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Clinical assessment of urinary prostate cancer antigen 3 in Chinese population: a large-scale, prospective and multicenter study

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Abstract

Background To assess the clinical utility of PCA3 in the diagnostic accuracy, the correlation between PCA3 and biopsy or pathological characteristics and the performance of PCA3 to reduce the unnecessary biopsies in Chinese population.

Methods A prospective study including patients with indication of prostate biopsies from 4 centers was conducted. All patients underwent PCA3 urine tests and prostate biopsies. The PCA3 score was analyzed by *PCA3 gene expression Detection Kit (Fluorescent RT-PCR) (York biotech, Cat.#YDM-B01, China)*. Base model (clinical information) and PCA3 model (PCA3 scores and clinical information) were constructed via multivariate logistic regression. Discrimination, calibration and decision curve analysis were evaluated.

Results In 1117 patients, 587 men with positive biopsy results had higher median PCA3 scores than those with negative biopsy results ($p < 0.001$). PCA3 scores had a greater area under the curve (AUC) than tPSA, %fPSA and PSAD in all PSA levels or PSA gray zone (4–10 ng/ml). Men with biopsy Gleason score < 7 had lower median PCA3 scores than those with Gleason score ≥ 7 ($p = 0.016$). In radical prostatectomy specimens, PCA3 scores were significantly associated with high-grade PCa ($p = 0.002$) and EAU biochemical recurrence risk ($p = 0.044$), but not extracapsular extension ($p = 0.072$), seminal vesicle invasion ($p = 0.482$) and T stage ($p = 0.457$). Regression analysis showed that the AUC increased from 0.806 (base model) to 0.873 (PCA3 model). PCA3 model with cutoff 0.15 could reduce 35.3% prostate biopsies and delay 5.8% high-grade PCa.

Conclusions PCA3 had a better diagnosis accuracy than tPSA, %fPSA and PSAD. PCA3 was a significantly independent predictor for risk stratification, suggesting that PCA3 could provide incremental value to reduce unnecessary prostate biopsies.

Keywords PCA3, Prostate cancer, Risk stratification

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Introduction

Prostate cancer (PCa) has become the most common cancer in men in many countries and regions [1]. Though prostate-specific antigen (PSA) based prostate screening can reduce the prostate cancer-specific mortality, the classical screening approach leads to the over-diagnosis and over-treatment of low-grade PCa, which might not require the treatment immediately [2–5]. Numerous PCa biomarkers and new techniques has developed for early detection and optimizing the screening algorithms, such as 4 K score, the Prostate Heath Index (PHI), SelectMDX, Stockholm3 test [6]. Josefsson et al. indicated that the 4 K score could potentially avoid the use of MRI for 41% men and the biopsies for 28% men at the cost of delaying the diagnosis of 4% intermediate-grade cancers [7]. Tosoian et al. constructed an 18-gene test for high-grade PCa and the model could reduce 35% to 42% unnecessary biopsies in initial biopsy population [8].

MRI has been widely used before prostate biopsies and plays a pivotal role in the diagnosis and risk stratification of PCa [9]. A meta-analysis found that MRI had 96% pooled sensitivity and 43% specificity when PI-RADS ≥ 3 [10]. But how to deal with patients with negative MRI was still a problem and debate [11]. The high cost, limited access to equipment and the need for experienced radiologists also limited the utilization of MRI [11].

Prostate cancer antigen 3 (PCA3), also known as DD3 gene, is specifically over-expressed specifically in prostate cancer tissues and had been well studied in the past several years [12]. Many researches showed that low PCA3 score had the predictive value to negative biopsies and low volume insignificant PCa, demonstrating the potential ability of PCA3 on risk stratification and active surveillance [13–17]. The PCA3 assays have been approved for use in patients with prior negative prostate biopsies to make decision on repeat biopsies. However, there remains some uncertainty and contradiction in clinical assessment for PCA3 [18].

In our study, we performed a large-scale, multi-center, prospective trial to evaluate the clinical utility of PCA3 and the performance to reduce the unnecessary biopsies in Chinese population with elevated PSA.

Patients and methods

Study design

The inclusion criteria were men above 45 years old with the abnormal digital rectal examination (DRE), suspicious transrectal ultrasound (TRUS) and magnetic resonance imaging (MRI) results, serum PSA > 10 ng/ml, abnormal %fPSA or PSAD when the PSA level was between PSA 4–10 ng/ml. The exclusion criteria included a prior diagnosis with PCa, untraceable clinical data, lack of prostate biopsies, medical therapies influencing serum PSA levels, no PCR results of PCA3 gene. Our study recruited the participants from 4 centers in China and all patients received systematic prostate biopsies following each hospital's standard procedure (8–12 cores). Low-grade PCa was defined as a Gleason score less than 7, while high-grade PCa was defined as a Gleason score of 7 or higher. The study protocol was approved by local ethnics committees and all participants signed informed consent statements.

Clinical evaluation

The following clinical information were collected: age, serum total PSA, %fPSA, prostate volume, MRI results, prior negative biopsies, biopsy results, pathological results. Prostate volumes were measured by TRUS or MRI. MRI results were evaluated by experienced radiologists with the Prostate Imaging Reporting and Data System (PI-RADS) v2.1. First-catch urine samples were collected after digital rectal examination. The PCA3 score was analyzed using *PCA3 gene expression Detection Kit (Fluorescent RT-PCR) (York biotech, Cat. #YDM-B01, China).* The specific fluorescent Taqman probes for PSA and PCA3 were designed. The PCA3 score was calculated as [PCA3 mRNA]/[PSA mRNA]*1000.

Statistical analysis

The correlation between PCA3 scores and clinical characteristics was evaluated using the chi-square and Mann–Whitney U test. Multivariate logistic regression model was consisted of PCA3 score and clinical information (age, serum PSA, %fPSA, prostate volume, family history, prior negative biopsy). PCA3 scores were converted to ln[PCA3 score] using logarithmic function before incorporating the model. Accuracy were quantified using the area under the curve (AUC) of the receiver operator characteristic analysis (ROC). SPSS 26.0 and R 4.2.2 were used for all analyses. P value lower than 0.05 showed the statistical significance.

Results

Study population

1348 patients were enrolled in this study from 4 centers between May 2020 and December 2022. 1117 patients were analyzed, while 77 patients with other tumors of urinary system served for specificity test. 154 were excluded (14 were diagnosed with PCa before, 68 had untraceable clinical data, 6 did not take prostate biopsies, 1 had medical therapies influencing PSA levels and 65 had no PCR results). All 1117 patients received serum PSA tests, PCA3 examinations and prostate biopsies. 587 patients were diagnosis with PCa and 367 took radical prostatectomy. Multivariate logistic regression model were conducted for risk stratification in 2 centers ($n = 521$) and

validated in the other centers($n=330$). The clinical utility of PCA3 scores and PCA3 model to reduce unnecessary prostate biopsies was analyzed in 851 patients and 447 MRI subgroup (Fig. 1). Table 1 showed the characteristics of the population.

The diagnosis accuracy and prognostic value of PCA3 score

Table 2 showed the diagnostic accuracy of PCA3 score and the correlation with biopsy data. In all PSA ranges, ROC analysis revealed that PCA3 scores had a greater AUC (0.813, 95%CI: 0.788–0.839) than tPSA (0.699, 95%CI: 0.669–0.730), %fPSA (0.640, 95%CI: 0.606–0.673) and PSAD (0.782, 95%CI: 0.754–0.808). In the PSA gray zone (PSA 4-10 ng/ml), ROC analysis indicated that the AUC of PCA3 score (0.802, 95%CI: 0.763–0.842) was significantly higher than tPSA (0.576, 95%CI: 0.523–0.629), %fPSA (0.606, 95%CI: 0.553–0.660), PSAD (0.677, 95%CI: 0.627–0.727). Patients with negative biopsies had lower median PCA3 scores than those with positive biopsies (46.94 vs. 192.11, $p<0.001$). The PCA3 scores were significantly lower in patients with biopsy Gleason score < 7 than those with biopsy Gleason score ≥ 7 (157.67 vs. 205.90, $p=0.016$). As for PCA3 scores and pathological characteristics, the median PCA3 scores were significantly lower in patients with low-grade PCa than those with high-grade PCa (137.74 vs. 190.78, $p=0.002$). The PCA3 score was also significantly correlated with ISUP grade ($p=0.036$) and EAU biochemical recurrence risk classification ($p=0.044$), but failed to have the association

Table 1 Characteristics of the patients

Variables	All evaluable men ($n=1117$) Median (range) or n (%)
Age,yr	68(46–95)
Serum PSA, ng/ml	10.95(0.83–11,557)
% Free PSA	0.14(0.01–0.61)
Prostate volume	39.71(11.88–169.36)
Prior negative biopsies	78(7.0%)
PCA3 score	110.34(1.24–7568.46)
No. prostate MRI:	447
PI-RADS 0–2	76(17.0%)
PI-RADS 3	154(34.5%)
PI-RADS 4	134(30.0%)
PI-RADS 5	83(18.6%)
No. Diagnosis PCa:	587
Gleason score < 7	118(20.1%)
Gleason score = 7	469(79.9%)
Radical prostatectomy	367(62.5%)

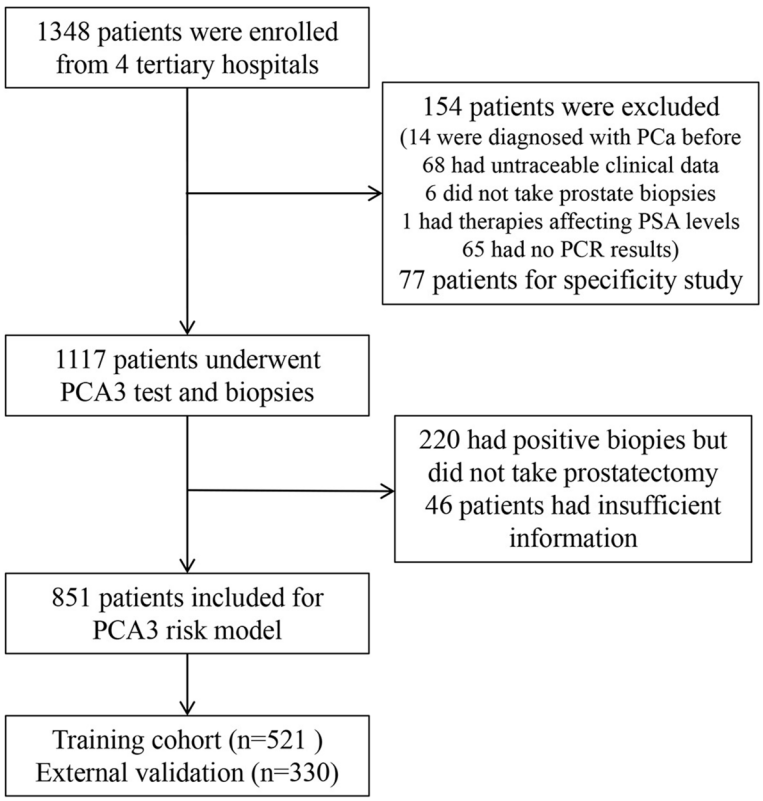

Fig. 1 Study Flow Diagram

Table 2 The diagnostic accuracy of PCA3 and the correlation between PCA3 scores and biopsy results

a) Diagnostic accuracy of tPSA, %fPSA, PSAD and PCA3 at different total PSA levels

Variables	tPSA			%fPSA			PSAD			PCA3 score		
	n	Median	AUC	n	Median	AUC	n	Median	AUC	n	Median	AUC
PSA gray zone	465	7.00(4.00–10.00)	0.576(0.523–0.629)	448	0.14(0.03–0.54)	0.606(0.553–0.660)	452	0.17(0.003–0.62)	0.677(0.627–0.727)	465	92.83(2.56–7464.26)	0.802(0.763–0.842)
all PSA ranges	1117	10.95(0.83–11,557.00)	0.699(0.669–0.730)	1065	0.14(0.01–0.61)	0.640(0.606–0.673)	1065	0.26(0.03–21.28)	0.781(0.754–0.808)	1117	110.34(1.24–7568.46)	0.813(0.788–0.839)

b) PCA3 score and Biopsy Gleason score

Variables	Biopsy Gleason score sum		*P* Value	Biopsy Negative	Biopsy Positive	*P* Value
	Gleason score < 7	Gleason score ≥ 7				
Age, Median (range), n	69(47–84), 118	70(49–95), 469	0.017	66(46–88), 530	70(47–95), 587	< 0.001
tPSA, Median (range), n	9.04(3.09–31.79), 118	16.90(3.36–11,557), 469	< 0.001	8.96(0.83–58.65), 530	14.04(3.09–11557), 587	< 0.001
%fPSA, Median (range), n	0.14(0.03–0.39), 111	0.11(0.01–0.56), 438	0.008	0.15(0.03–0.61), 515	0.12(0.01–0.56), 549	< 0.001
PSAD, Median (range), n	0.21(0.03–1.00), 114	0.52(0.09–21.28), 439	< 0.001	0.19(0.03–2.06), 503	0.41(0.03–21.28), 541	< 0.001
PCA3 score, Median (range), n	157.67(5.72–2620.79), 118	205.90(3.24–7568.46), 469	0.016	46.94(1.24–7464.26), 530	192.11(3.24–7568.46), 587	< 0.001

with extracapsular extension ($p=0.072$), seminal vesicle invasion ($p=0.482$) and T stage ($p=0.457$) (Table 3.).

The establishment and validation of PCA3 model to predict high-grade PCa

The PCA3 score was found to have a significant correlation with low-grade PCa. Among 367 patients receiving radical prostatectomy, we observed 51.9% of cases with low-grade PCa upgrading to a higher grade group. Therefore, we chose to conduct the risk model containing the patients with benign diseases and pathological results. Multivariable logistic regression models were constructed using clinical information (base model) or PCA3 scores plus clinical information (PCA3 model) for risk stratification in the training cohort from 2 centers ($n=521$) and were externally validated in the cohort from other centers ($n=330$). The clinical information included age, tPSA, %fPSA, prostate volume and prior negative biopsies.

Table 4 showed that the odds ratio (OR) of the PCA3 score and clinical information of predicting high-grade PCa. The AUC of the PCA3 score was 0.793 (95%CI: 0.762–0.824). The multivariate models indicated that PCA3 scores represented as an independent predictor for clinical model (OR: 2.531; 95% CI: 2.033–3.151; $p<0.001$). When the PCA3 score was added, The AUC increased from 0.807 (base model) to 0.872 (PCA3 model) (DeLong's test, $p<0.001$). Figure 2 showed the results of discrimination, calibration and decision curve analysis. The bootstrapped AUC of the PCA3

Table 3 The correlation between PCA3 scores and pathological characteristics

Variables	Total cohort	Pathological Gleason score					T stage		
		Gleason score < 7		Gleason score ≥ 7		*P* value	T1 and T2	T3 and T4	*P* value
No. of patients	367	44		323		-	253	114	-
PCA3 score,median (range)	183.01(3.24–3630.08)	137.74(5.72–870.55)		190.78(3.24–3630.08)		0.002	180.49(3.57–3386.98)	186.21(3.24–3630.08)	0.457
Variables	ISUP grade						Extraprostatic extension		
	1	2	3	4	5	*P* value	NO	YES	*P* value
No. of patients	44	133	93	37	60	-	276	91	-
PCA3 score,median (range)	137.74(5.72–870.55)	200.33(3.57–3630.08)	188.48(15.51–2620.79)	217.64(3.24–763.13)	166.49(15.04–1134.72)	0.036	172.42(3.57–3630.08)	220.68(3.24–2158.46)	0.072
Variables	EAU biochemical recurrence risk classification						Seminal vesicle invasion		
	Low-risk	Intermediate-risk		High-risk		P value	NO	YES	*P* value
No. of patients	23	116		228		-	319	48	-
PCA3 score,median (range)	117.44(27.39–870.55)	185.57(3.57–3386.98)		188.65(3.24–3630.08)		0.044	185.57(3.24–3386.98)	162.11(15.41–3630.08)	0.482

Table 4 Univariable and multivariable regression analysis for risk stratification

Variables	Univariable analysis			Multivariable analysis			
				Base model		(PCA3 model) Base model + PCA3 score	
	OR(95%CI)	*P* value	AUC	OR(95%CI)	*P* value	OR(95%CI)	*P* value
Age	1.065(1.045–1.087)	< 0.001	0.636(0.598–0.674)	1.073(1.043–1.103)	< 0.001	1.053(1.021–1.086)	< 0.001
tPSA	1.070(1.052–1.087)	< 0.001	0.678(0.640–0.715)	1.066(1.040–1.092)	< 0.001	1.071(1.042–1.101)	< 0.001
%fPSA	0.001(0.000–0.006)	< 0.001	0.669(0.631–0.707)	0.010(0.000–0.288)	0.007	0.005(0.000–0.202)	0.005
Prostate Volume	0.969(0.962–0.977)	< 0.001	0.682(0.646–0.719)	0.961(0.949–0.974)	< 0.001	0.962(0.949–0.975)	< 0.001
Prior negative biopsy	0.329(0.174–0.622)	< 0.001	0.535(0.496–0.575)	0.386(0.165–0.903)	0.028	0.385(0.152–0.977)	0.045
PCA3 score	2.603(2.234–3.034)	< 0.001	0.793(0.762–0.824)	-	-	2.531(2.033–3.151)	< 0.001
AUC	-	-	-	0.807	-	0.872	-
Increment of AUC	-	-	-	-	-	0.065	< 0.001

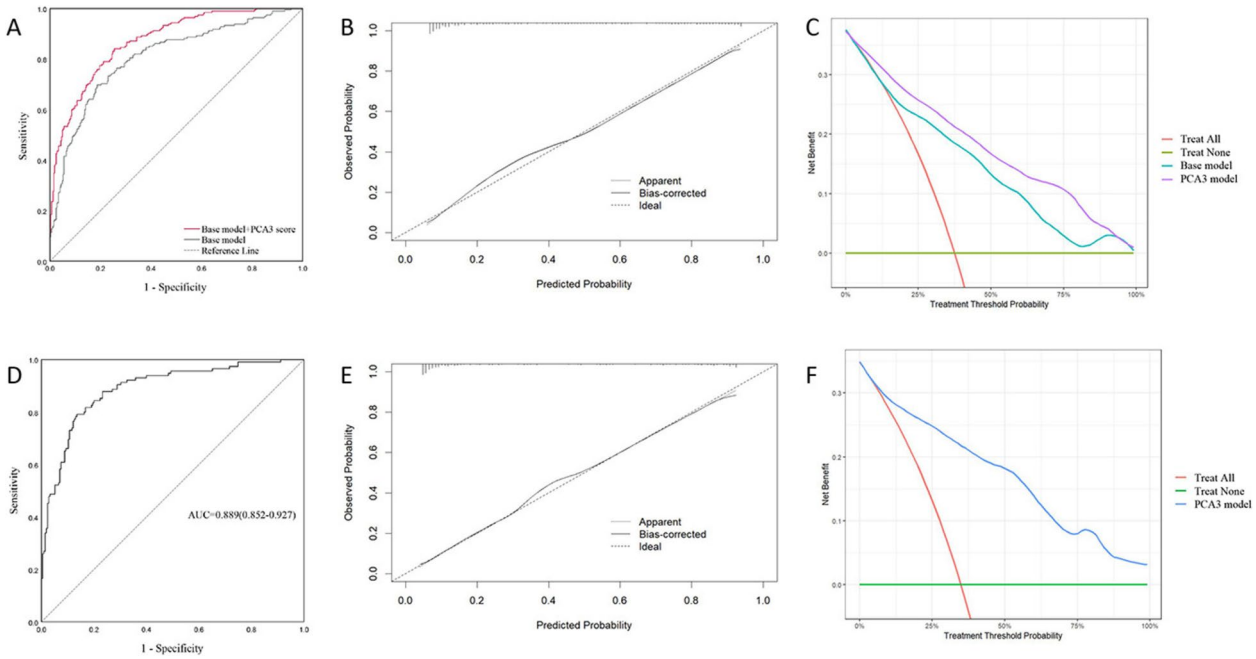

Fig. 2 The discrimination, calibration and decision curve analysis of base model and PCA3 model. **A** ROC analysis showed the AUC of base model and PCA3 model was 0.807 and 0.872, respectively in the training cohort ($n=521$). **B** The calibration curves with 1000 bootstrap resamples showed no significant deviations in PCA3 model in the training cohort. **C** Decision curve analysis showed the PCA3 model had the higher net benefit compared to base model in the training cohort. **D** ROC analysis indicated that the AUC of PCA3 model was 0.889 in externally validated cohort ($n=330$). **E** and **F** The bootstrapped calibration plots and decision curves were analyzed in externally validated cohort ($n=330$)

model was 0.872 (bootstrapped 95% CI: 0.841–0.902). The bootstrapped calibration plots demonstrated that there were no significant deviations between the predicted probabilities and observed probabilities in PCA3 model. Decision curve analysis showed that the PCA3 model had the higher net benefit than base model. In the validated cohort, ROC analysis showed that the AUC of the PCA3 model was 0.889. The bootstrapped calibration plots and decision curve analysis were also evaluated.

The performance of PCA3 to reduce unnecessary prostate biopsies

We explored the clinical utility of PCA3 serving as a useful tool to reduce unnecessary prostate biopsies (Table 5). As for PCA3 examinations after PSA test (PSA → PCA3),

Table 5 The clinical utility of PCA3 in different diagnostic strategies

a) PSA → PCA3			
	Prostate biopsies avoided ($n=851$), n%	**low-grade PCa avoided ($n=43$), n%**	**high-grade PCa missed ($n=310$), n%**
PCA3 score < 25	163(19.2%)	2(4.7%)	16(5.2%)
PCA3 score < 35	233(27.4%)	6(14.0%)	24(7.7%)
PCA3 mode < 0.1	230(27.0%)	9(20.9%)	10(3.2%)
PCA3 mode < 0.15	300(35.3%)	12(27.9%)	18(5.8%)
b) PSA → PCA3 → MRI			
	MRI avoided ($n=447$), n%	Prostate biopsies avoided ($n=447$), n%	high-grade PCa missed ($n=134$), n%
PCA3 score < 25	92(20.6%)	142(31.8%)	12(9.0%)
PCA3 score < 35	133(29.8%)	178(39.8%)	16(11.9%)
PCA3 mode < 0.1	143(32.0%)	189(42.3%)	10(7.5%)
PCA3 mode < 0.15	188(42.1%)	222(49.7%)	16(11.9%)

233 (27.4%) patients were found to have a low risk of PCa at the cutoff of PCA3 score 35. Reducing this proportion of patients' further examination could avoid the use of 233 (27.4%) biopsies but miss 24 (7.7%) high-grade PCa. PCA3 model could reduce 300 (35.3%) biopsies and miss 18 (5.8%) high-grade PCa at the cutoff 0.15.

In the 447-patient MRI subgroup, 371 had positive MRI results, while 76 patients had a negative MRI results, among whom 6 had high-grade PCa. The strategy 'PSA → PCA3 → MRI' meant that prostate biopsies were conducted when PCA3 showed a high risk followed by suspicious MRI results (PI-RADS ≥ 3). By avoiding the use of biopsies and MRI among the rest of patients, PCA3 scores with cutoff 35 could avoid 133 (29.8%) MRI and 178 (39.8%) biopsies, but miss 16 (11.9%) high-grade PCa. The PCA3 model with cutoff 0.15 could avoid 188 (42.1%) MRI and 222 (49.7%) biopsies, but miss 16 (11.9%) high-grade PCa. The benefits were also analyzed at the different cutoffs of PCA3 scores and the PCA3 model.

Discussion

Although European Randomized study of Screening for Prostate Cancer showed PSA based screening could decrease the mortality of PCa, the traditional algorithm resulted in over-treatment and a waste of healthcare resources [19, 20]. Recent studies have shown no significantly difference on prostate cancer-specific mortality between the active surveillance, surgery and radiotherapy, highlighting the importance of detecting clinical significant PCa [21]. MRI has been reported to play a great part in reducing the unnecessary prostate biopsies and the detection of low-grade PCa [22]. Due to the medical resources and healthcare policies, an increasing number of screening algorithms including biomarkers and MRI were evaluated [23, 24]. But most of the clinical trials combining MRI with biomarkers are conducted in European and North American countries [25].

PCA3 was widely recognized as a significant PCa biomarker and had better accuracy in PCa detection [26–31]. Chun et al. conducted a nomogram containing PCA3 for biopsy decision-making [32]. PCA3 was reported to have additional value to The Prostate Cancer Prevention Trial Risk Calculator (PCPTRC) and in patients with PI-RADS 3 lesions [33, 34]. However, the relationship between PCA3 with the characteristics of the biopsy or pathological specimens remained unclear, and previous studies with contradictory conclusions often involved a small number of patients, especially in the Chinese population [35–39].

In our study, we performed a large-scale, multi-center, prospective study including 1117 patients in Chinese population. PCA3 were superior to tPSA, %fPSA and PSAD in the diagnostic accuracy of PCa. Patients with biopsy or final pathology Gleason score < 7 had lower PCA3 score than those with biopsy or pathological Gleason ≥ 7, respectively. These results showed that PCA3 was not only a remarkably useful tool for PCa diagnosis, but also helped to risk stratification.

Some researched showed that a part of high-grade PCa had low PCA3 expression in initial biopsy setting[15, 40]. Considering a single biomarker was usually not enough for the diagnosis and treatment decision-making, we constructed a logistic regression PCA3 model using PCA3 scores and clinical information to improve the detection of high-grade PCa and assess the utility to avoid unnecessary prostate biopsies. The patients with negative biopsy and pathological results were included for the construction of PCA3 model, which suggested as a more accurate way to distinguish the benign diseases, low-grade and high-grade prostate tumors.

Many studies have indicated that PCA3 can reduce unnecessary prostate biopsies and perform better than tPSA in terms of diagnosis accuracy [18]. However, whether PCA3 can server as an accurate tool to predict aggressive features of prostate cancer remains a controversial topic. In our study, we found that PCA3 is superior to tPSA, %fPSA, and PSAD in the early diagnosis of prostate cancer, which is consistent with other studies. Moreover, we discovered that PCA3 scores are correlated with low-grade prostate cancer and not related to extracapsular extension and seminal vesicle invasion. However, some studies have not found the association between PCA3 and the pathological characteristics of samples after prostate biopsies or radical prostatectomy.

On one hand, we hypothesize that this discrepancy may be related to the distinct genomic profiles of prostate cancer between China and Western countries. It has been noted that Asian prostate cancer patients often exhibit higher tumor grades at the time of diagnosis, but have similar or better prognoses with androgen deprivation therapy [41]. Studies have shown that PCA3 expression is regulated by the androgen receptor (AR) [42]. Compared to patients in western countries, AR mutations are rare, in contrast to the higher prevalence of mutations in upstream activators of the androgen receptor, such as FOXA1 and SPOP [43]. Due to the tumor heterogeneity of prostate cancer, the activity of AR varies significantly among different molecular subtypes. with the SPOP and FOXA1-mutated tumors exhibiting the highest levels of AR transcripts, which may affect the PCA3 expression [44]. On the other hand, many previous studies were limited by small sample sizes, whereas our study has a substantial sample size and is conducted across multiple centers.

We conducted the first large-scale multi-center clinical study in the Chinese population to explore the clinical performance of PCA3, providing the strong evidence to support the clinical application of urine PCA3 detection. Given the excellent performance of PCA3 in the early diagnosis and risk stratification of prostate cancer, and considering that prostate cancer is often detected as high-grade tumors in low-income and middle-income countries [1], we believe that PCA3 has broad application prospects and definitely helps to promote the diagnosis and treatment of PCa. However, there were several limitations in our study. First, according to the final pathological results, only a small proportion of patients were diagnosis with low-grade PCa due to the upgraded Gleason score and epidemiology of PCa in China [45]. Second, our clinical trail was not performed in in a screening setting. Third, researches with higher grade evidence, like randomized controlled trial, are needed for better assessment of PCA3.

Conclusions

PCA3 performed well in the diagnosis of PCa and had a significantly predictive value for high-grade PCa. PCA3 showed a high accuracy for risk stratification, which could serve as a valuable tool to reduce unnecessary prostate biopsies.

Abbreviations

PCA3	Prostate cancer antigen 3
PCa	Prostate cancer
tPSA	Total prostate-specific antigen
%fPSA	The ratios of percent free prostate-specific antigen
PSAD	Prostate-specific antigen density
DRE	Digital rectal examination
TRUS	Transrectal ultrasound
MRI	Magnetic resonance imaging
PI-RADS	The Prostate Imaging Reporting and Data System
PCR	Polymerase chain reaction
ISUP	The International Society of Urological Pathology
ROC	Receiver operating characteristic
AUC	The area under the ROC curve
OR	Odds ratio
PCPTRC	The Prostate Cancer Prevention Trial Risk Calculator

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Authors' contributions

Xuan Shu, Jiaming Wang and Wen Cai: Data collection, Data analysis and Manuscript writing. Shen Lin, Jiangfeng Li, Xueyou Ma, Yufan Ying and Yat Sai Terry Wang: Data analysis. Xiao Wang and Hong Chen: Project development. Chunyu Jin, Ben Liu, Liping Xie and Jindan Luo: Study design, Project development and Manuscript editing. All authors read and approved the final manuscript.

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Data availability

All data sets used or analyzed in this study are available from the corresponding author upon request.

Declarations

Ethics approval and consent to participate

Approval was obtained from the respective ethics committee (The First Affiliated Hospital, Zhejiang University School of Medicine; the Second Affiliated Hospital, Zhejiang University School of Medicine; Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University; West China Hospital, Sichuan University). The procedures used in this study adhere to the tenets of the Declaration of Helsinki. The consents were given voluntarily by study participants and the approvals were obtained from all participants.

Consent for publication

Informed consent was obtained from all individuals participating in the study.

Competing interests

C.J is an employee of York Biotech Co., Ltd, which is developing products related to the research presented here. The other authors declare no competing interests.

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