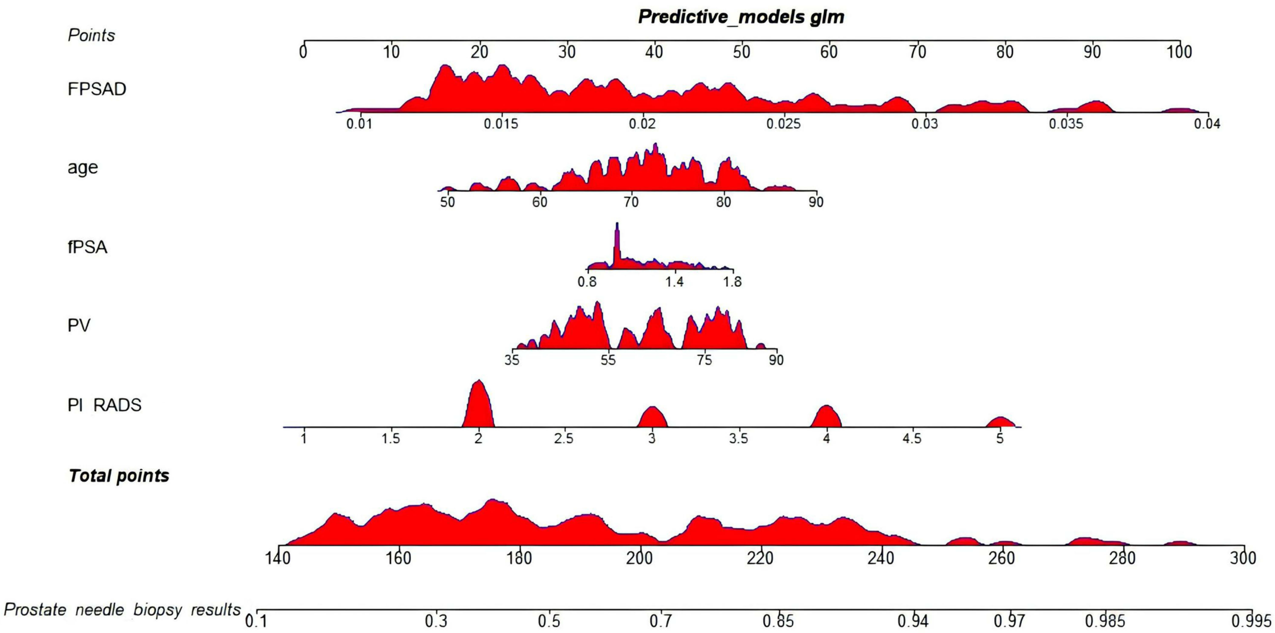

Figure 3 A nomogram for predicting prostate cancer.

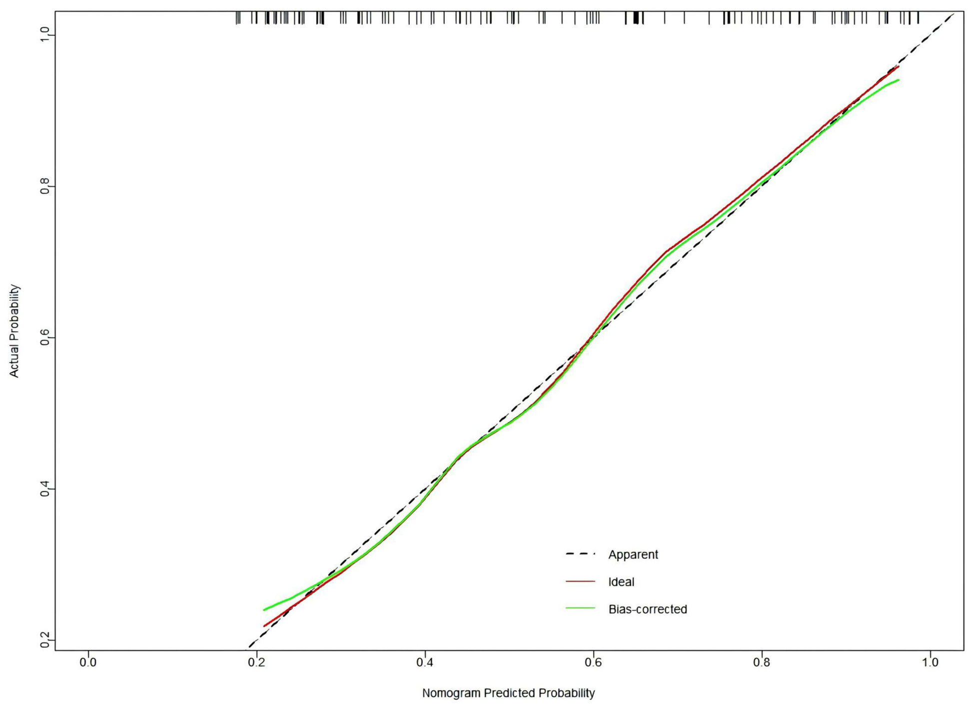

Figure 4 A calibration curve for predicting prostate cancer.

biopsies by 38.4% while maintaining 90% sensitivity for high-grade PCa. [12] However, our study specifically highlights the incremental value of FPSAD >0.017 in refining PI-RADS v2.1 classifications, particularly for indeterminate PI-RADS 3 lesions (72% reclassification accuracy). This aligns with emerging evidence that metabolite-based markers (eg, prostate fluid metabolic fingerprints with AUC=0.87.[13]

Previous studies have indicated that PI-RADS V2.1 (OR=3.57) is the strongest single-variable predictor for detecting csPCa in men with PSA in the gray zone and, when combined with PV, provides excellent predictive ability,[2] aligning with our findings. Several researchers have highlighted serum FPSAD as a promising new parameter for predicting csPCa.[14,15] Additionally, Ferro M et al found[16] that PHI and PHID, p2PSA/fPSA, and p2PSA/IPSAD demonstrated good diagnostic performance for csPCa after surgery in men with PSA levels between 2–10 ng/mL. This aligns with our findings: a higher FPSAD was associated with a greater likelihood of csPCa diagnosis (OR=1.95, 95% CI: 1.22–2.22, $P \leq 0.01$).

We also observed that the area under the receiver operating characteristic curve (AUC) for diagnosing csPCa using a combination of FPSAD and PI-RADS V2.1 score was 0.829, significantly higher than FPSAD alone (AUC: 0.692) and PI-RADS V2.1 score alone (AUC: 0.773), with statistically significant differences ($P<0.01$). In our study, the highest Youden index of 0.325 was achieved when the FPSAD value was 0.017.

While both parameters individually predict csPCa, our study reveals three clinically actionable advantages of their combination: First, it resolves the diagnostic ambiguity of PI-RADS 3 lesions (72% reclassification accuracy). Second, it provides population-specific thresholds (FPSAD>0.017 for Asians vs Western thresholds >0.06).[17] Third, it reduces biopsy rates without compromising detection (32% reduction, $P<0.05$). These findings address a critical gap in tPSA "gray zone" management, particularly for Asian populations where MRI access may be limited.

In our study, although we analyzed various variables such as diabetes and age, these did not show statistically significant differences. The lack of significance for these variables may be attributed to factors such as sample size, individual patient differences, and the variety of biomarkers and imaging parameters used. However, studies have shown that factors such as diabetes and age may have a potential impact on the diagnosis and prognosis of prostate cancer.[18–20]The effect of these variables may be influenced by factors such as sample size or other clinical parameters, so it is recommended that future research further explore their role.

Furthermore, while the FPSAD and PI-RADS V2.1 scoring method used in this study shows excellent diagnostic performance, careful consideration of its cost-effectiveness is required for its widespread adoption. Although the PI-RADS V2.1 scoring system is relatively straightforward and significantly enhances diagnostic accuracy, it still requires high-quality imaging, which may demand specialized equipment and expertise. Thus, in resource-limited settings, the widespread application of this method could face certain challenges. In terms of cost-effectiveness, we believe that combining FPSAD with PI-RADS V2.1 provides superior diagnostic value compared to traditional PSA screening, particularly in patients within the PSA gray zone. Although initial costs may be higher, this approach could reduce unnecessary biopsies and diagnostic errors in the long run, potentially saving healthcare costs. Future research should therefore assess the economic feasibility of this combined diagnostic strategy and evaluate its adaptability and practicality across different healthcare settings.

Conclusion

In patients with tPSA levels of 4–10 ng/mL, the combination of FPSAD and PI-RADS v2.1 significantly improves the diagnostic accuracy for csPCa, offering enhanced clinical utility over either parameter alone.

Data Sharing Statement

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Disclosure

The authors report no conflicts of interest in this work.

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