

The Value of Prostate-Specific Antigen Isoform 2 and Its Derived Parameters in Predicting Clinically Significant Prostate Cancer and Gleason Classification in the Chinese population

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Abstract

Objective: Prostate-specific antigen (PSA) screening has improved the early detection of Prostate cancer (PCa), but it has also led to more identification of clinically insignificant PCa (CISPCa, Gleason score 6), causing unnecessary biopsies and overtreatment. Lately, prostate-specific antigen isoform 2 (p2PSA) and its derivatives (such as %p2PSA, Prostate Health Index [PHI]) have become valuable tools, showing potential in diagnosing, grading, and predicting the prognosis of PCa. Notably, while there has been substantial research on these aspects abroad, relatively less research has been conducted in China. This study intends to assess the predictive value of p2PSA and related markers for Clinically significant PCa (CSPCa, Gleason score ≥ 7) and Gleason score grouping in Chinese patients with total PSA (tPSA) levels ≤ 20 ng/mL.

Methods: A retrospective analysis was conducted on 508 patients with a total tPSA level ≤ 20 ng/mL who underwent prostate biopsies between June 2021 and November 2024. Preoperative laboratory measurements comprised tPSA, free PSA (fPSA), and p2PSA. Derived parameters, namely the percentage of p2PSA (%p2PSA) and the Prostate Health Index (PHI), were calculated using established formulas. Based on the biopsy results, patients were categorized into two distinct groups: benign prostatic hyperplasia (BPH)/ CISPCa and CSPCa. Statistical analyses were performed using a comprehensive approach. T-tests and Mann-Whitney U tests were employed for group comparisons. Logistic regression analysis was conducted to identify independent risk factors and construct a predictive model. Additionally, receiver operating characteristic (ROC) curve analysis was carried out to evaluate the diagnostic performance of the biomarkers. A focused subgroup analysis was conducted on patients in the PSA gray zone (tPSA 4 ng/mL $\sim$ 10 ng/mL). The relationship between biomarkers and Gleason score progression (categorized as 6, 7, or ≥ 8) was assessed using Spearman's rank correlation coefficient. All statistical analyses were performed with SPSS 27.0, with two-tailed P-values < 0.05 considered statistically significant.

Results: Among the 508 patients, age, tPSA, prostate volume (PV), p2PSA, %p2PSA, PHI, and PI-RADS scores were significant predictors of CSPCa ($P < 0.05$). Multivariate analysis identified age, tPSA, PV, PI-RADS score, and PHI as independent risk factors. The composite predictive model was formulated as:

$\text{Logit}(P) = -8.652 + 0.045 \times \text{age} + 0.081 \times \text{tPSA} - 0.025 \times \text{PV} + 1.063 \times \text{PI-RADS score} + 0.028 \times \text{PHI}$. The area under the curve (AUC) values for age, tPSA, PV, p2PSA, PI-RADS scores, %p2PSA, PHI, and the composite model were 0.57, 0.68, 0.73, 0.78, 0.82, 0.85, 0.88, and 0.92, respectively. For patients in the PSA gray zone, tPSA, PV, p2PSA, %p2PSA, PHI, and PI-RADS scores remained diagnostically useful ($P < 0.05$), with PV, PI-RADS score, and PHI as independent predictors (AUCs: 0.60–0.90). Spearman analysis revealed positive correlations between Gleason score groups and p2PSA ($r_s=0.206$, $P=0.030$), %p2PSA ($r_s=0.277$, $P=0.002$), PHI ($r_s=0.303$, $P<0.001$), and PI-RADS scores ($r_s=0.203$, $P=0.022$).

Conclusions: Compared with traditional indicators (tPSA, fPSA), metrics derived from p2PSA—including %p2PSA and PHI—as well as combined prediction models, significantly enhance the discriminatory

ability for CSPCa when tPSA levels are ≤ 20 ng/mL or fall within the PSA gray zone. Additionally, these p2PSA-based biomarkers show positive correlations with Gleason score stratification.

1. Introduction

Prostate cancer (PCa) ranks among the most prevalent malignancies in men worldwide. According to Global Cancer Statistics (GLOBOCAN), PCa is the second most frequently diagnosed cancer in men (after lung cancer) and the second leading cause of cancer-related mortality in this population [1]. The Gleason score remains the gold standard for pathological grading of PCa, with significant prognostic implications tied to its stratification. Clinically significant PCa (CSPCa), defined by a Gleason score ≥ 7 , is characterized by aggressive tumor behavior, including rapid growth, high metastatic potential, and poorer outcomes. These cases typically necessitate immediate intervention—such as surgery or radiation—to mitigate disease progression and improve survival. In contrast, clinically insignificant PCa (CISPCa; Gleason score 6) exhibits indolent growth, low malignant potential, and minimal metastatic risk. For such patients, active surveillance or watchful waiting is often preferred, as overtreatment may lead to unnecessary complications (e.g., urinary incontinence, sexual dysfunction) without conferring survival benefits, thereby imposing undue physical and psychological burdens. Prostate-specific antigen (PSA) screening has markedly improved early PCa detection [2]. However, its limited specificity has also increased the diagnosis of CISPCa, resulting in unnecessary biopsies and overtreatment [3]. Recent advances highlight the potential of prostate-specific antigen isoform 2 (p2PSA) and its derived indices—such as the percentage of p2PSA (%p2PSA) and the Prostate Health Index (PHI)—to enhance diagnostic accuracy, risk stratification, and prognostic assessment in PCa [4–9]. Despite their proven utility in international research, these biomarkers have not yet been widely integrated into routine clinical practice in China. This study aims to evaluate the predictive utility of p2PSA and its derivatives for CSPCa and Gleason score stratification in Chinese patients with total PSA (tPSA) levels ≤ 20 ng/mL. By refining discrimination between aggressive and indolent disease, these biomarkers could guide more personalized clinical decision-making, reducing unnecessary interventions while ensuring timely treatment for high-risk cases.

2. Materials and Methods

2.1 Clinical Data

This multicenter retrospective cohort study included patients with tPSA levels ≤ 20 ng/mL who underwent prostate biopsy at Linyi People's Hospital and Qilu Hospital of Shandong University between June 2021 and November 2024. The study protocol adhered to international ethical guidelines for human research and was approved by the Scientific and Ethical Committees of both institutions. Written informed consent was obtained from all participants.

2.1.1 Inclusion and Exclusion Criteria

Inclusion criteria: 1. Serum tPSA ≤ 20 ng/mL. 2. Suspicious prostate nodules detected via digital rectal examination (DRE), transrectal ultrasound (TRUS) (hypoechoic nodules), or prostate multiparametric MRI (mpMRI) (PI-RADS score ≥ 3). 3. Good general health, with no significant hepatic/renal dysfunction, severe cardiovascular/cerebrovascular disease, or coagulation disorders; deemed eligible for transperineal prostate biopsy. 4. Preoperative MRI with clear images and complete key sequences.

Exclusion criteria: 1. History of prostate malignancy or treated benign prostatic hyperplasia (BPH) (surgery/medication). 2. Procedures affecting tPSA levels (e.g., catheterization, cystoscopy, prostate massage) within 3 days prior to blood sampling. 3. Use of tPSA-modifying medications (e.g., steroids, 5 α -reductase inhibitors, androgen inhibitors) within 2 weeks before blood collection. 4. Acute urinary tract infection, prostatitis, or urinary retention within 2 weeks of blood sampling.

2.1.2 Data Collection and Laboratory Analysis

2.1.2.1 Blood biomarkers:

Serum levels of tPSA, free PSA (fPSA), and p2PSA were quantified via enzyme-linked immunosorbent assay (ELISA) (Beckman Coulter Inc., USA). Derived indices were calculated as follows: %p2PSA = $(p2PSA / fPSA) \times 100$; Prostate Health Index (PHI) = $(p2PSA / fPSA) \times \sqrt{tPSA}$

2.1.2.2 Prostate mpMRI:

All patients underwent a prostate mpMRI examination before the operation. Prostate dimensions (transverse [D1], longitudinal [D2], anteroposterior [D3]) were measured, and prostate volume (PV) was calculated: $PV = (\pi/6) \times D1 \times D2 \times D3$. Lesions were scored per PI-RADS v2.1 guidelines (2019).

2.1.2.3 Biopsy and pathology:

Transperineal prostate biopsy was performed under imaging guidance. Two genitourinary pathologists independently evaluated specimens using the 2014 ISUP Gleason grading system.

2.2 Research Methods and Statistical Analysis

2.2.1 Research Methods

1. Prediction Model for CSPCa:

Group stratification: Patients were classified into BPH/CISPCa or CSPCa groups based on biopsy results. The clinical characteristics (age, tPSA, PV, %p2PSA, PHI, PI - RADS score, etc.) between the two groups were compared. Potential predictive factors were screened through univariate analysis, and multivariate Logistic regression analysis was further used to determine the independent risk factors for CSPCa. A combined prediction model was established, and the predictive abilities of each index and the combined prediction model for CSPCa were analyzed and compared.

2. tPSA Stratified Analysis:

Focused on the diagnostic gray zone (tPSA 4 ng/mL ~ 10 ng/mL), assessing the efficacy (AUC, sensitivity, specificity) of biomarkers and the combined model.

3. Correlation with Gleason Grading:

PCa patients were stratified by Gleason score: 6, 7, or ≥ 8. Spearman’s rank correlation analyzed associations between biomarkers (%p2PSA, PHI,etal) and tumor aggressiveness.

2.2.2 Statistical Analysis

All analyses were performed using SPSS 27.0 and Med Calc (for DeLong tests). Normality testing: Data distribution was assessed via the Kolmogorov-Smirnov test. Normally distributed data: Reported as mean ± SD; compared using Student’s t-test. Non-normal data: Reported as median (IQR); compared via Mann-Whitney Utest. Logistic regression: Identified independent predictors of CSPCa; model coefficients were derived. ROC analysis: AUC comparisons between indices used the DeLong test. Correlation analysis: Spearman’s pquantified relationships between biomarkers and Gleason scores. Significance threshold: P < 0.05 (two-tailed).

3. Results

3.1 Patient Characteristics

The final cohort comprised 508 patients, the characteristics are shown in Table 1.

Table 1 the characteristics of all the patients (n=508)

indicator	Value
Mean age	68.1 ± 8.8 years
tPSA (Median, Interquartile Range)	8.66 ng/mL (5.75 - 11.48)
fPSA (Median, Interquartile Range)	1.23 ng/mL (0.85 - 1.78)
PV (Median, Interquartile Range)	49.94 cm ³ (37.14 - 74.22)
p2PSA (Median, Interquartile Range)	16.68 pg/mL (9.17 - 22.74)
%p2PSA (Median, Interquartile Range)	14.55% (8.74 - 17.51)
PHI (Median, Interquartile Range)	41.55 (23.54 - 49.21)
PI-RADS score 1	122 cases (24.0%)
PI-RADS score 2	162 cases (31.9%)
PI-RADS score 3	123 cases (24.2%)
PI-RADS score 4	82 cases (16.1%)
PI-RADS score 5	19 cases (3.7%)

3.2 Comparative Analysis of Clinical Parameters Between the two Groups

Patient Stratification: Patients were stratified into two groups based on prostate biopsy findings: one comprising BPH and CISPCa (401 cases total: 381 with BPH and 20 with CISPCa), and the other consisting of CSPCa (107 cases). The statistical comparisons of two groups are shown in Table 2.

The results showed that there were statistically significant differences in age, tPSA, PV, p2PSA, %p2PSA, and PI-RADS scores between the two groups ($P < 0.05$); while no statistically significant difference was observed in fPSA ($P > 0.05$).

Table 2. Comparison of Clinical Parameters Between BPH/CISPCa and CSPCa Groups

PARAMETER	BPH/CISPCA GROUP (N=401)	CSPCA GROUP (N=107)	TEST STATISTIC	P- VALUE
Age (years)	67.64±9.03	69.74±7.84	-2.194	0.029
tPSA [ng/ml]	8.04 [5.75-11.48]	11.05 [7.89-14.86]	-5.578	0.001
fPSA [ng/ml]	1.22 [0.85-1.78]	1.24 [0.81-1.77]	-0.102	0.919
PV [ml ³]	53.36 [37.14-74.22]	32.90 [21.99-53.07]	-7.165	0.001
p2PSA [ng/ml]	14.65 [9.17-22.74]	29.32 [18.09-49.63]	-8.734	0.001
%p2PSA	13.10 [8.74-17.51]	24.45 [19.05-34.57]	-11.226	0.001
PHI	35.59 [23.54-49.21]	78.89 [59.64-107.15]	-12.198	0.001
PI- RADS Score				
1	122 [30.4%]	0		
2	146 [36.4%]	16 [15.0%]		
3	84 [20.9%]	39 [36.4%]	-10.461	0.001
4	46 [11.5%]	36 [33.6%]		
5	3 [0.7%]	16 [15.0%]		

Multivariate Analysis: Logistic regression identified age, tPSA, PV, PI-RADS scores, and PHI as independent risk factors for CSPCa (Table 3).

A composite predictive model was established via logistic regression:

$$\text{Logit(P)} = -8.652 + 0.045 \times \text{age} + 0.081 \times \text{tPSA} - 0.025 \times \text{PV} + 1.063 \times \text{PI-RADS} + 0.028 \times \text{PHI}$$

Table 3. Logistic Regression Analysis of Predictive Factors for CSPCa

VARIABLE	COEFFICIENT (B)	ODDS RATIO (OR)	P-VALUE	95% CI FOR OR
Age (years)	0.045	1.046	0.01	1.011-1.083
tPSA [ng/ml]	0.081	1.084	0.026	1.010-1.164
PV [ml ³]	-0.025	0.975	0.001	0.962-0.988
PI-RADS Score	1.063	2.896	0.001	2.130-3.940
PHI	0.028	1.029	0.001	1.019-1.038
Constant	-8.652	0.001	0.001	

3.3 Diagnostic Performance Comparison of CSPCa Predictors ROC Analysis

The predictive performance of individual biomarkers and the combined model was evaluated using ROC curves, The optimal cutoff values for each indicator were determined based on the Youden index (Figure 1, Tables 4).

Table 4. Diagnostic Performance of Clinical Parameters for Predicting CSPCa

PARAMETER	CUT-OFF VALUE	SENSITIVITY	SPECIFICITY	AUC (95% CI)	P-VALUE*
Age (years)	63.50	0.83	0.31	0.57	0.508-0.627
tPSA[ng/ml]	9.09	0.69	0.59	0.68	0.620-0.731
PV[ml ³]	34.48	0.55	0.83	0.73	0.668-0.783
p2PSA[ng/ml]	21.93	0.67	0.74	0.78	0.727-0.822
%p2PSA	17.21	0.84	0.74	0.85	0.815-0.891
PHI	54.10	0.83	0.81	0.88	0.852-0.915
PI-RADS Score	2.5	0.85	0.67	0.82	0.778-0.858
Combined Model	-0.81	0.80	0.91	0.92	0.896-0.949

The area under the curve (AUC) values for age, tPSA, PV, p2PSA, PI-RADS scores, %p2PSA, PHI, and the composite model were 0.57, 0.68, 0.73, 0.78, 0.82, 0.85, 0.88, and 0.92 , respectively. PHI and the combined model demonstrated superior discrimination (AUC > 0.85),and PI-RADS score and %p2PSA showed comparable performance (AUC 0.82–0.85).

3.4 Stratified Analysis (PSA in the Gray Zone: tPSA 4 ng/mL ~10 ng/mL)

3.4.1 Comparative Analysis of Clinical Parameters Between the two Groups

There is a total of 281 patients whose PSA values are in the gray zone. 228 patients with BPH[11 with CISPCa, 42 with CSPCa. Comparisons of clinical parameters between the BPH/CISPCa group and the CSPCa group are presented in Table 5.

The results showed that there were statistically significant differences in tPSA,PV, p2PSA,%p2PSA,PHI and PI-RADS scores between the two groups (P < 0.05),while no statistically significant difference was

observed in age and fPSA (P > 0.05).

Table 5. Comparison of Clinical Parameters Between BPH/CISPCa and CSPCa Groups (tPSA 4 ng/mL ~10 ng/mL)

PARAMETER	BPH/CISPCA (N=239)	CSPCA (N=42)	P-VALUE	TEST USED
ageyear	67.55±8.93	67.62±7.15	-0.046	0.963
tPSAng/ml	6.685.40-8.25	7.646.00-8.78	-2.063	0.039
fPSAng/ml	1.060.82-1.39	0.920.69-1.32	-1.619	0.105
PVml ³	50.9635.96-72.38	28.9720.21-44.82	-5.704	0.001
p2PSAng/ml	13.168.55-20.12	22.1815.99-34.16	-5.476	0.001
%p2PSA	13.279.12-18.24	25.0920.33-35.40	-7.498	0.001
PHI	34.4123.63-45.66	68.2153.66-94.20	-7.675	0.001
PI-RADS				
1	7832.6%	0		
2	7732.2%	716.7%		
3	5322.2%	1638.1%	-6.469	0.001
4	2912.1%	1228.6%		
5	20.8%	716.7%		

3.4.2 Multivariable Logistic Regression Independent predictors of CSPCa:

Multivariate Analysis: Logistic regression identified PV,PI-RADS scores and PHI were independent risk factors for CSPCa (Table 6).

Table 6. Multivariable Logistic Regression Analysis of CSPCa Predictors (tPSA 4 ng/mL ~10 ng/mL)

VARIABLE	B-COEFFICIENT	ADJUSTED OR (95% CI)	P-VALUE	CLINICAL INTERPRETATION
PVml ³	-0.032	0.968	0.002	0.948-0.989
PI-RADS Score	0.89	2.434	0.001	1.626-3.644
PHI	0.027	1.027	0.001	1.014-1.041
Constant	-4.228	0.015	0.001	

Predictive Model:

$$\text{Logit(P)} = -4.228 - 0.032 \times \text{PV} + 0.89 \times \text{PI-RADS} + 0.027 \times \text{PHI}$$

3.4.3 Diagnostic Performance Comparison of CSPCa Predictors ROC Analysis

The predictive performance of individual biomarkers and the combined model was evaluated using ROC curves. The AUC of tPSA, p2PSA, PV, PI-RADS scores, %p2PSA, PHI and combined prediction model were 0.60, 0.77, 0.78, 0.80, 0.86, 0.87 and 0.90, respectively. The optimal cutoff values for each indicator were determined based on the Youden index (Figure 2, Tables 7).

In terms of the diagnostic hierarchy ranked by area under the curve (AUC), the combined model achieved the highest discriminative ability (AUC=0.90) and was classified into Tier 1, followed by prostate health index (PHI, AUC=0.87) and percentage of [-2]prostate-specific antigen (%p2PSA, AUC=0.86) which showed comparable performance in the same tier; Tier 2 included Prostate Imaging Reporting and Data System (PI-RADS, AUC=0.80), prostate volume (PV, AUC=0.78), and p2PSA (AUC=0.77) with similar AUC values, while total prostate-specific antigen (tPSA, AUC=0.60) served as the baseline with the lowest diagnostic value. Regarding optimal diagnostic thresholds, the combination of PHI >46.75 and %p2PSA >18.64% yielded balanced sensitivity (86%) and specificity (79%), whereas the combined model (with a Logit P threshold of -1.68) achieved an equilibrium between the two indicators, with both sensitivity and specificity reaching 83%.

Table 7. Diagnostic Performance of Clinical Parameters for CSPCa Prediction (tPSA 4 ng/mL ~10 ng/mL)

PARAMETER	CUT-OFF VALUE	SENSITIVITY (%)	SPECIFICITY (%)	AUC (95% CI)	P-VALUE (VS TPSA)
tPSA ng/ml	7.11	0.64	0.59	0.60	0.508-0.691
PV ml ³	35.84	0.69	0.76	0.78	0.697-0.855
p2PSA ng/ml	13.65	0.90	0.54	0.77	0.695-0.835
%p2PSA	18.64	0.86	0.79	0.86	0.812-0.914
PHI	46.75	0.86	0.79	0.87	0.822-0.921
PI-RADS Score	2.5	0.83	0.65	0.80	0.740-0.865
Combined model	-1.68	0.83	0.83	0.90	0.844-0.947

3.5 Correlation Between Clinical Indicators and Gleason Grading in Prostate Cancer Patient Characteristics

A cohort of 127 prostate cancer patients was stratified by Gleason grade groups based on biopsy pathology. The clinical characteristics and statistical description of clinical indicators in patients with different Gleason score groups are showed in table 8 and 9.

A Spearman correlation analysis was conducted on age, tPSA, fPSA, PV, p2PSA, %p2PSA, PHI, and PI-RADS scores. In the prostate cancer (PCa) group, the analysis yielded three key results: First, PHI exhibited the strongest correlation with Gleason grade progression (correlation coefficient $r=0.303$). Specifically, PHI values increased by 10% when the Gleason score (GS) progressed from ≤ 6 to 7, and further rose by 32% when GS advanced from 7 to ≥ 8 . Second, %p2PSA showed superior correlation with relevant clinical outcomes compared to conventional PSA metrics (including tPSA and fPSA). Its association strength with Gleason grade progression was 2.1 times higher than that of tPSA ($r=0.277$ vs. $r=0.152$), and this significant correlation remained stable even after adjusting for multiple confounding variables. Additionally, the correlation of PI-RADS scores with Gleason grade progression ($r=0.203$) was comparable to that of p2PSA. This finding supports two important clinical implications: first, the combined application of imaging (i.e., PI-RADS) and biochemical biomarkers can effectively improve the accuracy of Gleason grade prediction; second, PI-RADS 5 lesions are associated with a 35.3% probability of harboring $GS \geq 8$ disease. However, tPSA did not show a significant correlation ($r = 0.152$, $P = 0.088$). See Table 10.

Table 8. Clinical Characteristics Stratified by Gleason Grade Groups (n=127)

PARAMETER	GS ≤ 6 (N=20)	GS=7 (N=73)	GS ≥ 8 (N=34)	P-VALUE*
Age (years)	69.0 $\pm$ 7.5	69.0 $\pm$ 8.0	71.4 $\pm$ 7.4	0.185
PSA Metrics				
tPSA (ng/mL)	8.54 (5.53-13.20)	11.05 (7.66-15.06)	11.46 (9.04-14.85)	0.032†
fPSA (ng/mL)	1.16 (0.89-1.49)	1.15 (0.75-1.71)	1.28 (1.01-1.82)	0.217
Advanced Biomarkers				
p2PSA (pg/mL)	22.1 (14.2-39.3)	25.2 (16.4-44.3)	37.6 (25.2-54.1)	0.003†
%p2PSA	19.8 (16.6-25.0)	22.2 (17.6-31.8)	27.7 (21.3-39.4)	<0.001†
PHI	65.7 (40.1-85.3)	72.0 (57.1-99.3)	95.2 (72.3-114.8)	<0.001†
Prostate Volume (mL)	35.6 (29.2-48.5)	35.2 (22.5-53.8)	27.0 (21.8-41.8)	0.047†
PI-RADS Distribution				<0.001†
• Score 2	2 (10.0%)	13 (17.8%)	3 (8.8%)	
Score 3	9 (45.0%)	29 (39.7%)	10 (29.4%)	
• Score 4	9 (45.0%)	27 (37.0%)	9 (26.5%)	
• Score 5	0	4 (5.5%)	12 (35.3%)	

Table 2-9 Statistical Description of Clinical Indicators in Patients with Different Gleason Score Groups

PARAMETER	GS ≤6 (N=20)	GS=7 (N=73)	GS ≥8 (N=34)
age∓years∓	69.00±7.51	68.96±7.97	71.41±7.37
tPSA∓ng/ml∓	8.54∓5.53-13.20∓	11.05∓7.66-15.06∓	11.46∓9.04-14.85∓
fPSA∓ng/ml∓	1.16∓0.89-1.49∓	1.15∓0.75-1.71∓	1.28∓1.01-1.82∓
PV∓ml ³ ∓	35.64∓29.24-48.52∓	35.16∓22.46-53.84∓	26.99∓21.76-41.78∓
p2PSA∓ng/ml∓	22.14∓14.15-39.28∓	25.24∓16.41-44.29∓	37.63∓25.16-54.14∓
%p2PSA	19.79∓16.57-25.02∓	22.22∓17.60-31.76∓	27.72∓21.33-39.38∓
PHI	65.69∓40.05-85.26∓	72.02∓57.14-99.31∓	95.18∓72.29-114.75∓
PI-RADS Score			
1	0	0	0
2	2∓10.0%∓	13∓17.8%∓	3∓8.8%∓
3	9∓45.0%∓	29∓39.7%∓	10∓29.4%∓
4	9∓45.0%∓	27∓37.0%∓	9∓36.5%∓
5	0	4∓5.5%∓	12∓35.3%∓

Table 2-10 Correlation Analysis Between Clinical Indicators and Gleason Grading in Patients with Prostate Cancer

PARAMETER	Correlation coefficient r	P
age∓years∓	0.112	0.208
tPSA∓ng/ml∓	0.152	0.088
fPSA∓ng/ml∓	0.126	0.157
PV∓ml ³ ∓	-0.175	0.050
p2PSA∓ng/ml∓	0.206	0.030
%p2PSA	0.277	0.002
PHI	0.303	∓0.001
PI-RADS score	0.203	0.022

4. Discussion

In recent years, there has been a remarkable growth trend of prostate cancer in China. The statistical data in 2022 shows that the total incidence rate has exceeded that of bladder tumors and kidney tumors,

ranking first among male urogenital tumors[10]. This is closely related to the screening of prostate cancer based on serum PSA testing, and more localized prostate cancers have been detected. However, we should also be aware of the problems of overdiagnosis and overtreatment of prostate cancer brought about by this screening method. In order to reduce unnecessary prostate biopsies and improve the accuracy of prostate cancer diagnosis, especially for patients in the PSA gray zone, new tumor markers such as p2PSA are continuously being developed and utilized. A multi-center study conducted a decade ago evaluated the diagnostic performance of %p2PSA and PHI. In univariate analysis, %p2PSA and PHI were the best predictors of prostate cancer detection, outperforming t-PSA and %f-PSA in the 1.6-8.0 ng/ml PSA range for initial and repeat biopsies and predicting significant prostate cancer in men aged ≤ 65 years[11]. Since then, related research has continuously advanced, expanding the functionality of these markers and the scope of PSA-based applications [12–13]. Chiu PK et al had reported a large-volume, multicenter study, demonstrating that the PHI is more effective for cancer detection than PSA in both European and Asian settings[14]. Other research indicates that PHI cut-off of 42.7 predicts positive biopsy better than mpMRI, PHI density, and MRI PIRADS score (with an AUC difference of 0.14). A PHI value of 61.68 and a PI-RADS score of 4, whether used alone or with a model of age, PSA, fPSA/tPSA ratio, and prostate volume, can identify csPCa (Gleason 7). Additionally, both PHI (cut-off 61.68) and MRI PIRADS ≥ 4 are equally effective in detecting clinically significant CaP (AUC 0.75) [15]. A study of 2900 men found prebiopsy MRI avoided 31% of biopsies, increased csPCa detection by 13%, reduced GG1 diagnosis by 3% and negative biopsies by 10%. Also, Black men used MRI less often [16]. The results of this study show that when tPSA is less than 20 ng/mL, the tPSA of patients in the CSPCa group increases, and the difference is statistically significant ($P < 0.05$). However, the AUC of tPSA for predicting CSPCa is only 0.63. meanwhile the AUC of p2PSA, %p2PSA and PHI are 0.78, 0.85, 0.88 respectively. Among patients in the tPSA gray zone, the AUC of tPSA further drops to 0.60, which is far lower than the diagnostic efficacy of other clinical indicators (p2PSA, %p2PSA and PHI are 0.77, 0.86, 0.87 respectively) in this article. In the entire sample, the optimal cut-off value of tPSA is 9.09 ng/mL, with a sensitivity of 0.69 and a specificity of 0.59. These findings suggest that PHI and %p2PSA could supplement or even surpass tPSA in clinical decision-making, particularly in biopsy or active surveillance candidates.

This study also evaluated the correlation between clinical indicators and Gleason grading in 127 PCa patients, revealing significant associations between advanced biomarkers (PHI, %p2PSA, p2PSA) and tumor aggressiveness. Our findings support the growing evidence that traditional PSA-based parameters (tPSA, fPSA) have limited predictive value for Gleason grading, whereas novel biomarkers and imaging modalities offer superior risk stratification.

When Heidegger et al stratified the p2PSA levels according to the Gleason score, they found that the p2PSA level was the highest in patients with a Gleason score of ≥ 8 and the lowest in patients with a Gleason score of ≤ 6 [17]. Furthermore, a multicenter prospective study found that PHI was highly correlated with the Gleason score. According to their research, PHI was superior to tPSA in predicting CSPCa. When the optimal threshold of PHI was set as ≥ 30 , 33% of CSPCa cases could be avoided from being over diagnosed [14]. Loeb et al showed in a multicenter trial that PHI outperformed tPSA, fPSA,

and [-2]proPSA (AUCs: 0.707 vs. 0.661–0.551) in identifying Gleason 7 prostate cancer [18]. Catalona et al conducted a large multicenter trial on 892 men with PSA 2–10 ng/mL and normal DRE, who had PHI testing before prostate biopsy. The study showed an AUC of 0.72 for PHI in distinguishing GG 2 prostate cancer from lower - grade or negative biopsies. Higher PHI values correlated significantly with a greater proportion of GG 2 on biopsy, with rates of 26% for PHI < 25 and 42% for PHI < 55[19]. In a small-size study (114patients,37 PCa, PSA levels between 2.5 and 10 ng/mL), the correlation between PHI results and biopsy examinations, including Gleason score (G/S), was investigated. As PHI increased, the detection rates of prostate cancer and clinically significant prostate cancer gradually rose. A PHI cutoff of 27 was associated with a G/S of 7, and a PHI of 36 was a boundary for G/S 8 and 9[20].

The results of this study showed that the PI - RADS score has good clinical value in predicting CSPCa. When tPSA (total Prostate Specific Antigen) is less than 20 ng/mL, the PI - RADS score is one of the independent risk factors for predicting CSPCa, and the AUC of its prediction for CSPCa is 0.82. Especially when tPSA is in the range of 10 ng/mL – 20 ng/mL, the AUC of the PI - RADS score for predicting CSPCa even reaches 0.84.Foreign scholars such as Oerther evaluated the application value of the PI - RADS score in CSPCa in a meta - analysis. This study covered 70 relevant literatures and a total of 13,330 patients. The results showed that the PI - RADS score could effectively distinguish between benign and malignant lesions of PCa. Especially when the PI - RADS score was ≥ 4 points, the meta - analysis found that its sensitivity was 89% and the specificity was 66%[21]. For patients with tPSA in the gray zone, the importance of the PI - RADS score is more prominent. The disease risk of these patients is rather ambiguous, and traditional PSA screening often has false - negative or false - positive results. However, the PI - RADS score provides more accurate diagnostic information through imaging, helping clinicians identify potential high - risk patients. This study showed that when tPSA is in the gray zone, the PI - RADS score is one of the independent risk factors for predicting CSPCa, and the AUC of its prediction for CSPCa is 0.80. Thus, it can be seen that the PI - RADS score can effectively identify CSPCa, help reduce the missed - diagnosis rate, and increase the opportunity of early intervention, which has important clinical value for high - risk populations. Smaller prostates (median PV: 27.0 mL in $GS \geq 8$ vs. 35.6 mL in $GS \leq 6$, $P = 0.047$) were associated with more aggressive tumors in this study. This inverse correlation ($r=-0.175$, $P = 0.050$) may reflect tumor-induced stromal compression or a biological predisposition for high-grade disease in smaller glands. Clinically, this supports the notion that PV should be considered alongside biomarkers when assessing PCa risk. Mir MC et al had reported that the TRUS volume was statistically related to the rate of high-grade tumors at biopsy and Radical prostatectomy (RP). On multivariate analyses, TRUS volume was a significant predictor of high-grade tumor for biopsy and RP specimens, with an inverse relationship between high-grade tumors and prostate volume for biopsy and RP specimens [22]. And systematic reviews and Meta-analyses showed that smaller prostate volume predicts clinically substantial GS upgrading in patients diagnosed with low-risk prostate cancer after RP [23].

This study has several limitations. Firstly, the sample size for cases with a Gleason score (GS) ≤ 6 is relatively small, with only $n = 20$. Such a limited sample size may lead to unreliable results, and further validation in larger cohorts is essential to confirm the observed associations. Secondly, the study lacks

long-term outcome data, such as biochemical recurrence. Without these data, it is challenging to comprehensively assess the prognostic value of the relationship between prostate volume and Gleason grades, hindering a more complete understanding of the clinical implications of these findings.

5. Conclusion

PHI and %p2PSA outperform traditional PSA metrics in predicting Gleason grade, while prostate volume and PI-RADS provide complementary insights. These findings advocate for integrating advanced biomarkers and imaging into PCa diagnostics to enhance risk stratification and reduce unnecessary biopsies. Future studies should explore whether PHI-guided strategies improve long-term oncologic outcomes.

Declarations

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of QILU Hospital of Shandong University. (KYL-202011-095-2 and April 12, 2021).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The datasets analyzed during the current study are available in the QILU Hospital of Shandong University.

Conflicts of Interest: The authors declare no conflict of interest.

Author Contribution

ZZ and ZQ S were responsible for designing the experiments. XW, AL C, WK S, KW, WC D, DL P, and RC M conducted most of the data collection, statistical analyses, and clinical parameter assessments. XW, AL C, and WK S carried out the ROC curve analyses, logistic regression modeling, and correlation analyses. KW, WC D, DL P, and RC M contributed to some of the data verification and pathological evaluation. All authors assisted with the analysis and interpretation of certain experiments. XW, AL C, and WK S wrote the initial draft of the manuscript. ZZ and ZQ S conceived the study and provided project supervision. All authors have reviewed and approved the final submission. XW, AL C, and WK S contributed equally to this work and share first authorship. ZZ and ZQ S are co-corresponding authors.

Data Availability

The datasets analyzed during the current study are available in the QILU Hospital of Shandong University.

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Figures

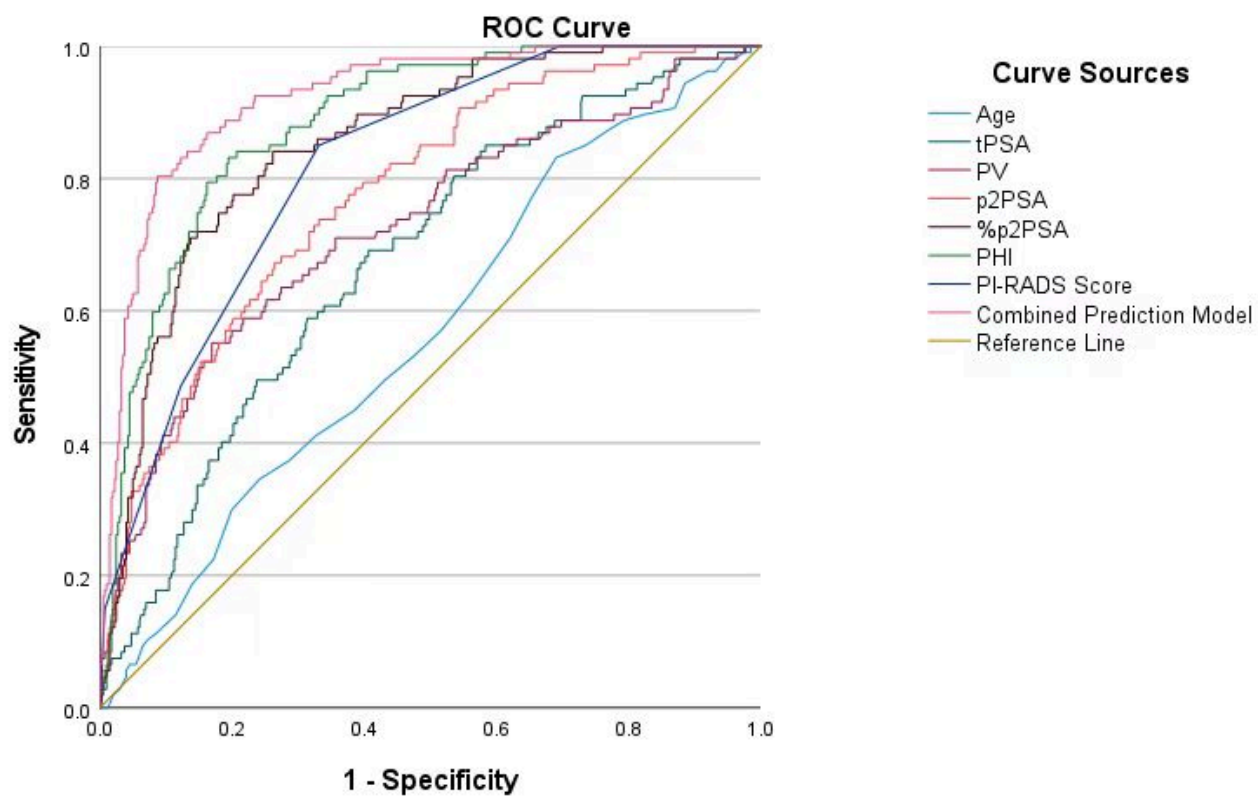


Figure 1

ROC Curves Comparing Predictive Performance for CSPCa

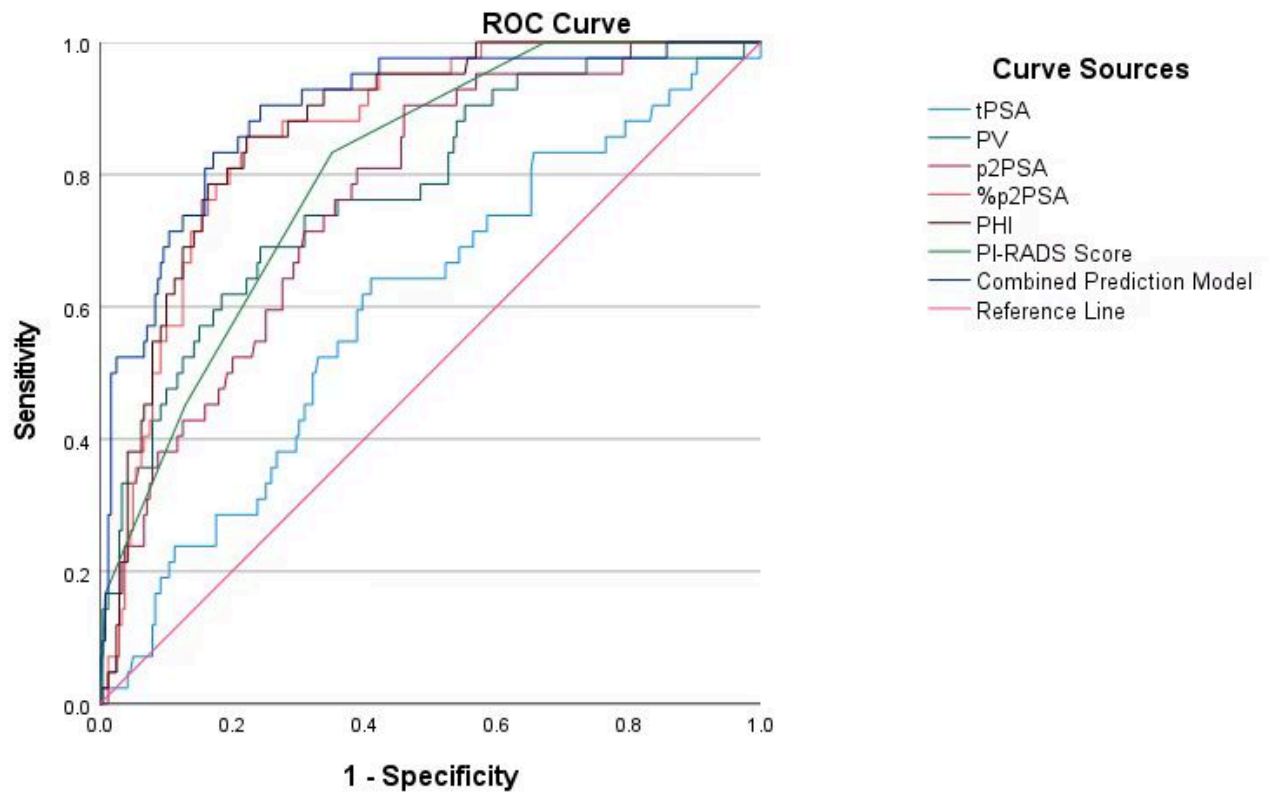


Figure 2

ROC curves for predicting CSPCa value by various indicators (tPSA: 4 ng/mL - 10 ng/mL)