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Research Article

A Quantifiable Risk Stratification Tool with Machine Learning-Comparable Performance Enables Non-Invasive Diagnosis of Prostate Cancer in Specific Populations without PSMA-PET Imaging: A Retrospective and Prospective Study

Jincheng Luo[1,2,3#], Shuiping Yin[1,2,3#], Jia Chen[1,2,3#], Guangyue Luo[1,2,3], Yongwei Zhang[4,5], Bing Wu[1,2,3], Yifan Chang[1,2,3], Lingfan Xu[1,2,3], Sheng Tai[1,2,3], Chao Zhao Liang[1,2,3], Jun Zhou[1,2,3*], Cheng Yang[1,2,3*] and Hui Wang[1,2,3*]

[1]*Department of Urology, the First Affiliated Hospital of Anhui Medical University, Anhui Medical University, Hefei, Anhui, P. R. China*
[2]*Institute of Urology, Anhui Medical University, Hefei, Anhui, P. R. China*
[3]*Anhui Province Key Laboratory of Genitourinary Diseases, Anhui Medical University, Hefei, Anhui, P. R. China*
[4]*University of Science and Technology of China, Hefei, Anhui, P. R. China*
[5]*Chinese Academy of Sciences, Hefei Institutes of Physical Science, Institute of Plasma Physics, Hefei, Anhui, P. R. China*
[#]*Contributed equally*

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ABSTRACT

Background: Prostate-specific antigen (PSA) and multiparametric magnetic resonance imaging (MP-MRI) screening for prostate cancer (Pca) frequently results in unnecessary prostate biopsy (PB), especially in patients with non-clinically significant Pca (NCS-Pca). This study aimed to validate the performance of the Prostate Biopsy Risk Score (PBRS) and machine learning (ML) models in predicting Pca and to streamline the PB and subsequent treatment workflow.

Methods: A retrospective and prospective study was conducted across multiple hospital branches, enrolling 3,467 participants. Cohort I (retrospective training set, Jan 201-Dec 2018, n = 1,078) was used to develop PBRS and ML models. Cohort II (retrospective internal validation, Dec 2018-Dec 2023, n = 2,190) validated model performance and established PBRS thresholds for biopsy avoidance. Cohort III (prospective validation, Jan-May 2025, n = 199) validated these results. Diagnostic performance was assessed using area under the curve (AUC), decision curve analysis, and net reclassification improvement.

Results: PBRS achieved an AUC of 0.89 for Pca prediction, comparable to ML models (0.88-0.89) and superior to PSA (0.76) and MP-MRI (0.84). In retrospective Cohort II, PBRS ≤5 or ≥18 yielded high predictive accuracy (95-100%). PBRS ≤5 showed negative predictive values of 100% (scores 1-4) and 95% (score 5), while PBRS ≥18 demonstrated positive predictive values of 95-99%. These results were confirmed prospectively in Cohort III, with 100% predictive values at the defined thresholds. Based on high prediction accuracy, a one-stop clinical pathway was implemented, incorporating 3D visual ultrasound-targeted biopsy and immediate radical prostatectomy (RP) for patients with PBRS ≥18. Additionally, for RP patients without prior biopsy, analysis confirmed that all patients with PBRS ≤5 had NCS-Pca, whereas all with PBRS ≥18 had clinically significant Pca requiring intervention.

Conclusion: PBRS performs comparably to ML models in predicting Pca and effectively identifies candidates for biopsy-free (PBRS ≤5 or ≥18), enabling non-invasive risk stratification and personalized management in men with suspected Pca.

[*]*Corresponding author: Department of Urology, The First Affiliated Hospital of Anhui Medical University, Institute of Urology, Anhui Province Key Laboratory of Genitourinary Diseases, No. 218 Jixi Road, Hefei, 230022 Anhui, China; E-mail: zhoujun@ahmu.edu.cn* (Jun Zhou); *E-mail: yang_cheng@ahmu.edu.cn (Cheng Yang); E-mail: whayd@sina.cn (Hui Wang)*

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1. Introduction

Prostate cancer (Pca) incidence is steadily increasing, ranking as the top male malignancy [1]. Optimizing early screening and treatment strategies is essential to improve diagnostic accuracy and allocate clinical resources efficiently. Prostate-specific antigen (PSA) remains the most widely used biomarker for initial PCa risk assessment [2]. However, its limited specificity poses significant challenges in evidence-based clinical decision-making. Elevated PSA levels may result from various benign conditions, including prostatitis, benign prostatic hyperplasia (BPH), urinary tract infections, or recent prostate procedures [3]. Multiparametric magnetic resonance imaging (MP-MRI) offers superior sensitivity and specificity compared to PSA [4, 5]. Using the Prostate Imaging Reporting and Data System (PI-RADS) version 2, MP-MRI stratifies PCa risk on a 5-point scale. Studies reported cancer detection rates of 4%, 22.2%, 39.1% and 87.8% for PI-RADS 2, 3, 4 and 5, respectively [6]. Despite the strong predictive value of a PI-RADS 5 score, a false-positive rate of 12.2% (18/147) remains, underscoring the need for complementary diagnostic tools [6]. Additional markers such as PSA density (PSAD), free PSA (fPSA), and prostate volume have also been utilized to improve detection [7-9]. Although combined predictive models incorporating these parameters outperform single markers, their clinical adoption has been limited by practical constraints, such as reliance on nomograms or linear regression equations.

In recent years, prostate-specific membrane antigen positron emission tomography (PSMA-PET) has demonstrated diagnostic performance surpassing that of PSA or Mp-MRI alone. A study by Mazzone *et al.* reported sensitivity and positive predictive values (PPV) of 82% and 77%, respectively, for PSMA-PET alone, which rose to 91% sensitivity and 78% PPV when combined with Mp-MRI [10]. This combined approach enhances lesion detection, particularly in MRI-negative or indeterminate cases (e.g., PI-RADS 3). However, the high cost of PSMA-PET limits its use in routine early screening. It is primarily reserved for cases with strong clinical suspicion of malignancy, such as significantly elevated PSA or abnormal MP-MRI, with due consideration of patient preferences. PSMA-PET also plays a critical role in detecting distant metastases. Definitive diagnosis of PCa typically requires prostate biopsy, often followed by radical prostatectomy upon pathological confirmation. MRI-ultrasound fusion transperineal biopsy, currently the recommended technique, has a positivity rate of approximately 50.5% [11]. While systematic 12- or 13-core biopsies, sometimes combined with targeted biopsies, represent the standard approach, saturation biopsies (>20 cores) do not significantly improve detection rates and may increase complications such as hematuria and infection, as well as healthcare costs [12]. Although MRI fusion-targeted biopsy can enhance detection efficiency while reducing core numbers [13]. Research indicates that MRI fusion-targeted biopsy can improve the detection rate while reducing the number of cores [14, 15], its implementation in primary hospitals remains limited due to technical complexity and equipment requirements.

Capitalizing on the diagnostic advantages of PSMA-PET, some institutions have explored performing radical prostatectomy without prior biopsy. Studies suggest that when multiple screening markers (PSA, Mp-MRI, and PSMA-PET) strongly indicate malignancy, direct radical prostatectomy may be feasible, with postoperative pathology confirming PCa in all reported cases [16, 17]. Nevertheless, this approach remains experimental. No standardized criteria currently exist for selecting patients suitable for biopsy-free prostatectomy, and treatment decisions rely heavily on multidisciplinary team judgment, lacking a uniform and widely applicable framework. The high cost of PSMA-PET further hinders the broader adoption of this strategy.

In response to these challenges, our research team has developed a novel early screening strategy tailored to the characteristics of the Chinese population. This approach integrates multiple clinical indicators into a practical, cost-effective screening model. We previously introduced the Prostate Biopsy Risk Score (PBRS), which excludes expensive PSMA-PET testing. The present study aims to validate the diagnostic performance of PBRS against machine learning models and establish a quantifiable risk stratification framework to enhance assessment consistency and generalizability. Based on this framework, we propose a personalized clinical management pathway: patients with high suspicion of PCa may be considered for biopsy-free radical prostatectomy; those with intermediate risk may undergo minimized biopsy cores for definitive diagnosis; and low-suspicion individuals may avoid biopsy and enter active surveillance with dynamic follow-up.

2. Methods

2.1. Study Population

The study employed a combined retrospective and prospective design. Routine clinical data were retrieved and collected from hospital's information system for patients who underwent initial prostate biopsy between January 2015 and May 2025. The data originated from four hospital: the main campus and the branch campuses. The inclusion criteria were meeting the indications for prostate biopsy as per guideline recommendations and being the first biopsy procedure. The exclusion criteria were incomplete clinical data or a history of previous prostate biopsy [1].

2.2. Study Design

The clinical data were divided into three cohorts: Cohort I (January 2015 to December 2018) for model training and development; Cohort II was utilized as a retrospective internal validation cohort (December 2018 to December 2023) and Cohort III was being a prospective validation cohort (January 2025 to May 2025) for model validation. Cohort I was utilized to train both machine learning models and the previously reported PBRS model (Supplementary Table S1) [11]. The four machine learning models employed were deep neural network (DNN) [18], random forest (RF) [19], attentive interpretable tabular learning (TabNet) [20], and gradient boosting machine (GBM) [21]. All models were developed and validated using identical input features and evaluation protocols to ensure scientific rigor and comparative fairness throughout the investigation. The diagnostic performance of the PBRS and the four machine learning models was validated using data from Cohort II (detailed workflow is illustrated in Figure 1). An in-depth and subgroup analysis was performed on patients in Cohort II to determine

the positive biopsy rate under different PBRS scores, which was used to establish thresholds for identifying candidates who may avoid biopsy. These thresholds were subsequently validated in Cohort I and Cohort III.

2.3. Preliminary Clinical Application of PBRS

To streamline care and avoid separate hospital visits for biopsy and radical prostatectomy, our team implemented a one-stop comprehensive treatment strategy for diagnosis and treatment of patients with PBRS ≥ 18, based on the high positive biopsy rate (95-100%) observed in this group. Specifically, under anesthesia, patients with PBRS ≥ 18 points first undergo MRI-fusion targeted biopsy guided by transrectal 3D visual ultrasound (a reference video of the procedure is available in the supplementary video). In this procedure, two or three cores are sampled from each suspicious lesion (totaling 2-6 cores, significantly fewer than standard protocols such as 12-core protocols). The 3D visual ultrasound system integrates MRI images with real-time ultrasound, color-highlighting suspicious areas identified on MRI to facilitate targeted sampling (the product of Caben (Shenzhen) Medical Technology Co., Ltd., "VENUS Multimodal Image Fusion Ultrasound System"). The biopsy specimens are immediately sent for intraoperative frozen section analysis. If pathological results confirm Pca, the patient proceeds directly to radical prostatectomy during the same anesthetic session. Additionally, we collected clinical data from other cancer centers on patients who underwent biopsy-free radical prostatectomy based on PSMA-PET imaging and analyzed the role of PBRS in supporting the decision to proceed directly to radical prostatectomy without prior biopsy [17].

2.4. Ethics Approval

This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Anhui Medical University (Ethics Approval No: PJ20250597) and complies with the ethical standards of the Declaration of Helsinki and relevant regulatory requirements. The study did not involve the use of tissues or other biological samples, did not interfere with clinical treatment plans, and contained no identifiable personal information. The informed consent of the participants was not applicable as this study only collected clinical data from the hospital system.

2.5. Statistical Analysis

Continuous variables that conform to the assumptions of normal distribution and homogeneity of variance are represented as mean ± standard deviation and analyzed using t-test, while categorical variables are evaluated for inter group differences using chi-square test. Evaluate the discriminating ability of the selected model for Pca using indicators such as receiver operating characteristic curve (ROC), decision curve analysis (DCA), and net reclassification index (NRI). SPSS 27.0 statistical software was used to analyze the above criteria, and a P-value less than 0.05 indicates that the difference is statistically significant. R language (version 4.3.3), RStudio (version 2024.04.0), and pytorch (version 1.11.1) were used to construct and validate the model. The chart was generated using GraphPad Prism software (version 9).

3. Results

3.1. Clinical Characteristics of the Study Population

Our team previously established the value of PBRS for Pca screening using a clinical database of 1,078 patients from 2015-2018 (Cohort I; Supplementary Table S1). In the present study, we expanded the database by including an additional 2,190 patients from 2018-2023 (Cohort II; Figure 1), which served as a validation cohort to further evaluate the performance of PBRS. The clinical characteristics of the training and validation cohorts are summarized in (Table 1) and (Supplementary Table S2). Subgroup analyses based on different PSA values and PI-RADS scores were also conducted. The results revealed distinct PSA and PI-RADS characteristics between Pca patients and those with benign prostatic hyperplasia (BPH). Notably, PI-RADS demonstrated higher accuracy than PSA in diagnosing Pca, indicating its greater clinical reference value. Importantly, the mean PBRS was significantly higher in PCa patients (16.87 ± 3.39) than in the non-cancer group (10.86 ± 3.11, $p < 0.001$), indicating a clear association between elevated PBRS and prostate cancer.

Table. 1. Detail demographics and clinical characteristics of training and validation groups.

Variables	Cohort I: Training group			P value	Cohort II: Validation group			P value
	Total (n = 1078)	Pca (n = 544)	BPH (n = 534)		Total (n = 2190)	Pca (n =1247)	BPH (n = 943)	
Age (year)	68.90 (8.28)	70.91 (7.85)	66.85 (8.22)	<0.001	68.71 (8.63)	70.79 (8.12)	65.96 (8.51)	<0.001
PSA (ng/ml)	30.95 (10.90)	43.76 (15.11)	17.90 (8.31)	<0.001	31.04 (32.24)	43.29 (36.48)	14.85 (13.96)	<0.001
PSA (n/%)								
＜10	281 (26.07)	72 (13.24)	209 (39.14)	<0.001	623 (28.45)	217 (17.40)	406 (43.05)	<0.001
10~20	329 (30.52)	137 (25.18)	192 (35.96)	<0.001	684 (31.23)	317 (25.42)	367 (38.92)	<0.001
＞20	468 (43.41)	335 (61.58)	133 (24.90)	<0.001	883 (40.32)	713 (57.18)	170 (18.03)	<0.001
PI-RADS (n/%)								
≤2	224	28	196 (36.70)	<0.001	233	49	184 (19.51)	<0.001

	(20.78)	(5.15)			(10.64)	(3.93)		
3	331 (30.71)	123 (22.61)	208 (38.95)	<0.001	563 (25.71)	113 (9.06)	450 (47.72)	<0.001
4	306 (28.39)	192 (35.29)	114 (21.35)	<0.001	670 (30.59)	413 (33.12)	257 (27.25)	<0.001
5	217 (20.12)	201 (36.94)	16 (3.00)	<0.001	724 (33.06)	672 (53.89)	52 (5.51)	<0.001
PV (ml)	53.87 (37.22)	49.08 (35.68)	58.76 (36.15)	<0.001	53.69 (38.67)	47.01 (37.87)	62.49 (37.96)	<0.001
PSAD	0.74 (0.9)	1.07 (1.07)	0.40 (0.51)	<0.001	0.81 (1.63)	1.21 (2.06)	0.28 (0.28)	<0.001
PBRS	13.24 (4.29)	15.94 (3.26)	10.49 (3.36)	<0.001	14.28 (4.43)	16.87 (3.39)	10.86 (3.11)	<0.001

Continuous variables were represented as mean and (standard deviation). The t-test and chi square test were used to analyse the data.

PSA: Prostate-Specific Antigen; PSAD: PSA Density; PV: Prostate Volume; BPH: Benign Prostatic Hyperplasia; PI-RADS: Prostate Imaging Reporting and Data System; Pca: Prostate Cancer; PBRS: Prostate Biopsy Rating Scale.

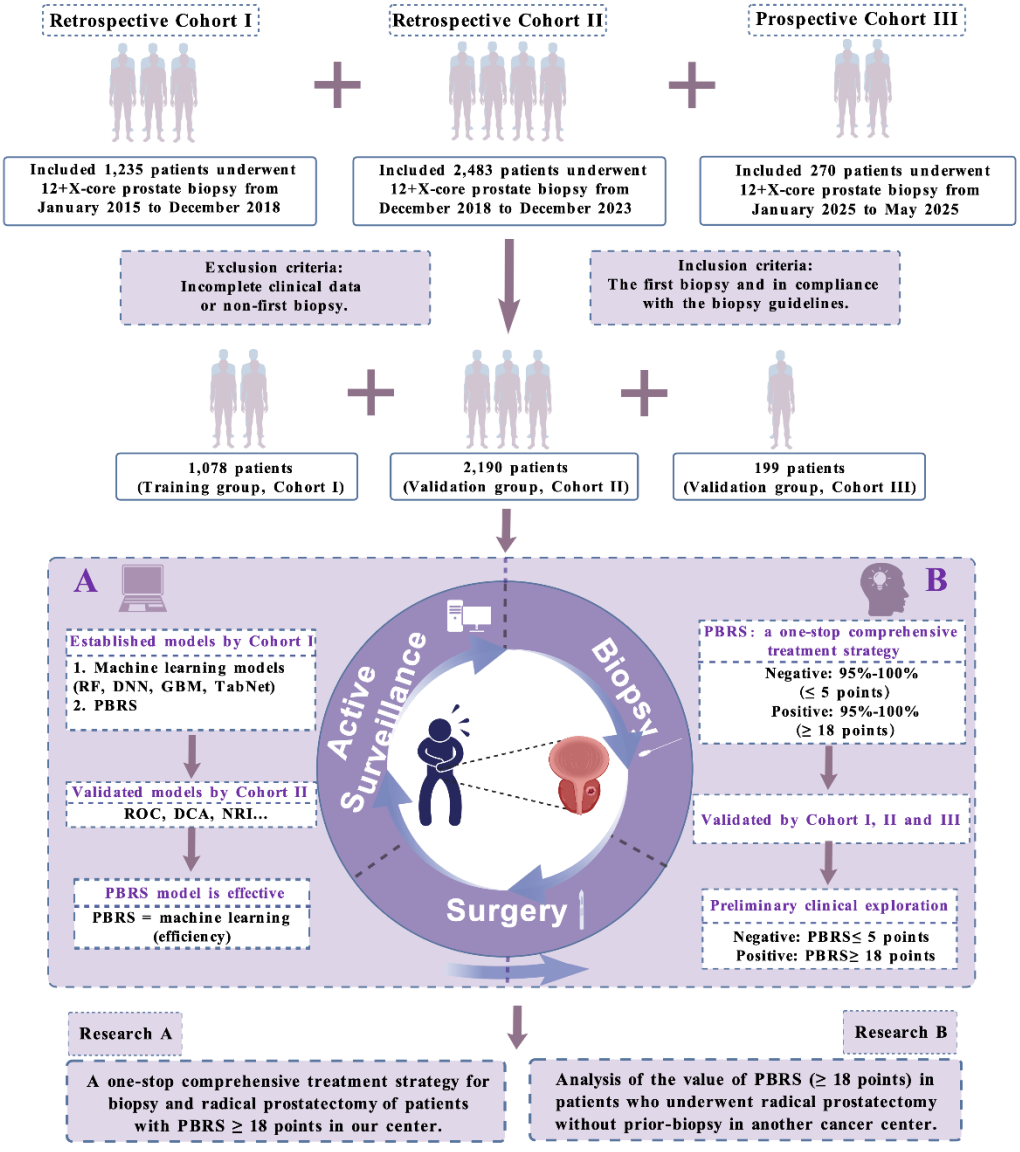
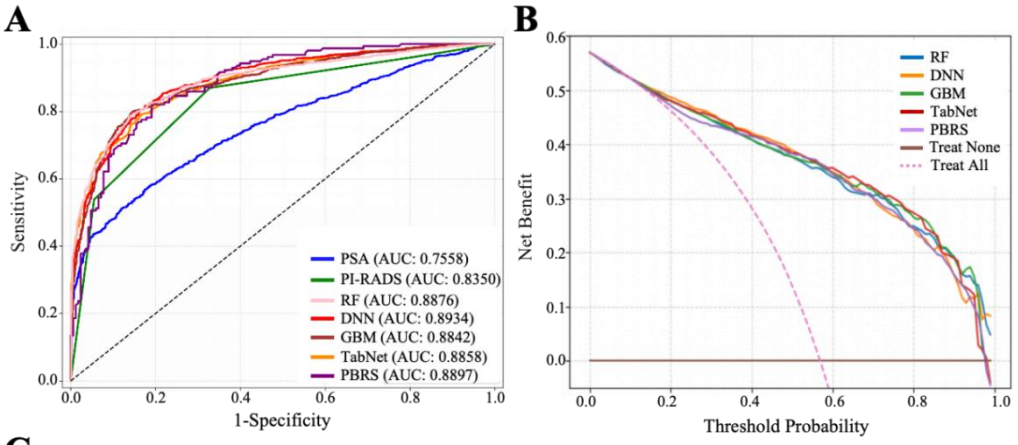


Fig. 1. The patients and basic design of the study.

A) Comparison of the advantages of PBRS and machine Learning models in prostate cancer diagnosis. **B)** Analysis of characteristics for patients with different PBRS scores.
PBRS: Prostate Biopsy Rating Scale; DNN: Deep Neural Network; RF: Random Forest, TabNet: Attentive Interpretable Tabular Learning; GBM: Gradient Boosting Machine.

3.2. Diagnostic Performance and Model Comparison

We compared the diagnostic performance of PBRS against PSA, PI-RADS, and four machine learning models: RF, DNN, GBM, and TabNet. PBRS demonstrated high discriminative ability, with an area under the curve (AUC) of 0.89, significantly outperforming PSA (AUC: 0.76) and PI-RADS (AUC: 0.83). Notably, the AUC of PBRS was not significantly different from those of the four machine learning models (Figure 2A). The DCA analysis further revealed highly similar clinical net benefit between PBRS and the machine learning approaches (Figure 2B), indicating comparable real-world utility. We also assessed model performance using NRI. The NRI of PBRS showed no significant difference from RF, GBM, or TabNet, though it was slightly lower than that of DNN. Further analysis indicated that DNN offered higher negative predictive accuracy, whereas PBRS showed better positive predictive accuracy (Figure 2C, Supplementary Table S3). Together, these findings support PBRS as a robust and clinically competitive tool for PCa screening.



C

Pca N=1247	RF		BPH N=943	RF	
PBRS	−	+	PBRS	−	+
−	124	29	−	637	40
+	96	998	+	105	161
NRI=−0.0537+0.0689=0.0152, Z≈0.99, P≈0.32					

Pca N=1247	DNN		BPH N=943	DNN	
PBRS	−	+	PBRS	−	+
−	126	27	−	644	33
+	72	1022	+	102	164
NRI=−0.036+0.073=0.037, Z≈2.57, P≈0.010					

Pca N=1247	GBM		BPH N=943	GBM	
PBRS	−	+	PBRS	−	+
−	134	19	−	639	38
+	87	1007	+	103	163
NRI=−0.0545+0.0689=0.0144, Z≈0.97, P≈0.33					

Pca N=1247	TabNet		BPH N=943	TabNet	
PBRS	−	+	PBRS	−	+
−	122	31	−	632	45
+	94	1000	+	120	146
NRI=−0.0505+0.0795=0.0290, Z≈1.81, P=0.0702					

Fig. 2. Receiver operating characteristic curves (ROC), decision curve analysis (DCA) and net reclassification index (NRI) for the performance of PBRS and machine learning models on predicting the prostate cancer.
A) ROC curves of PSA, PI-RADS, PBRS and machine learning models. **B)** DCA curves of PBRS and machin learning models. **C)** NRI analysis of PBRS and machin learning models.
PSA: Prostate-Specific Antigen; BPH: Benign Prostatic Hyperplasia; PI-RADS: Prostate Imaging Reporting and Data System; Pca: Prostate Cancer; PBRS: Prostate Biopsy Rating Scale; DNN: Deep Neural Network; RF: Random Forest; TabNet: Attentive Interpretable Tabular Learning; GBM: Gradient Boosting Machine.

3.3. Defining Biopsy-Free Thresholds and Prospective Validation

We analyzed the relationship between PBRS scores (range: 1-21) and PCa detection rates (Figure 3). In both training and validation cohorts, a PBRS ≥18 was associated with a positive biopsy rate exceeding 95%, while a PBRS ≤5 corresponded to a negative predictive value above 95%, establishing these as critical thresholds for clinical decision-making. Clinical characteristics of patients with PBRS ≥18 or ≤5 are summarized in (Table 2). Within these subgroups, no significant differences in age (P = 0.501 and P = 0.092, respectively) or prostate

volume (P = 0.214 and P = 0.443, respectively) were observed between patients with and without Pca.

To prospectively validate these thresholds, we enrolled 199 patients from an independent cancer center (Cohort III). The clinical characteristics of this cohort were consistent with the validation set (Table 3), supporting sample representativeness. In this prospective cohort, the Pca positivity rate was 100% among patients with PBRS ≥18, and the negative predictive value reached 100% for those with PBRS ≤ 5 (Figure 3), confirming the robust diagnostic utility of these cut-offs.

Further analysis of the high-risk subgroup (PBRS ≥ 18) revealed that none of these patients had non-clinically significant PCa (NCS-PCa, defined as Gleason score < 7 and PSA <10 ng/mL; Figure 4), indicating that all warranted clinical intervention. These findings suggest that patients with PBRS ≤ 5 may avoid immediate biopsy in favor of active surveillance, while those with PBRS ≥18 may be considered for treatment, potentially with a reduced number of biopsy cores or with biopsy-free management relying on supporting imaging evidence (PSMA-PET).

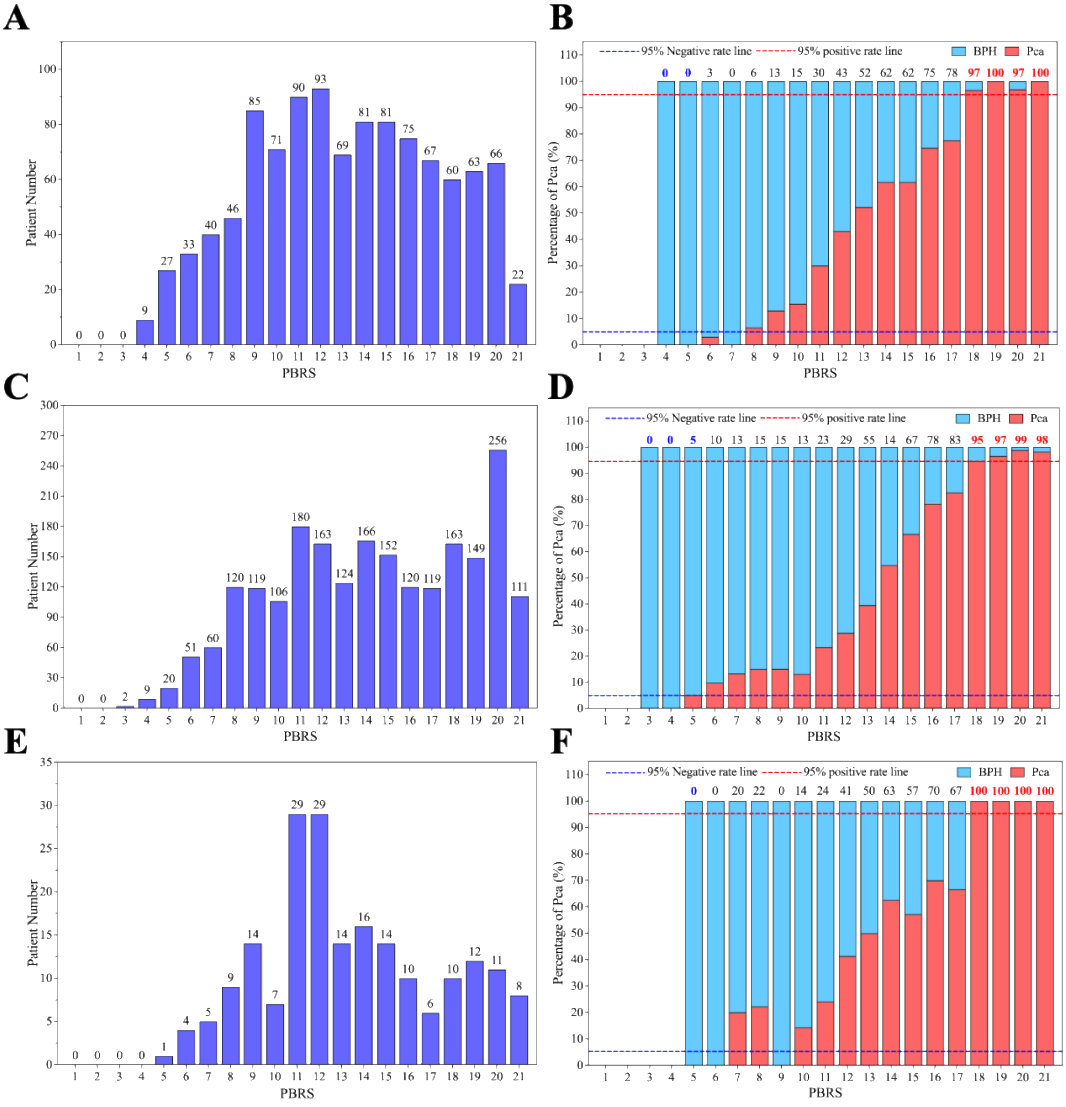


Fig. 3. The distribution of patients with different PBRS scores in the three cohorts.

A) The number of patients with different PBRS in cohort I. **B)** The proportion of Pca patients with different PBRS scores in cohort I and the 95% negative and positive predictive thresholds. **C)** The number of patients with different PBRS in cohort II. **D)** The proportion of Pca patients with different PBRS scores in cohort II and the 95% negative and positive predictive thresholds. **E)** The number of patients with different PBRS in cohort III. **F)** The proportion of Pca patients with different PBRS scores in cohort III and the 95% negative and positive predictive thresholds.

BPH: Benign Prostatic Hyperplasia; Pca: Prostate Cancer; PBRS: Prostate Biopsy Rating Scale.

Table. 2. Detail demographics and clinical characteristics of patients with different PBRS (≥18 and≤5 points).

Variables	PBRS ≥ 18 points			P	PBRS ≤ 5 points			P
	Total (n = 679)	Pca (n =660)	BPH (n = 19)	value	Total (n = 31)	Pca (n = 1)	BPH (n = 30)	value
Age (year)	72.25 (7.86)	72.28 (7.91)	71.05 (5.56)	0.501	59.26 (6.48)	70.00 (NA)	58.90 (6.27)	0.092
PSA (ng/ml)	62.54 (34.76)	63.48 (34.68)	29.98 (17.56)	<0.001	6.99 (2.05)	8.69 (NA)	6.93 (2.06)	0.407
PI-RADS (n/%)				<0.001				<0.001
≤2	0 (0)	0 (0)	0 (0)		31 (100)	1 (100)	30 (100)	
4	56 (8.25)	55 (8.33)	1 (5.26)		0 (0)	0 (0)	0 (0)	
5	623 (91.75)	605 (91.67)	18 (94.74)		0 (0)	0 (0)	0 (0)	
PV (ml)	48.60 (36.95)	48.56 (37.28)	49.87 (23.21)	0.214	67.50 (24.16)	86.11 (NA)	66.88 (24.32)	0.443
PSAD	1.76 (2.60)	1.79 (2.63)	0.72 (0.54)	<0.001	0.11 (0.04)	0.10 (NA)	0.11 (0.04)	0.791

Continuous variables were represented as mean and (standard deviation). The t-test and chi square test were used to analyse the data.

PSA: Prostate-Specific Antigen; PSAD: PSA Density; PV: Prostate Volume; BPH: Benign Prostatic Hyperplasia; PI-RADS: Prostate Imaging Reporting and Data System; Pca: Prostate Cancer; PBRS: Prostate Biopsy Rating Scale.

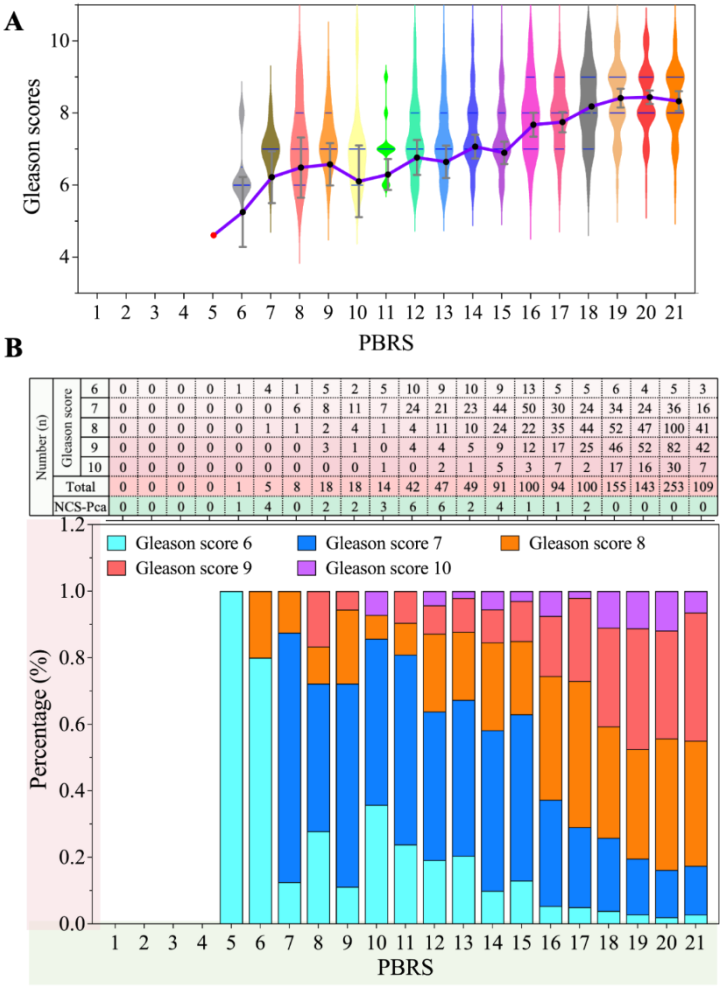


Fig. 4. The changes and distribution of Gleason score in Pca patients with different PBRS scores.

A) The changes of Gleason score in Pca patients with different PBRS scores. **B)** The distribution of Gleason score and NCS-Pca in Pca patients with different PBRS scores.
Pca: Prostate Cancer; PBRS: Prostate Biopsy Rating Scale; NCS-Pca: Non-Clinically Significant Pca.

3.4. Preliminary Clinical Application of PBRS

Guided by these results, we prospectively evaluated an integrated biopsy-treatment pathway for patients with PBRS ≥18. Under anesthesia, targeted biopsies were first performed, sampling 2 cores per suspicious lesion (total of 2-6 cores, significantly fewer than standard 12-core protocols). The samples were sent for intraoperative frozen section analysis, which confirmed Pca in all cases. Radical prostatectomy was subsequently performed (detailed in Figure 5). Additionally, we collected clinical data from patients who underwent direct radical prostatectomy without prior-biopsy (Table 4). These data were obtained from previously published reports. The results similarly showed that none of the patients with a PBRS ≥ 18 were found to have NCS-Pca. When supported by PSMA-PET imaging, all were able to proceed directly to surgery, with final pathology confirming PCa in 100% of cases. Based on these cumulative findings, we propose a streamlined PBRS-guided diagnostic and treatment pathway for PCa, as illustrated in (Figure 6).

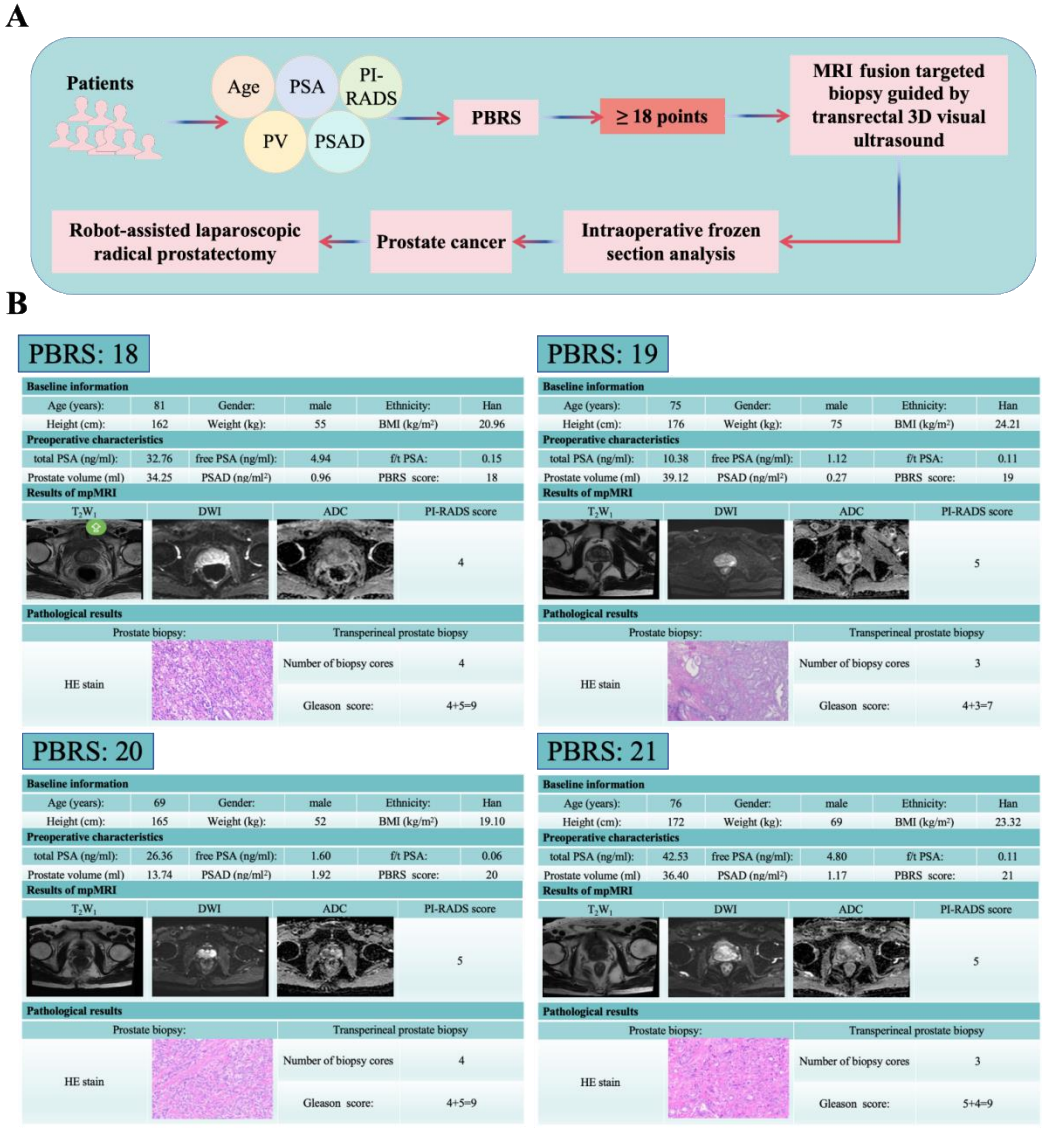


Fig. 5. Preliminary clinical exploration of a one-stop comprehensive treatment strategy for diagnosis and treatment of patients with PBRS ≥ 18 points.
A) The flow chart of a one-stop comprehensive treatment strategy. **B)** The detailed characteristics of a one-stop comprehensive treatment strategy for patients with PBRS ≥ 18 points.

PSA: Prostate-Specific Antigen; BPH: Benign Prostatic Hyperplasia; PI-RADS: Prostate Imaging Reporting and Data System; Pca: Prostate Cancer; PBRS: Prostate Biopsy Rating Scale; BMI: Body Mass Index; DWI: Diffusion Weighted Imaging; ADC: Apparent Diffusion Coefficient.

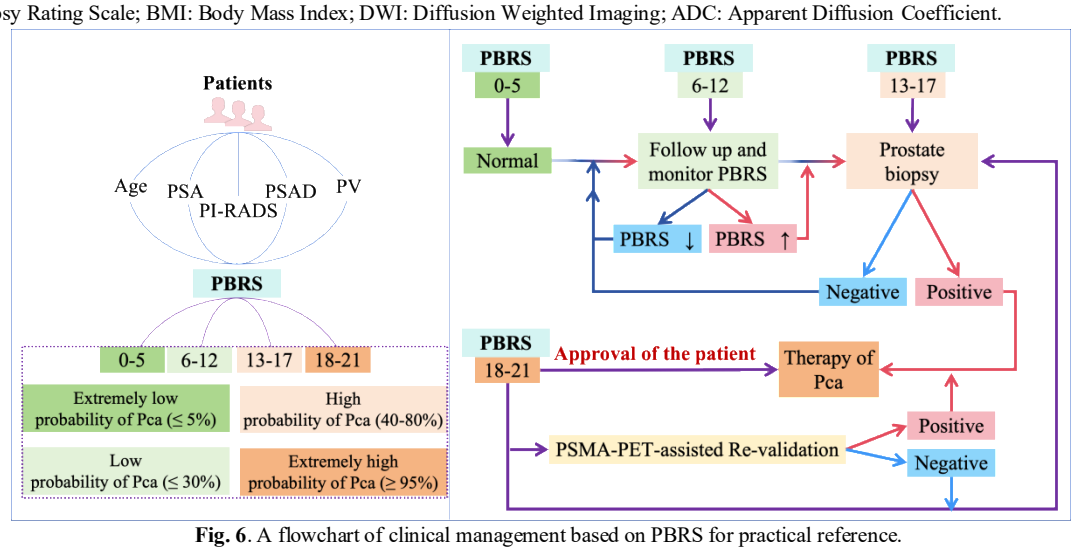


Fig. 6. A flowchart of clinical management based on PBRS for practical reference.

PSA: Prostate-Specific Antigen; PSAD: PSA Density; PV: Prostate Volume; PI-RADS: Prostate Imaging Reporting and Data System; Pca: Prostate Cancer; PBRS: Prostate Biopsy Rating Scale; PSMA-PET: Prostate-Specific Membrane Antigen Positron Emission Tomography.

Table. 3. Detail demographics and clinical characteristics of prospective validation groups which was collected by other center.

Variables	Total (n = 199)	Pca (n =100)	BPH (n = 99)	P value
Age (year)	70.17 (8.41)	71.90 (8.22)	68.42 (8.28)	0.003
PSA (ng/ml)	26.87 (49.99)	40.38 (67.07)	13.23 (11.41)	< 0.001
PSA (n/%)				
＜10	76 (38.19)	29 (29)	47 (47.47)	
10~20	70 (35.18)	29 (29)	41 (41.41)	
＞20	53 (26.63)	42 (42)	11 (11.11)	
PI-RADS (n/%)				< 0.001
≤2	13 (6.53)	2 (2)	11 (11.11)	
3	70 (35.18)	16 (16)	54 (54.55)	
4	68 (34.17)	39 (39)	29 (29.29)	
5	48 (24.12)	43 (43)	5 (5.05)	
PV (ml)	58.37 (31.92)	49.41 (29.59)	67.42 (31.78)	< 0.001
PSAD	1.74 (18.01)	0.69 (0.68)	2.79 (25.55)	< 0.001
PBRS	13.43 (3.93)	15.81 (3.55)	11.03 (2.61)	< 0.001

Continuous variables were represented as mean and (standard deviation). The t-test and chi square test were used to analyse the data.

PSA: Prostate-Specific Antigen; PSAD: PSA Density; PV: Prostate Volume; BPH: Benign Prostatic Hyperplasia; PI-RADS: Prostate Imaging Reporting and Data System; Pca: Prostate Cancer; PBRS: Prostate Biopsy Rating Scale.

Table. 4. Characteristics of patients who underwent radical prostatectomy without prior-biopsy.

Variables	Total	PBRS			
		18	19	20	21
Number	46	12	15	14	5
Age (year)	70.96 (6.90)	71.08 (7.59)	70.20 (7.44)	70.07 (6.62)	75.40 (3.36)
PSA (ng/ml)	33.49 (21.78)	15.64 (4.27)	31.09 (24.12)	45.67 (17.98)	49.39 (19.67)
PV (ml)	41.64 (16.80)	44.29 (19.87)	42.75 (21.17)	40.24 (11.56)	35.9 (3.53)
PSAD	0.84 (0.54)	0.39 (0.15)	0.71 (0.44)	1.19 (0.52)	1.36 (0.48)
PI-RADS (5)	46	12	15	14	5
Positive of PSMA-PET-CT (n)	46	12	15	14	5
Gleason score (n/%)					
6	2 (4.35)	0 (0)	1 (6.67)	1 (7.14)	0 (0)
7	20 (43.48)	6 (50.00)	6 (40.00)	4 (28.57)	4 (80.00)
≥8	24 (52.17)	6 (50.00)	8 (53.33)	9 (64.29)	1 (20.00)
NCS-Pca (n)	0	0	0	0	0

Continuous variables were represented as mean and (standard deviation). The t-test and chi square test were used to analyse the data.
PSA: Prostate-Specific Antigen; PSAD: PSA Density; PV: Prostate Volume; PI-RADS: Prostate Imaging Reporting and Data System; Pca: Prostate Cancer; PSMA-PET-CT: Prostate-Specific Membrane Antigen Positron Emission Tomography-Computed Tomography; PBRS: Prostate Biopsy Rating Scale; NCS-Pca: Non Clinically Significant Prostate Cancer.

4. Discussion

We have successfully developed a PBRS scoring system based on various clinical data of Pca patients in our previous study [11]. In this study, we further validated the performance of the model by comparing it with multiple machine learning algorithms, and the results showed that the model performed equally well as the machine learning algorithms in predicting benign and Pca and evaluating the degree of Ca malignancy. In addition, we captured from clinical data of Pca patients that with different natures or malignant degrees have different clinical manifestations, which were expressed in the form of scores by the PBRS scoring system. For extremely low-risk patients with the scores of PBRS ≤ 5, the benign probability exceeded 95%, and biopsy could be postponed for close follow-up. For extremely high-risk patients with the scores ≥ 18, whose malignancy probability exceeded 95%, treatment intervention might be directly considered. Based on this pattern and combined with clinical treatment guidelines, we proposed the concept of "biopsy-avoidance thresholds", aiming to provide a new approach for optimizing clinical diagnosis and treatment.

Previous model studies have also established models by incorporating basic experimental blood indicators of Pca patients, combining with demographic information and imaging, emphasizing the enormous potential of these models in early diagnosis of the Pca. For example, the models established Ankers *et.al.* and Tolksdorf et.al have shown good diagnostic ability for Pca, but have not been able to establish machine learning algorithms for comparison [22, 23]. However, the applicability of these linear models in these patient data has not been validated, and a lack of performance benchmark testing (without comparison validation with other models), which could not prove the rationality of model selection. And more likely to miss key predictive factors due to methodological limitations. Therefore, in order to enhance the credibility of the research model, this study included comparisons between models and found that RF, GBM, and TabNet models did not show statistically significant improvements compared to the PBRS scoring system. It is worth noting that the DNN model performed outstandingly in terms of TNR, but was accompanied by an increase in FNR.

This performance characteristic suggested that the model have advantages in specificity, but comed at the cost of sacrificing some sensitivity. And in the high-risk group (such as PBRS scores ≥ 18 points), the predictive consistency of each model for malignant cases was high, while in the low-risk group (≤ 5 points), the false positive rate remained low. These results further confirmed that the PBRS scoring system achieved diagnostic accuracy comparable to advanced machine learning models while preserving superior clinical interpretability, providing empirical evidence for its subsequent research applications. The PBRS scoring system rivals various machine learning algorithms in diagnostic accuracy, while also providing quantifiable indicators for Pca risk assessment. With a scoring range of 1 to 21 points, it enables more refined and precise risk stratification. In contrast, models such as RF, DNN, GBM and TabNet can only provide binary classification results

(positive/negative), which have certain limitations in the practical application of clinical risk assessment. In addition, compared to machine learning algorithms, PBRS was easier to deploy in resource scarce areas and had higher clinical practicality. In the current medical decision-making environment, these advantages were more practically valuable than small performance differences between models. Therefore, it was worth choosing as the focus of our subsequent research.

Based on the excellent integration ability of deep learning in big data analysis, many researchers have chosen the models as the main research objects in previous studies. For example, in the studies of Suh *et al.* and Song *et al.*, machine learning algorithms were used to predict diseases using more laboratory blood indicators as parameters [24, 25]. Although these indicators and new biomarkers have a certain role in predicting Pca [26], adding new indicators to patients in most countries means high costs, and most new technologies require professional training and lack large-scale randomized trials to verify clinical benefits. Therefore, there are obstacles to clinical application. Simultaneously incorporating more small impact factor variables into the prediction model may dilute the weight of core impact factors and reduce prediction accuracy [27]. However, these small variables did not include PSAD and MRI, which have previously proposed as important indicators for predicting Pca [28]. And PSAD and MRI were also included as important influencing factors in this study. It is worth noting that PSA, as an important indicator for the diagnosis of Pca, has not been overlooked by researchers for its diagnostic role. However, most existing studies have included PSA levels ranging from 4-20ng/ml [29-31], lacking specialized predictive analysis for patients across the entire PSA range. This has led to a drawback in clinical practice, where Pca with low PSA levels may be missed, while benign patients with high PSA levels might be over treated. Therefore, we collected a wider range of patients to reduce the risk of missed diagnosis and overtreatment, providing a more comprehensive risk assessment capability.

The application of PBRS scoring system in clinical practice can help clinicians develop better plans by scoring patients who are about to undergo puncture, evaluating whether patients could delay biopsy or closely follow up based on the biopsy avoidance threshold. At present, prostate biopsy is routinely performed using a systematic 12 or 13 core regimen, or in combination with targeted puncture for several needles. Previous studies have shown that saturation puncture does not significantly improve the overall puncture positivity rate. For patients with high PBRS scores indicating an elevated risk of Pca, this study proposes that a reduction in the number of puncture needles may still achieve comparable positive detection rates. This hypothesis, however, requires further validation through prospective studies. For lower-scoring patients, the active surveillance could help minimize the risk of biopsy-related complications. Overall, this model scores the condition of Pca patients who have completed examinations and are facing puncture decisions to quickly guide the development of clinical plans, which could effectively reduce the psychological pressure caused by long waiting times and the harm caused by unnecessary biopsy.

In addition, we analyzed the correlation between Gleason score and PBRS, showing that the Gleason score increased with the increase of PBRS score. This provides two key references for clinical practice: i) The PBRS score can assess the pathological grade of patients before surgery. For patients with a lower score, the possibility of Pca is low. Even for patients with Pca, their pathological risk level is low, and active follow-up monitoring measures can be taken. ii) For patients with higher scores, according to the current guidelines, lymph node dissection is recommended to be considered in addition to radical prostatectomy. This enables patients to have a more intuitive understanding of individualized risks, the possibility of active monitoring, and the necessity of surgical treatment.

Currently, the noninvasive diagnostic strategy based on PSMA-PET imaging has become an emerging direction in the field of Pca [32, 33], but its application is still limited by high examination costs and the current situation where lesion interpretation mainly relies on qualitative or semi quantitative evaluation. The PBRS scoring system proposed in this study (with a threshold set to $\geq$ 18 points) exhibits performance comparable to PSMA-PET in terms of positive predictive values, and does not rely on expensive imaging examinations, making it more economical and affordable. This result provides reliable evidence-based medical support for further promoting puncture free treatment pathways in high-risk populations. Before the promotion of non-biopsy treatment approaches among high-risk groups, We adopted a one-stop comprehensive treatment strategy for diagnosis and treatment of patients with PBRS $\geq$ 18 points. This can simplify the diagnosis and treatment procedures for patients and save medical resources. It also provides a more solid basis for the subsequent implementation of non-biopsy Pca treatment.

Although the model developed by our team has been compared and verified to have sufficient advantages, it still has certain shortcomings. Although the model developed by our team has been compared and verified to have sufficient advantages, it still has certain shortcomings. Firstly, the data collected in this study are all from different hospitals in the same region. It is necessary to incorporate data from more central units in different regions. Therefore, more regional data need to be included to verify the PRBS scoring system. Second, the PI-RADS scores included in this study were influenced by human factors, as the study spanned nearly 10 years and there were differences in the seniority of radiologists. Third, the amount of extreme value data in this study may be insufficient, and multi center validation needs to be supplemented in the future. Next, there is an inherent risk of false negatives in biopsy technology, which may result in a lower positive rate of Pca observed based on biopsy results compared to the actual incidence rate. It should be emphasized that in the high-risk patient population with a PBRS score of $\geq$ 18, the true positive rate of Pca is likely to be higher than the results reported by current biopsy.

5. Conclusion

In this retrospective and prospective combined study with data from multiple hospitals in the same region, we demonstrated that as a decision support tool, PBRS exhibited performance comparable to that of machine learning models in predicting Pca. Effectively identify candidate patients (PBRS $\leq$5 or $\geq$ 18), accurately classify "true negative"

and "true positive" cases among suspected Pca patients, thereby promoting non-invasive risk stratification and personalized treatment for suspected Pca patients. Moreover, a one-stop comprehensive treatment strategy independent of PSMA-PET was successfully implemented for patients with PBRS ≥ 18, which provides a cost-effective composite biomarker for the subsequent promotion of RP without biopsy based on PBRS.

Data Sharing Statement

All related data have been presented within the manuscript. The data supporting the conclusions of this article is available from the authors upon reasonable request.

Author Contributions

Jincheng Luo, Shuiping Yina, Jia Chen and Hui Wang: investigation, conceptualization, methodology, data analysis, formal analysis, writing-original draft; Guangyue Luo, Yongwei Zhang and Bing Wu: investigation, methodology, data analysis, formal analysis, writing-original draft; Yifan Chang and Linfan Xu: conceptualization, methodology, data analysis, writing-original draft; Sheng Tai and ChaoZhao Liang: investigation, data analysis, writing-review & editing; Jun Zhou: resources, methodology, data analysis, funding acquisition, formal analysis, writing-review & editing. Cheng Yang: supervision, resources, funding acquisition, writing-review & editing. Hui Wang: conceptualization, supervision, resources, project administration, funding acquisition, writing-review & editing. all authors have accessed and verified the study data and approved the final manuscript.

Competing Interests

None.

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