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ORIGINAL RESEARCH

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Detection of prostate cancer in the PSA gray zone using prostate-specific antigen mass ratio combined with PI-RADS score

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Abstract

Background: The study aimed to assess the diagnostic performance of prostate-specific antigen mass ratio (PSAMR) in combination with the Prostate Imaging Reporting and Data System (PI-RADS) score for detecting prostate cancer (PCa) in patients presenting with mildly elevated prostate-specific antigen (PSA) levels (4–10 ng/mL). **Methods**: A retrospective analysis was conducted involving 208 patients with PSA levels between 4 and 10 ng/mL who underwent multiparametric magnetic resonance imaging (mpMRI) and transrectal ultrasound-guided transperineal prostate biopsy. PSA-derived parameters and PI-RADS scores were incorporated into logistic regression models to predict the presence of PCa. Diagnostic accuracy was assessed using receiver operating characteristic (ROC) curve analysis. Additionally, Spearman's correlation analysis was performed to determine the relationship between each parameter and the prediction model with disease severity ratings. **Results**: Of the 208 patients, PCa was confirmed by biopsy in 62 cases. The combination of PSAMR and PI-RADS score yielded an area under the ROC curve (AUC) of 0.874 (95% confidence interval (CI): 0.821–0.916, $p < 0.001$), which was higher than the AUCs for PSAMR or PI-RADS score alone, indicating superior diagnostic accuracy. Correlation analysis also revealed that the combined model had the strongest association with disease severity. The order of correlation coefficients was as follows: PSAMR combined with PI-RADS score (Model A) > Prostate-specific antigen density (PSAD) combined with PI-RADS score (Model B) > PI-RADS score alone > PSAMR alone > PSAD alone. **Conclusions**: The combination of PSAMR and PI-RADS score significantly enhances the accuracy of PCa detection in patients with PSA levels of 4–10 ng/mL. This approach may contribute to more effective screening strategies while minimizing unnecessary biopsies. Furthermore, given their positive correlation with disease severity, PSAMR and PI-RADS scores together may also assist in predicting PCa progression risk.

Keywords

Prostate cancer; Prostate specific antigen; Magnetic resonance imaging; PI-RADS; PSAMR

1. Introduction

Prostate cancer (PCa) is the second most common malignancy among men worldwide [1]. In China, the incidence of PCa has steadily increased in parallel with the aging population [2]. The prostate-specific antigen (PSA) test, which is widely used for PCa screening, has notably improved early detection rates and contributed to a decline in PCa-related mortality [3, 4]. However, PSA lacks specificity, particularly in patients with serum PSA levels between 4 and 10 ng/mL. This range, often referred to as the "PSA gray area", is problematic because less than 30% of patients within this interval are ultimately diagnosed with PCa [5, 6]. Consequently, many patients often undergo unnecessary biopsies, with approximately two-thirds receiving negative results [7]. Thus, to optimize the utility of PSA testing, it is necessary to identify and adjust for factors influencing PSA levels.

PSA levels may be affected by several non-cancerous factors, including age, prostate volume (PV), body mass index (BMI), and insulin resistance. Choi *et al.* [8] addressed this issue by proposing the PSA mass ratio (PSAMR), a parameter designed to mitigate the confounding effects of such factors. Their findings indicated that, among men aged 56 to 80 years, the demographic in which PCa predominantly occurs, PSAMR remains relatively stable despite variations in BMI, plasma volume and PV, contrasting with younger men aged 30 to 55 years, whose PSAMR fluctuates more substantially. This discrepancy may be attributed to age-dependent changes in

prostate physiology, as PSA production increases progressively with prostate enlargement over time, as reported by Park JH *et al*. [9]. Although these findings suggest that PSAMR may improve PCa detection compared to PSA levels alone, further studies are required to validate its diagnostic value.

While PSAMR provides important biochemical information, anatomical and morphological assessment is essential to accurately localize prostate lesions. Multiparametric magnetic resonance imaging (mpMRI) has become a valuable adjunct to PSA-based screening in this regard. In 2012, the European Society of Urogenital Radiology introduced the Prostate Imaging Reporting and Data System (PI-RADS) to standardize mpMRI interpretation [10]. The second iteration, PI-RADS version 2 (v2), published in 2019 [11], is now widely adopted for PCa diagnosis. PI-RADS v2 plays a key role in tumor localization [12], risk classification [13], and guiding biopsy decisions [14]. Furthermore, the PI-RADS score has been validated as a reliable diagnostic indicator [15], with the second version demonstrating improved sensitivity for clinically significant PCa compared to the original version [16]. One limitation of the PI-RADS system is its reliance on subjective interpretation, making its diagnostic performance highly dependent on the radiologist's experience. Additionally, the numerical scores assigned by PI-RADS do not always translate into clear clinical decision-making pathways. For instance, a PI-RADS v2 score of 3 out of 5 represents an intermediate level of suspicion, often resulting in diagnostic uncertainty and unnecessary puncture biopsies when PI-RADS is used in isolation without supplementary diagnostic tools.

Given the limitations of relying solely on either biochemical markers or imaging scores, combining PSAMR with PI-RADS v2 may offer superior diagnostic accuracy. Therefore, the present study investigated the value of integrating PSAMR and PI-RADS v2 in detecting PCa among patients with PSA levels of 4–10 ng/mL. This subgroup, which falls within the PSA gray area, represents a clinically significant cohort in which improved diagnostic precision is urgently needed. Additionally, we sought to compare the performance of this combined approach with other predictors, including PSA density (PSAD) alone and PSAD combined with PI-RADS v2, to comprehensively evaluate the most effective model for PCa detection.

2. Materials and methods

2.1 Study population

This study was approved by the Ethics Committee of Taizhou Hospital of Zhejiang Province, affiliated with Wenzhou Medical University (approval number: K20221103). The requirement for informed consent was waived due to the retrospective nature of the analysis. Clinical and examination data were retrospectively reviewed for 606 patients who underwent transrectal ultrasound (TRUS)-guided transperineal prostate biopsy following mpMRI between March 2020 and January 2022. Among them, patients with pre-biopsy PSA levels between 4 and 10 ng/mL were selected, and the age range was limited to 56–80 years. This age criterion was established based on previous research suggesting that PSAMR is more stable within this group [8]. Patients were excluded if they met any of the following criteria: (a) history of prostate biopsy or PCa treatment; (b) biopsy performed more than two months after mpMRI; (c) blurred mpMRI images or non-compliance with PI-RADS version 2 (v2) technical requirements; or (d) incomplete clinical data. Based on these criteria, 208 patients were included for analysis, comprising 62 patients with biopsy-confirmed PCa and 146 patients without PCa. The patient selection process is summarized in Fig. 1.

2.2 Calculation of related parameters

Height and weight were routinely recorded before performing biopsy. PV was calculated using mpMRI images. Axial T2-weighted imaging (T2WI) was used to measure the maximum transverse and anteroposterior diameters of the prostate, while sagittal T2WI was used to determine the maximum longitudinal diameter. PV (mL) was then calculated using the following formula: PV (mL) = maximum transverse diameter (cm) $\times$ maximum anteroposterior diameter (cm) $\times$ maximum longitudinal diameter (cm) $\times$ 0.52. Body surface area (BSA) was calculated based on the Stevenson formula: BSA (m^2) = 0.0061 $\times$ height (cm) + 0.0128 $\times$ weight (kg) $-$ 0.1529. Plasma volume was calculated using the following formula: plasma volume (L) = BSA (m^2) $\times$ 1.670. PSAMR was calculated according to the following formula: PSAMR (μg/mL) = PSA (ng/mL) $\times$ plasma volume (L)/PV (mL) [8]. Finally, PSAD (ng/mL) was calculated as follows: PSA (ng/mL)/PV (mL).

2.3 MRI acquisition and image analysis

MRI examinations were performed using a 3.0-T system equipped with an 8-channel body phased-array coil (Discovery MR750 3.0T, GE Healthcare, Florence, SC, USA). The scanning protocol followed PI-RADS v2 guidelines. Sequences included axial, coronal and sagittal T2WI, axial diffusion-weighted imaging (DWI), and dynamic contrast-enhanced imaging. The scanning area covered the pelvis, prostate, and seminal vesicles.

The lesions were scored in accordance with PI-RADS v2 criteria by two radiologists who were blinded to the clinical and biopsy results. If discrepancies in the scoring were observed, the radiologists reached a consensus through discussion to establish the final PI-RADS score.

2.4 Prostate biopsy and pathology

All patients underwent TRUS-guided transperineal 12-core systematic biopsy. In addition, 2–3 targeted cores were obtained from suspicious lesions identified on MRI. These procedures were performed by a urologist with more than three years of experience in prostate biopsy. Pathological diagnosis was conducted by a senior pathologist with expertise in prostate pathology. Tissue specimens were evaluated using routine histopathology and immunohistochemistry. The pathological results were classified according to the 2014 International Society of Urological Pathology (ISUP) grading system [17]. Specifically, Gleason score $\leq$6 was defined as ISUP grade 1, Gleason 3 + 4 as grade 2, Gleason 4 + 3 as grade 3, Gleason 4 + 4, 3 + 5 or 5 + 3 as grade 4, and Gleason 9–10 as grade 5.

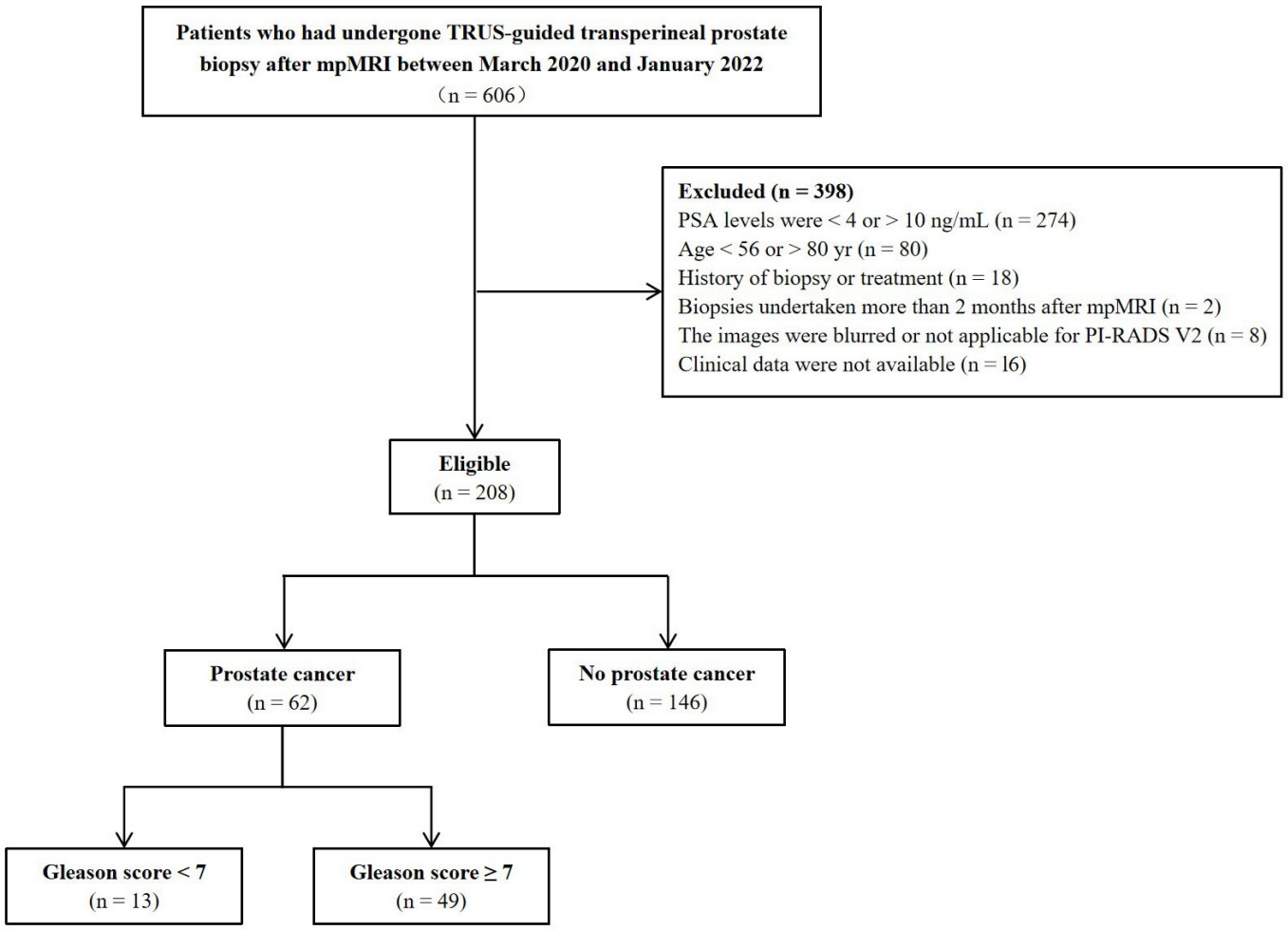

FIGURE 1. Flowchart of the study selection process. TRUS: transrectal ultrasound; PSA: prostate-specific antigen; PI-RADS v2: Prostate Imaging Reporting and Data System version 2; mpMRI: multiparametric magnetic resonance imaging.

2.5 Statistical analysis

Statistical analyses were conducted using SPSS version 25.0 (IBM Corp., Armonk, NY, USA) and MedCalc version 20.022 (MedCalc Software Ltd, Ostend, Belgium). Continuous variables were expressed as mean ± standard deviation if normally distributed or as median (interquartile range) if not. Categorical variables were reported as counts (percentages). Normality was assessed using the Kolmogorov-Smirnov test. Comparisons of normally distributed continuous variables between PCa and non-PCa groups were performed using the *t*-test, while the Mann-Whitney U test was used for non-normally distributed data. The Chi-square test was used to compare categorical variables. To ensure normality, %fPSA, PSAD and PSAMR were logarithmically transformed before analysis. Univariable and multivariable logistic regression analyses were conducted to evaluate the diagnostic value of these variables in predicting PCa. Model performance was assessed using receiver operating characteristic (ROC) curve analysis and expressed as the area under the curve (AUC). Comparisons between AUCs were performed using the *Z*-test. The optimal cut-off points for prediction models were determined using the maximum Youden index to calculate sensitivity and specificity. Furthermore, Spearman's correlation analysis was used to assess the relationship between ISUP grade and the AUC values of each model. A two-tailed p-value < 0.05 was considered statistically significant.

3. Results

Patient characteristics are summarized in Table 1. Among the 208 patients included in the study, 62 (29.8%) were diagnosed with PCa through biopsy.

The Kolmogorov-Smirnov test for the overall sample indicated that BMI followed a normal distribution ($p = 0.20$), whereas age ($p = 0.002$), PV ($p < 0.001$), PSA level ($p < 0.001$), percent free PSA (%fPSA) ($p < 0.001$), PSAD ($p < 0.001$), and PSAMR ($p < 0.001$) did not. No significant differences were observed between the PCa and non-PCa groups in terms of PSA levels and BMI. However, significant differences were found in age, PV, %fPSA, PSAD and PSAMR. Specifically, patients with PCa were significantly older, had smaller PVs, lower %fPSA, and higher levels of PSAD and PSAMR. Additionally, the distribution of patients across PI-RADS v2 categories (≥4, 3 and ≤2) differed significantly between the two groups ($p < 0.001$). Univariable logistic regression analysis further demonstrated that increases in PSAMR, PSAD and PI-RADS v2 score, along with a decrease in %fPSA, were associated with an increased probability of PCa detection (Table 2).

TABLE 1. Patients' characteristics.

Variables	Overall (n = 208)	PCa (n = 62)	Non-PCa (n = 146)	*p* value
Age (yr)	67.5 (63.0–73.0)	70.0 (63.8–73.3)	67.0 (63.0–72.0)	0.040
BMI (kg/m^2)	23.97 ± 2.46	24.47 ± 2.35	23.76 ± 2.49	0.057
PSA (ng/mL)	7.05 (5.21–8.66)	6.98 (5.19–8.57)	7.10 (5.21–8.70)	0.935
PV (mL)	42.18 (30.32–58.32)	29.56 (24.45–40.77)	47.94 (36.87–61.73)	<0.001
%fPSA (%)	0.19 (0.13–0.25)	0.16 (0.10–0.21)	0.20 (0.14–0.26)	0.005
PSAD (ng/mL)	0.16 (0.11–0.22)	0.20 (0.16–0.31)	0.14 (0.11–0.19)	<0.001
PSAMR (μg/mL)	0.45 (0.32–0.60)	0.58 (0.50–0.91)	0.39 (0.31–0.55)	<0.001
PI-RADS (%)				
1–2	67 (32.2)	7 (10.4)	60 (89.6)	
3	83 (39.9)	11 (13.3)	72 (86.7)	<0.001
4–5	58 (27.9)	44 (75.9)	14 (24.1)	
Gleason score (%)				
Less than 7	NA	13 (21.0)	NA	NA
7 or Greater	NA	49 (79.0)	NA	NA

PCa: prostate cancer; BMI: body mass index; PSA: prostate-specific antigen; PV: prostate volume; %fPSA: percent of free prostate-specific antigen; PSAD: prostate-specific antigen density; PSAMR: prostate-specific antigen mass ratio; PI-RADS: Prostate Imaging Reporting and Data System version 2; NA: Not Applicable.

TABLE 2. Logistic regression analyses of predictors of prostate cancer.

Variables	OR	95% CI	*p* value
Univariable logistic regression model			
%fPSA*	0.472	0.269–0.829	0.009
PSAD*	5.476	2.678–11.199	<0.001
PSAMR*	6.388	3.068–13.301	<0.001
PI-RADS	6.548	3.769–11.375	<0.001
Multivariable logistic regression model			
Model A			
PSAMR*	4.643	1.997–10.794	<0.001
PI-RADS	5.917	3.348–10.458	<0.001
Model B			
PSAD*	3.992	1.758–9.067	0.001
PI-RADS	5.938	3.376–10.443	<0.001
Model C			
%fPSA*	0.530	0.267–1.052	0.070
PI-RADS	6.503	3.715–11.385	<0.001

**Parameters were logarithmically transformed.*
OR: odds ratio; CI: confidence interval; %fPSA: percent of free prostate-specific antigen; PSAD: prostate-specific antigen density; PSAMR: prostate-specific antigen mass ratio; PI-RADS: Prostate Imaging Reporting and Data System version 2.

Among all PSA-related parameters, PSAMR demonstrated favorable diagnostic performance in ROC analysis, yielding an optimal threshold of 0.48, with a sensitivity of 77.4% and a specificity of 70.5%. The diagnostic ability of PSAMR alone was significantly superior to that of %fPSA (AUC = 0.738 *vs.* AUC = 0.624, $p = 0.006$). However, there was no significant difference between the diagnostic performance of PSAMR and PSAD, despite a marginally higher AUC for PSAMR (AUC = 0.738 *vs.* AUC = 0.730, $p = 0.231$). Additionally, the PI-RADS v2 score demonstrated strong diagnostic value, with an AUC of 0.824 (95% CI: 0.765–0.873, $p < 0.001$). When a threshold score of ≥4 was applied, the PI-RADS v2 score achieved a sensitivity of 71.0% and specificity of 90.4% for diagnosing PCa (Table 3 and Fig. 2).

PSAMR, PSAD and %fPSA were each combined with the PI-RADS v2 score to construct multivariable logistic regres-

TABLE 3. ROC curve analysis for predicting the probability of prostate cancer at biopsy.

Variable	AUC	95% CI	Threshold*	Sensitivity	Specificity	*p* value
Univariable logistic regression model						
%fPSA	0.624	0.554–0.690	≤0.21	77.40%	45.90%	0.004
PSAD	0.730	0.664–0.789	>0.15	79.00%	62.30%	<0.001
PSAMR	0.738	0.673–0.796	>0.48	77.40%	70.50%	<0.001
PI-RADS	0.824	0.765–0.873	≥4.00	71.00%	90.40%	<0.001
Multivariable logistic regression model						
PSAMR + PI-RADS (Model A)	0.874	0.821–0.916	>0.26	80.60%	82.20%	<0.001
PSAD + PI-RADS (Model B)	0.865	0.810–0.908	>0.35	74.20%	87.70%	<0.001

**Threshold was estimated by using the Youden index maximum.*
ROC: receiver operating characteristics; AUC: area under the curve; CI: confidence interval; %fPSA: percent of free prostate-specific antigen; PSAD: prostate-specific antigen density; PSAMR: prostate-specific antigen mass ratio; PI-RADS: Prostate Imaging Reporting and Data System version 2.

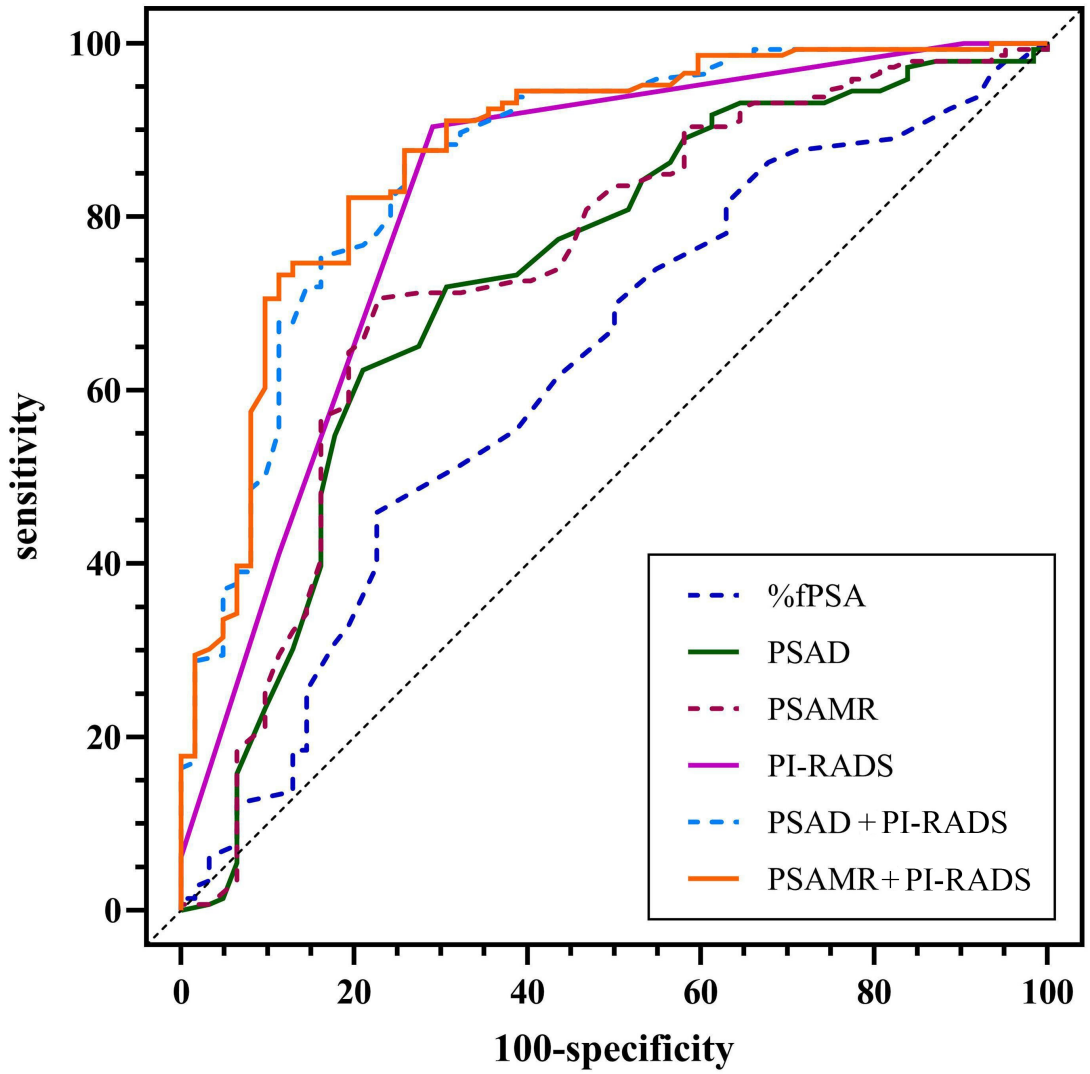

FIGURE 2. Receiver operating characteristic curves showing the accuracies of single indicator and multivariable models in predicting prostate cancer. %fPSA: percent of free prostate-specific antigen; PSAD: prostate-specific antigen density; PSAMR: prostate-specific antigen mass ratio; PI-RADS: Prostate Imaging Reporting and Data System version 2.

sion models A, B and C, respectively. In these models, both PSAMR ($p < 0.001$) and PSAD ($p = 0.001$) were identified as robust, independent predictors of PCa. In contrast, %fPSA did not retain predictive significance ($p = 0.070$), and accordingly, Model C was excluded from further analysis (Table 2). Notably, combining PSAMR with the PI-RADS v2 score (Model A) significantly improved diagnostic performance compared with either variable alone (Model A AUC = 0.874 *vs.* PSAMR AUC = 0.738, $p < 0.001$; Model A AUC = 0.874 *vs.* PI-RADS v2 AUC = 0.824, $p = 0.007$). The optimal threshold for Model A was 0.26, yielding a sensitivity of 80.6% and a specificity of 82.2%. As shown in Table 3, the AUC of Model A was also significantly higher than that of Model B (AUC = 0.874 *vs.* 0.865, $p = 0.049$), indicating superior performance in diagnosing PCa.

Among the 62 patients diagnosed with PCa, ISUP grades were distributed as follows: grade 1 (n = 13), grade 2 (n = 21), grade 3 (n = 14), grade 4 (n = 4), and grade 5 (n = 10). The Kruskal-Wallis H test revealed significant differences in PSAMR ($p = 0.023$), PSAD ($p = 0.046$), PI-RADS v2 score ($p = 0.008$), Model A ($p = 0.001$), and Model B ($p = 0.001$) across ISUP categories. In contrast, PSA levels ($p = 0.689$) and %fPSA ($p = 0.208$) did not show significant differences. Furthermore, Spearman's correlation analysis demonstrated positive correlations between ISUP grade and PSAMR ($r = 0.380$), PSAD ($r = 0.317$), and PI-RADS v2 score ($r = 0.428$). In addition, stronger correlations were observed for the multivariable models, with Model A and Model B yielding coefficients of 0.506 and 0.492, respectively (Fig. 3).

4. Discussion

4.1 Clinical implications

Since its introduction in 1979, PSA has been the most widely used tumor marker for PCa, with extensive applications in diagnosis, treatment planning and prognosis assessment. However, the limited specificity of PSA as a screening tool can lead to overdiagnosis and overtreatment [18]. This limitation is particularly evident in men with mildly elevated PSA levels, for whom there is a pressing need for non-invasive diagnostic strategies with improved predictive accuracy. To address this, several PSA-derived parameters, such as %fPSA and PSAD, have been adopted in clinical settings to enhance diagnostic precision. While these parameters have modestly improved the sensitivity and specificity of PSA, the PSAMR has emerged as a more promising alternative, as it accounts for the influence of confounding variables that affect PSA levels [19].

Our findings demonstrate that PSAMR offers significantly better predictive value for PCa among individuals with PSA levels between 4 and 10 ng/mL compared with PSA alone, corroborating the results reported by Hong *et al.* [20]. Building on these findings, we further compared the diagnostic performance of PSAMR to that of other PSA-related parameters. The AUC for PSAMR was 0.738, which was significantly higher than that of %fPSA, though not statistically different from that of PSAD. Notably, PSAMR achieved a specificity of 70.5% at the optimal diagnostic threshold, which exceeded the corresponding values for both PSAD and %fPSA. This improved specificity is clinically meaningful, as it may contribute to reducing unnecessary prostate biopsies.

Although PSAMR adjusts for both PV and plasma volume, its diagnostic capacity remains limited when used alone. To further enhance predictive performance, we evaluated the combined use of PSAMR and the PI-RADS v2 score. Our results confirmed a high diagnostic value of the PI-RADS v2 score in patients within the PSA gray area, with an AUC of 0.824 and high specificity. These findings are consistent with those of a meta-analysis by Li Zhang *et al.* [21], which reported a sensitivity and specificity of 0.85 and 0.71, respectively, for PI-RADS v2 in detecting PCa. Similar results were reported by Woo *et al.* [22]. In a cohort of 235 patients with PSA levels in the gray area, the PI-RADS v2 score (threshold $\geq$4) yielded an AUC of 0.853, with sensitivity, specificity, positive predictive value, and negative predictive value of 60.0%, 89.7%, 50.0% and 92.9%, respectively [23]. Although the AUC in our study was slightly lower, this may be attributed to differences in mpMRI technical parameters and the level of radiologist experience.

We also analyzed the relationship between prediction models and clinical outcomes using the ISUP grading system. Both PSAMR and PI-RADS v2 scores were significantly associated with ISUP grades, and their combination demonstrated an even stronger correlation with PCa severity. These findings suggest that integrating PSAMR with PI-RADS v2 could enhance risk stratification, support prognosis estimation, and inform individualized treatment decisions. Although emerging markers such as PCa antigen 3 (PCA3) [24] and the Prostate Health Index [25] have shown potential for improving the detection of clinically significant PCa in patients with mildly elevated PSA levels, the high cost of developing and validating these novel biomarkers currently limits their widespread clinical application. Therefore, PSA and its derived parameters, including PSAMR, remain essential and practical tools for PCa screening.

4.2 Clinical practice

In this study, the combination of PSAMR and PI-RADS v2 score demonstrated significantly higher diagnostic performance than either variable alone. This combined model significantly improved the detection rate of PCa among patients with PSA levels in the 4–10 ng/mL range. By applying this predictive model, clinicians can estimate the likelihood of PCa before proceeding with prostate biopsy, thereby facilitating more informed decision-making. Furthermore, Model A, which incorporated both PSAMR and PI-RADS v2 score, achieved superior sensitivity and specificity compared with models that included only one of the parameters. Given that PSAMR is derived from PSA, its predictive accuracy was also compared with that of PSAD to assess its added value as a diagnostic tool.

4.3 Limitations

Several limitations of this study should be acknowledged. First, the study was conducted at a single center using a retrospective design, which may have introduced selection bias. Second, no universally accepted diagnostic threshold for

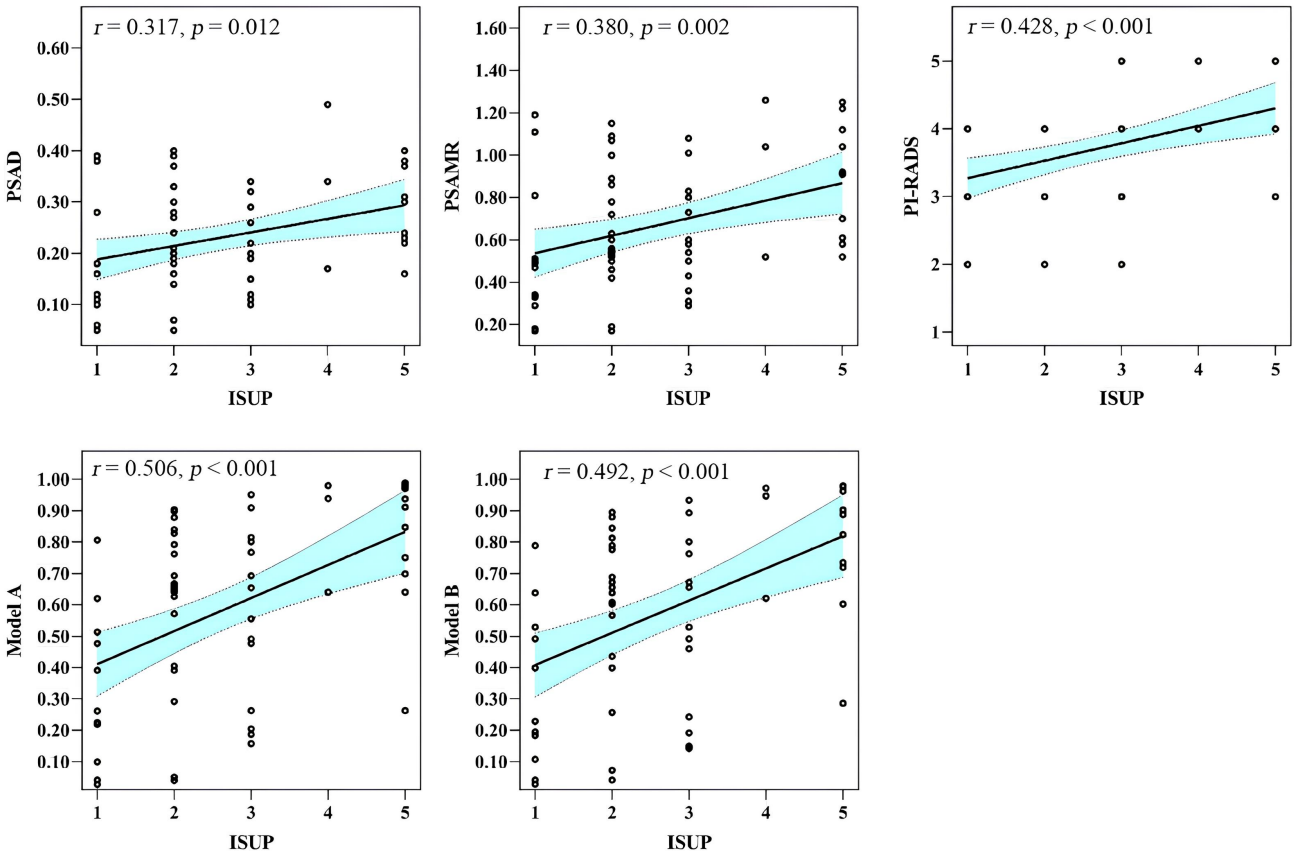

FIGURE 3. Correlations between PSAD, PSAMR, PI-RADS, model A, model B and ISUP grading system. PSAD: prostate-specific antigen density; PSAMR: prostate-specific antigen mass ratio; PI-RADS: Prostate Imaging Reporting and Data System version 2; ISUP: International Society of Urological Pathology Prostate Cancer Grading Guidelines.

PSAMR currently exists, and assessing its diagnostic performance based solely on sensitivity and specificity at a single ROC curve cut-off may be insufficient. Further prospective studies are needed to validate PSAMR and determine an optimal threshold. Third, our study focused only on subjects in the gray zone of PSA and did not consider that prostate cancer can also develop in subjects with PSA values less than 4 ng/mL. In our study, there were only four patients with PSA values less than 4 ng/mL. It is not only very difficult to further explore the predictive rate of prostate cancer in the normal population using PSAMR, but also to indicate whether PSAMR could be extended to all subjects as a complement of screening. In the future, we can establish a database, including research data on outpatients with PSA values less than 4 ng/mL. Fourth, due to the limited sample size, only a restricted number of variables could be included in the multivariable prediction models. Finally, there is currently no database capturing patients who underwent PSA testing but did not proceed to biopsy. Consequently, it is not possible to determine PSAMR values for this population or to track the proportion of these individuals subsequently diagnosed with PCa during follow-up. Future studies should aim to explore whether PSAMR can be used to identify patients who may safely avoid biopsy or to guide the extension of follow-up intervals.

5. Conclusions

In summary, the combination of PSAMR and PI-RADS v2 score enhances the diagnostic accuracy for detecting PCa in men with PSA levels between 4 and 10 ng/mL. This combined approach improves both sensitivity and specificity, thereby supporting earlier identification of PCa and helping to avoid unnecessary biopsies. Additionally, both PSAMR and PI-RADS v2 scores were positively correlated with ISUP grading, indicating their potential utility in evaluating tumor aggressiveness and informing prognostic assessments. As a relatively new PSA-derived parameter, PSAMR holds promise for clinical application; however, further research is required to establish standardized diagnostic thresholds and to validate its predictive value in broader populations.

AVAILABILITY OF DATA AND MATERIALS

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

WLL, ZQW and WHZ—performed the study and drafted the manuscript. GBZ, MMP and ZCS—designed the study and performed data synthesis. THT—conceived the study and

participated in its design and coordination. All authors have read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The studies were exempted from written informed consent and was approved by the Ethics Committee of Taizhou Hospital of Zhejiang Province (approval number: K20221103) in China. All methods were performed following the relevant guidelines and regulations stipulated in the Declaration of Helsinki.

ACKNOWLEDGMENT

Not applicable.

FUNDING

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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