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Diagnosis of Prostate Cancer in Patients with Prostate-Specific Antigen (PSA) in the Gray Area: Construction of 2 Predictive Models

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Statistical Analysis C
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Background: Two diagnostic models of prostate cancer (PCa) and clinically significant prostate cancer (CS-PCa) were established using clinical data of among patients whose prostate-specific antigen (PSA) levels are in the gray area (4.0-10.0 ng/ml).


Material/Methods: Data from 181 patients whose PSA levels were in the gray area were retrospectively analyzed, and the following data were collected: age, digital rectal examination, total PSA, PSA density (PSAD), free/total PSA (f/t PSA), transrectal ultrasound, multiparametric magnetic resonance imaging (mpMRI), and pathological reports. Patients were diagnosed with benign prostatic hyperplasia (BPH) and PCa by pathology reports, and PCa patients were separated into non-clinically significant PCa (NCS-PCa) and CS-PCa by Gleason score. Afterward, predictor models constructed by above parameters were researched to diagnose PCa and CS-PCa, respectively.

Results: According to the analysis of included clinical data, there were 109 patients with BPH, 44 patients with NCS-PCa, and 28 patients with CS-PCa. Regression analysis showed PCa was correlated with f/t PSA, PSAD, and mpMRI ($P < 0.01$), and CS-PCa was correlated with PSAD and mpMRI ($P < 0.01$). The area under the receiver operating characteristic curves of 2 models for PCa (sensitivity=73.64%, specificity=64.23%) and for CS-PCa (sensitivity=71.41%, specificity=81.82%) were 0.79 and 0.87, respectively.

Conclusions: The prediction models had satisfactory diagnostic value for PCa and CS-PCa among patients with PSA in the gray area, and use of these models may help reduce overdiagnosis.

Keywords: Logistic Models • Magnetic Resonance Imaging • Prostate-Specific Antigen • Prostatic Neoplasms

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Background

Prostatic cancer (PCa) is a common malignant tumor of the male urinary system, the morbidity of which ranks fifth in overall global malignancies [1]. In China, the incidence rate of PCa is lower than that in Western countries [2]. However, with the change of lifestyle and the prolongation of life expectancy, the incidence rate of PCa has been increasing rapidly [2]. Epidemiological surveys showed the incidence rate of PCa in 2014 was nearly 1.5 times higher than that in 2012 (6.10/10 000 vs 4.39/10 000), ranking sixth in male cancer mortality [3,4].

The major prognostic benefit of PCa is early diagnosis and hence treatment [5]. Prostate-specific antigen (PSA) as a serum marker is the usual diagnostic method for biopsy-driven PCa. In the European Association of Urology Guidelines, the higher levels of PSA indicate likelihood of PCa [6]. However, PSA levels between 4.0 ng/ml and 10.0 ng/ml are often called the "gray area", within which it is controversial to diagnose PCa [7]. According to a survey, when PSA level is within this range, the positive rate of prostate biopsy was only 15.9% to 26.0%, so it is often necessary to combine it with other clinical parameters to improve the detection rate [8].

Traditionally, the digital rectal examination (DRE), which is based on the perceived diversities in the stiffness of normal prostatic tissue and neoplasm, is always used as a primary method for detecting PCa [5]. Total PSA (tPSA) is a commonly used diagnostic indicator in prostatic disease, whose derivatives, including free PSA (fPSA), PSA density (PSAD), and free/total PSA (f/t PSA), have reference value for PCa with the PSA in the gray area. Huang et al reported the summary sensitivity of fPSA was 70% in patients with PSA in the gray area [9]. In addition, another 2 studies indicated the indication for prostate biopsy is that f/t PSA is $\leq 15\%$ and PSAD is >0.15 ng/ml [10,11].

TRUS is a commonly used imaging method in clinical practice, and it is non-invasive and simple. Some scholars pointed out that the sensitivity and specificity of transrectal ultrasound (TRUS) measurements in diagnosing the PCa were 17% to 57% and 40% to 63%, respectively [12]. Multiparametric magnetic resonance imaging (mpMRI) is well-established as an important aide for diagnosis of PCa [13]. The diagnostic rate of mpMRI for PCa was 73%, which is helpful in the staging of PCa [14].

Therefore, the diagnosis of PCa with PSA in the gray area is not satisfactory using a single diagnostic mode. The present study aimed to improve the diagnostic rate of PCa with PSA in the gray area by analyzing the comprehensive clinical parameters, including age, DRE, tPSA, f/t PSA, PSAD, TRUS, mpMRI, and construct modes, based on the significant parameters.

Material and Methods

Patients

This retrospective research was approved by the Ethics Review Board of the First Affiliated Hospital of Medical College of Shihezi University (No. 2019-123-01), with waiver of patient consent. There were 1243 patients who underwent prostate biopsy from August 2013 to October 2019 at the First Affiliated Hospital of Medical College, Shihezi University. Inclusion criteria were: 1) patient accepted prostate biopsy and pathology reports could be consulted; and 2) patient had complete electronic patient records and clinical data, including age, DRE, tPSA, f/t PSA, PSAD, TRUS, and mpMRI. The exclusion criterion was patients with contraindications for prostate biopsy. Of these patients, 181 (11.73%) had PSA levels between 4.0 ng/ml and 10.0 ng/ml, and all patients had either benign prostatic hyperplasia (BPH) or PCa. The collected medical records were divided into a BPH group and a PCa group according to pathology results. The patients in the PCa group were divided into a clinically significant PCa (CS-PCa) group and a non-clinically significant PCa (NCS-PCa) group by Gleason score (GS) modified 2005 International Society of Urological Pathology (ISUP) [15]. The PCa patients with GS <7 were assigned to the NCS-PCa group, while other patients were assigned to the CS-PCa group.

Equipment and Methods

Clinical parameters of all enrolled patients were collected, including age at diagnosis and treatment, DRE, serum tPSA, f/t PSA, PSAD, TRUS, and mpMRI in the medical records system. DRE was performed by a deputy senior urologist. The tPSA and f/t PSA was collected by immunofluorescence assay. From ultrasound prostate scanning reports, we collected data on prostatic volume (PV) using the exact prolate ellipsoid formula ($PV = \text{anteroposterior diameter} \times \text{left-right diameter} \times \text{vertical diameter} \times \pi / 6$), then PSAD was calculated by $tPSA/PV$ [16].

All mpMRI of prostate examinations were performed with a Discovery MR 750 3.0-tesla (General Electric Medical Systems, Wisconsin, USA). The T1-weighted (T1WI), T2-weighted (T2WI), diffusion-weighted imaging (DWI), and dynamic contrast-enhanced (DCE) perfusion imaging were obtained, as described previously. The parameters of diffusion sequences were the following: (1) Tri-plane positioning scanning: T2 Single Shot Fast Spin Echo (SS FSE) included Echo Time (TE)=80 ms, Repetition Time (TR)=1140 ms, matrix=384×160, Field of View (FOV)=48×48 cm, and depth: 5 mm. (2) FSE was used in axial view T2WI, including TR=10 270 ms, TE=65 ms, depth=3 mm, FOV=40×40 cm, matrix=384×384, and the number of excitations (NEX)=2. (3) FSE was used in axial view T1WI, including TR=607 ms, TE=13 ms, depth=5 mm, FOV=40×40 cm, matrix=286×320, and NEX=1. (4) SE echo-planar imaging and the

Parallel acquisition were used in the Diffusion Tensor Imaging (DTI), including TR=4600 ms, TE=89 ms, FOV=250×250 mm, matrix =220×240, depth=3 mm, the number of the diffusion sensitive gradient directions=5, the diffusion weighting coefficient=800 s/mm², and NEX=2. (5) Liver Acquisition with Volume Acceleration (LAVA) was used in DCE scanning, whose parameters included TR=4600 ms, TE=89 ms, FOV=250×250 mm, matrix=220×240, and depth=3 mm. The images of mpMRI were diagnosed by 2 experienced radiologists, one of whom was above the deputy senior level, in MRI diagnosis. The diagnostic results of DRE were shown as “positive” and “negative”. The results of TRUS and mpMRI for detecting PCa had 3 types: “positive”, “suspicious”, and “negative”.

The criterion standard for diagnosing enrolled patients was TRUS-guided 12-point systematic prostate biopsy, and the diagnosis of specimens was performed using GS. The pathology was diagnosed by an experienced pathologist, who was not aware of clinical information about these patients.

Statistical Analyses

SPSS version 21.0 (IBM, Armonk, NY, USA) and MedCalc version 15.2 (MedCalc Software, Ltd, Acacialaan 22, Ostend, Belgium) were used for statistical analysis. For normally distributed continuous variables, means and standard deviations are used in descriptive analysis, and the 2-sample *t* test or separate variance estimation *t* test was used to analyze differences between groups. Ranked data were described by median and interquartile range (IQR) and analyzed by Mann-Whitney U test. Enumeration data are expressed by rate and percentage and were analyzed with the chi-Square test or continuity correction test. The analysis of correlations between measurement data and enumeration data was performed using the Spearman correlation test. Binary logistic regression with forward stepwise analysis was performed to predict PCa and CS-PCa. We assessed the differences among each clinical parameter and model according to the area under the curve (AUC) from the summary receiver operating characteristic (ROC) curve. Differences with 2-tailed *P* values <0.05 were regarded as statistically significant.

Results

After applying inclusion and exclusion criteria, a total of 181 eligible patients were included. All patients had clear clinical examination reports and pathological results. In these patients, the median age, tPSA, f/t PSA, and PSAD were 75.00 years (IQR: 68.00, 78.00), (7.05±1.40) ng/ml, 0.17 (IQR: 0.11, 0.25), and 0.16 ng/ml·cm³ (IQR: 0.09, 0.22), respectively. According to pathological diagnosis, 109 patients were assigned to the BPH group and 72 patients were assigned to the PCa group. In these PCa patients, 44 patients with GS <7 were assigned

to the NCS-PCa group, while 28 patients with GS ≥7 were assigned to the CS-PCa group.

Characteristics of Clinical Parameters of Enrolled Patients

The characteristics of included patients are shown in **Table 1**. Comparing the BPH group with the PCa group, clinical parameters consisted of f/t PSA (0.21±0.12 vs 0.15±0.06; *P*<0.01), PSAD (0.14 ng/ml·cm³, IQR: 0.07, 0.19 vs 0.19 ng/ml·cm³, IQR: 0.12, 0.25; *P*<0.01) and mpMRI (*P*<0.01) had statistically significant differences, while age (74.00 years, IQR: 66.00-77.00 vs 76.00 years, IQR: 69.00-79.00; *P*=0.07), tPSA (6.91±1.35 ng/ml vs 7.25±1.47 ng/ml; *P*=0.12), DRE (*P*=0.09), and TRUS (*P*=0.72) results did not have significant differences. The PSAD (0.15±0.08 ng/ml·cm³ vs 0.24±0.05 ng/ml·cm³; *P*<0.01) and mpMRI (*P*=0.01) results were significantly different between the NCS-PCa group and CS-PCa group. Conversely, the differences for age (76.00 years, IQR: 69.00-78.00 vs 75.50 years, IQR: 66.50-79.00; *P*=0.86), tPSA (7.14±1.64 ng/ml vs 7.42±1.18 ng/ml; *P*=0.44), f/t PSA (0.14±0.07 vs 0.15±0.04; *P*=0.57), DRE (*P*=0.53), and TRUS (*P*=0.82) were not significant between the NCS-PCa group and CS-PCa group.

In correlation analysis, the pathology and mpMRI had a moderate correlation (*r*=0.36, *P*<0.01) between the BPH group and PCa group, while there was no correlation between other factors. Between the NCS-PCa group and CS-PCa group, pathology results were moderately correlated with PSAD (*r*=0.56, *P*<0.01) and MRI (*r*=0.31, *P*<0.01), respectively.

Verifying the Diagnostic Value of Clinical Parameters by Using Univariate and Multivariate Logistic Regression Analyses in Predicting BPH vs PCa

In univariate analysis, the risk of PCa was positively correlated with log-transformed PSAD (OR=2.52, 95% CI: 1.53-4.15, *P*<0.01) and mpMRI (*P*<0.01) classification, and was negatively correlated with f/t PSA (OR=0.01, 95% CI: 0.00-0.06, *P*<0.01) (**Table 2**). In analysis of diagnostic value, the univariate parameters including f/t PSA (AUC=0.68, 95% CI: 0.61-0.75, *P*<0.01), PSAD (AUC=0.68, 95% CI: 0.62-0.75, *P*<0.01), and grade of mpMRI (AUC=0.69, 95% CI: 0.62-0.77, *P*<0.01) had predictive ability, and log-transformed PSAD (AUC=0.82, 95% CI: 0.76-0.87, *P*<0.01) showed the best predictive power for PCa (**Table 3**).

In binary logistic regression analysis with stepwise regression, f/t PSA (*P*<0.01), log-transformed PSAD (*P*<0.01), and grade of mpMRI (*P*<0.01) were brought into the prediction model. Finally, the logistic model (AUC=0.79, 95% CI: 0.73-0.84, *P*<0.01) for predicting PCa was significantly better than other clinical parameters, and it also had good sensitivity (73.64%) and specificity (64.23%) when its cut-off value was >0.36 (**Figure 1**).

Table 1. Characteristics of clinical information for enrolled patient.

Parameter	All enrolled patients			Patients with PCa		
	BPH group (n=109)	PCa group (n=72)	P	NCS-PCa group (n=44)	CS-PCa group (n=28)	P
Age (years)	74.00 (66.00, 77.00)	76.00 (69.00, 79.00)	0.07 ^a	76.00 (69.00, 78.00)	75.50 (66.50, 79.00)	0.86 ^a
tPSA (ng/ml)	6.91±1.35	7.25±1.47	0.12 ^b	7.14±1.64	7.42±1.18	0.44 ^b
f/t PSA	0.21±0.12	0.15±0.06	<0.01 ^c	0.14±0.07	0.15±0.04	0.57 ^c
PSAD (ng/ml-cm ⁻³)	0.14 (0.07, 0.19)	0.19 (0.12, 0.25)	<0.01 ^a	0.15±0.08	0.24±0.05	<0.01 ^c
DRE [No. (%)] ^d	Positive	3 (2.75)	0.09	3 (6.82)	4 (14.29)	0.53
	Negative	106 (97.25)		65 (90.28)	41 (93.18)	
TRUS [No. (%)] ^e	Positive	21 (19.27)	0.72	8 (18.18)	6 (21.43)	0.82
	Suspicious	38 (34.86)		29 (40.28)	17 (38.64)	
mpMRI [No. (%)] ^e	Negative	50 (45.87)	<0.01	19 (43.18)	10 (35.71)	0.01
	Positive	16 (14.67)		29 (40.28)	11 (25.00)	
mpMRI [No. (%)] ^e	Suspicious	15 (13.76)	<0.01	10 (22.73)	8 (28.57)	0.01
	Negative	78 (71.57)		27 (37.50)	23 (52.27)	

PCa – prostate cancer; NCS-PCa – nonclinically significant prostate cancer; CS-PCa – clinically significant prostate cancer; PSA – prostate-specific antigen; tPSA – total PSA; f/t PSA – free/total PSA; PSAD – PSA density; DRE – digital rectal examination; TRUS – transrectal ultrasound; mpMRI – multiparametric magnetic resonance imaging. ^a These parameters were presented as median (interquartile range) and analyzed by Mann-Whitney U test; ^b These parameters were performed as means±standard deviations and analyzed by two-sample t-test; ^c These parameters were performed as means±standard deviations and analyzed by separate variance estimation t-test; ^d These parameters were analyzed by Continuity Correction test; ^e These parameters were analyzed by Chi-Square test.

Table 2. Verifying the diagnostic value of clinical parameters by using univariate and multivariate logistic regression analyses in predicting BPH vs PCa.

Parameters	Univariable analysis			Multivariable analysis			
	OR (95% CI)	Standard error	P	Coefficient	Standard error	OR (95% CI)	P
Constant	–	–	–	1.95	0.71	–	<0.01
Age	1.03 (0.99, 1.07)	0.02	0.15	–	–	–	–
tPSA	1.18 (0.96, 1.47)	0.11	0.12	–	–	–	–
f/t PSA	0.01 (0.00, 0.06)	1.64	<0.01	-6.61	1.86	0.01 (0.00, 0.05)	<0.01
PSAD ^a	2.52 (1.53, 4.15)	0.25	<0.01	0.88	0.28	2.41 (1.40, 4.16)	<0.01
DRE	3.81 (0.95, 15.24)	0.71	0.06	–	–	–	–
TRUS (1) ^b	1.32 (0.68, 2.56)	0.34	0.42	–	–	–	–
TRUS (2) ^c	1.15 (0.51, 2.60)	0.42	0.74	–	–	–	–
mpMRI (1) ^d	3.08 (1.34, 7.06)	0.42	<0.01	1.04	0.46	2.83 (1.14, 6.99)	0.02
mpMRI (2) ^e	5.24 (2.47, 11.10)	0.38	<0.01	1.41	0.42	4.11 (1.81, 9.33)	<0.01

PCa – prostate cancer; PSA – prostate-specific antigen; OR – odds ratio; CI – confidence interval; tPSA – total PSA; f/t PSA – free/total PSA; PSAD – PSA density; DRE – digital rectal examination; TRUS – transrectal ultrasound; mpMRI – multiparametric magnetic resonance imaging. ^a – Not applicable. ^b Negative vs Equivocal in TRUS; ^c Equivocal vs Suspicious in TRUS; ^d Negative vs Equivocal in mpMRI; ^e Equivocal vs Suspicious in mpMRI.

Table 3. Diagnostic value of clinical parameters and logistic regression models in predicting PCa and CS-PCa.

Parameter	BPH group vs PCa group				NCS-PCa group vs CS-PCa group			
	AUC (95% CI)	Cut-off value	z statistic	P	AUC (95% CI)	Cut-off value	z statistic	P
Age (years)	0.58 (0.50, 0.65)	75	1.79	0.07	0.51 (0.39, 0.63)	78	0.14	0.89
tPSA (ng/ml)	0.56 (0.48, 0.63)	7.63	1.38	0.16	0.56 (0.43, 0.67)	6.16	0.81	0.42
f/t PSA	0.68 (0.61, 0.75)	0.20	4.62	<0.01	0.55 (0.43, 0.68)	0.15	0.72	0.47
PSAD (ng/ml·cm ⁻³)	0.68 (0.62, 0.75)	0.18	4.54	<0.01	0.83 (0.73, 0.91)	0.20	7.20	<0.01
DRE	0.53 (0.46, 0.61)	–	1.81	0.07	0.54 (0.42, 0.66)	–	0.96	0.34
TRUS	0.52 (0.45, 0.60)	–	0.57	0.56	0.54 (0.42, 0.66)	–	0.61	0.54
mpMRI	0.69 (0.62, 0.77)	–	4.87	<0.01	0.67 (0.54, 0.77)	–	2.70	<0.01
Logistic Model	0.79 (0.73, 0.84)	0.36	8.58	<0.01	0.87 (0.77, 0.93)	0.50	8.87	<0.01

PCa – prostate cancer; NCS-PCa – nonclinically significant prostate cancer; CS-PCa – clinically significant prostate cancer; PSA – prostate-specific antigen; tPSA – total PSA; f/t PSA – free/total PSA; PSAD – PSA density; DRE – digital rectal examination; TRUS – transrectal ultrasound; mpMRI – multiparametric magnetic resonance imaging; AUC – area under receiver operating characteristic curve; CI – confidence interval. ‘–’ – Not applicable.

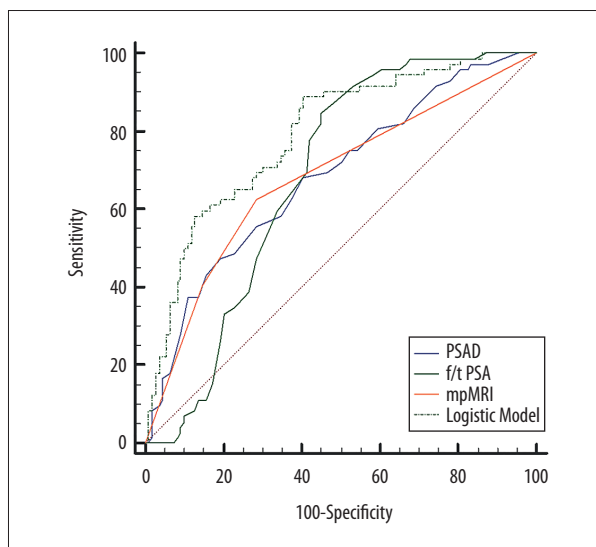


Figure 1. The ROC curve of univariate and multivariate analysis for predicting PCa. PSAD – prostate-specific antigen density; f/t PSA – free/total prostate-specific antigen; mpMRI – multiparametric magnetic resonance imaging.

Verifying the Diagnostic Value of Clinical Parameters by Using Univariate and Multivariate Logistic Regression Analyses in Predicting NCS-PCa and CS-PCa

The risk of CS-PCa increased with log-transformed PSAD (OR=66.46, 95% CI: 6.93-637.02) and grade of mpMRI ($P<0.01$) in univariate analysis. In multivariate analysis, regression analysis also verified the relationship between log-transformed PSAD (OR=85.73, 95% CI: 6.95-1058.08), mpMRI ($P<0.01$) classification,

and risk of CS-PCa increasing (Table 4). In evaluating the diagnostic efficacy, the logistic model (AUC=0.87, 95% CI: 0.77-0.93, $P<0.01$) for predicting CS-PCa was significantly higher than the separate mpMRI (AUC=0.67, 95% CI: 0.54-0.77, $P<0.01$) (Figure 2). When choosing cut-off value >0.50 , the sensitivity and specificity of the logistic model were 71.41% and 81.82%, respectively.

Discussion

PSA has a revolutionary significance for diagnosing PCa, particularly in the diagnosis of early-stage asymptomatic PCa. Notably, when PSA level is between 4 ng/ml and 10 ng/ml, the number of patients with BPH and PCa significantly overlapped [17].

The systematic prostate biopsy usually has been considered as the criterion standard for diagnosing PCa. Nevertheless, this invasive method can cause psychological distress in patients with PSA in the gray area, so it was essential to combine multiple parameters to diagnose these patients [7]. On this issue, many scholars have tried to use regression analysis to construct models to predict PCa. Liu et al used PSA and PSA derivatives to build a prediction model of PCa in 197 patients with PSA in the gray area, which predicted the sensitivity and specificity of PCa to be 75.4% and 75.8%, respectively [18]. However, that study did not consider imageology examination. Liu et al constructed a prediction model of PCa by using PSA derivatives and mpMRI, and the multivariate models performed significantly better for detection of PCa (AUC=0.79) and CS-PCa (AUC=0.84), but the authors did not assess the sensitivity and specificity of these 2 regression models in the article [19].

Table 4. Verifying the diagnostic value of clinical parameters by using univariate and multivariate logistic regression analyses in predicting NCS-PCa and CS-PCa.

Parameters	Univariable analysis			Multivariable analysis			
	OR (95% CI)	Standard error	P	Coefficient	Standard error	OR (95% CI)	P
Constant	–	–	–	5.73	1.97	–	<0.01
Age	1.00 (0.94, 1.06)	0.03	0.89	–	–	–	–
tPSA	1.14 (0.82, 1.58)	0.13	0.43	–	–	–	–
f/t PSA	0.25 (0.01, 1.72)	4.05	0.59	–	–	–	–
PSAD ^a	66.46 (6.93, 637.02)	1.15	<0.01	4.45	1.28	85.73 (6.95, 1058.08)	<0.01
DRE	2.28 (0.47, 11.05)	0.81	0.31	–	–	–	–
TRUS (1) ^b	1.34 (0.46, 3.89)	0.54	0.59	–	–	–	–
TRUS (2) ^c	1.43 (0.39, 5.26)	0.67	0.60	–	–	–	–
mpMRI (1) ^d	4.40 (1.11, 17.48)	0.70	0.03	2.10	0.95	8.17 (1.27, 52.71)	0.02
mpMRI (2) ^e	4.71 (1.40, 15.87)	0.62	0.01	1.35	0.73	3.84 (0.91, 16.17)	0.04

PCa – prostate cancer; NCS-PCa – nonclinically significant prostate cancer; CS-PCa – clinically significant prostate cancer; OR – odds ratio; CI – confidence interval; PSA – prostate-specific antigen; tPSA – total PSA; f/t PSA – free/total PSA; PSAD – PSA density; DRE – digital rectal examination; TRUS – transrectal ultrasound; mpMRI – multiparametric magnetic resonance imaging. ‘–’ – Not applicable. ^a This parameter has been log-transformed; ^b Negative vs Equivocal in TRUS; ^c Equivocal vs Suspicious in TRUS; ^d Negative vs Equivocal in mpMRI; ^e Equivocal vs Suspicious in mpMRI.

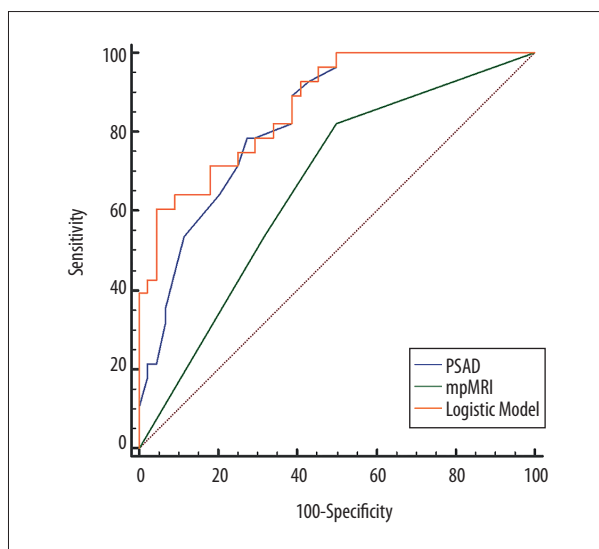


Figure 2. The ROC curve of univariate and multivariate analysis for predicting CS-PCa. PSAD – prostate-specific antigen density; mpMRI – multiparametric magnetic resonance imaging.

In this study, we used logistic regression to analyze not only relevant biochemical indexes PSA including f/t PSA, PSAD, but also some frequently-used clinical examinations such as age, DRE, TRUS, and mpMRI. We also explored which clinical indicators were more valuable in differentiating between NCS-PCa

and CS-PCa. Finally, binary logistic regression analysis, log-transformed PSAD, f/t PSA, and grade of mpMRI have identified the relevance of rising of PCa, and the log-transformed PSAD and grade of mpMRI helped identify NCS-PCa and CS-PCa. The diagnostic models of PCa (sensitivity=73.64%; specificity=64.23%; AUC=0.79), and CS-PCa (sensitivity=71.41%; specificity=81.82%; AUC=0.87) both exhibited good diagnostic utility.

Nowadays, screening and detection PCa primarily depend on DRE, tPSA, f/t PSA, PSAD, TRUS, and mpMRI. Several studies have linked an abnormal DRE and a high GS [20,21]. However, our results did not confirm the statistical significance of this association. The China Prostate Cancer Coalition (CPC) reported that Chinese patients with PCa have the characteristics of smaller PV, higher tPSA level, and higher GS score than their counterparts in Europe and America [22]. Therefore, the main reason why the correlation between DRE and PCa was inconspicuous in the present study is that the enrolled patients were all Chinese. Whether there is racial diversity in the relationship between abnormal DRE and high GS score may require large-scale and multicenter studies.

PSA derivatives, including f/t PSA and PSAD, usually are recommended to assist detection of PCa among patients with a PSA level in the gray area in clinical practice. The free PSA (fPSA) is the fraction of tPSA that does not bind in serum, whose concentration is lower in malignancy patients than in BPH patients,

so detection of f/t PSA is most valuable for clinical application when PSA level are in the gray area [23,24]. Our results also show that increased f/t PSA level (OR=0.01, $P<0.01$) was negatively correlated with the risk of PCa, which was different from the results of Liu et al [19]. The unstable state of fPSA in the serum may be the reason for the inconsistent detection results of f/t PSA, and some scholars believe that f/t PSA may be affected by a variety of clinical factors [25]. Although the reference value of f/t PSA is 0.15, we still suggest detecting PCa by cautiously using f/t PSA.

PSAD is the ratio of tPSA concentration to PV, which offers good guidance on whether to perform a prostate biopsy in patients with a PSA level in the gray zone [26,27]. A previous article reported PSAD value >0.15 ng/ml-cm³ necessitated prostate biopsy [28]. Our results showed PSAD was an independent clinical parameter for predicting of PCa and CS-PCa. However, the cut-off value of PSAD in distinguish BPH from PCa was 0.18 ng/ml-cm³ in our study. The reason why the cut-off value of PSAD is higher than the previous reference value may also be that Chinese patients with PCa have smaller PV and higher tPSA levels [22].

TRUS and mpMRI are both frequently used imaging examinations in prostate disease. Generally, gray-scale TRUS has a certain value in the diagnosis of BPH, but it is not reliable for detecting PCa [6,29]. Our results also verified TRUS had little value for detection of PCa with PSA level in the gray area, while mpMRI including T1WI, T2WI, DWI, and DCE technologies was confirmed to have a perfect diagnostic value, which was similar to other studies [30-32]. Liu et al just reported the AUCs of mpMRI for PCa and CS-PCa were 0.69 and 0.79, respectively [19]. In our study, the sensitivities of mpMRI for predicting PCa and CS-PCa were 0.63 and 0.82, respectively, which is similar to the results of other scholars. Notably, the Prostate Imaging Reporting and Data System (PI-RADS) is a standardized evaluation pattern for prostate mpMRI, whose second version was published in 2015 [33]. PI-RADS second version (PI-RADS V2) showed a better diagnostic value (AUC for PCa=0.79; AUC for CS-PCa=0.86) for evaluating PCa in PSA with gray area [34]. Besides, some scholars reported the PI-RADS score was correlated with the pathological results of PCa, but was not correlated with the levels of PSA [35,36]. Nevertheless, because this retrospective study lacks popularization of PI-RADS, the results of mpMRI for patients were only classified as "positive", "suspicious", and "negative", which resulted in low diagnostic values of predicting PCa and CS-PCa (AUC for PCa=0.69; AUC for CS-PCa=0.67). Therefore, PI-RADS V2 could be used as a dependable standardized evaluation pattern for further promotion in prostate mpMRI for PSA level in the gray area.

Binary logistic regression models also were used to predict and evaluate PCa and CS-PCa among patients with PSA in the gray area. We brought clinical parameters consisting of age, DRE,

tPSA, f/t PSA, log-transformed PSAD, TRUS, and mpMRI into regression analysis to construct the prediction model. Finally, the 2 prediction models both showed better diagnostic value than all single parameters. When selecting cut-off value >0.36 , the sensitivity, specificity, and AUC of predicting PCa model were 73.64%, 64.23%, and 0.79, respectively, which is a more reliable way to predict PCa in clinical practice.

According to GS, PCa patients were divided into the NCS-PCa group (GS <7) and the CS-PCa group (GS ≥ 7), and different groups received different treatments. NCS-PCa could be monitored closely without surgical intervention, which has a good prognosis and a low mortality rate, while high-risk PCa patients must be actively treated [37,38]. Therefore, accurate identification of low-risk PCa patients could reduce the risk of performing unnecessary invasive biopsies, without increasing the risk to patient health [18]. In the present study, we developed a satisfactory diagnostic model for predicting NCS-PCa and CS-PCa, whose sensitivity and specificity were 71.41% and 81.82%, respectively. Compared with the model of Jun Liu et al, who just analyzed PSA and its derivatives for CS-PCa, our prediction model also included mpMRI and had a better detection value (AUC: 0.82 vs 0.87) [18].

Our study was subject to several limitations. Firstly, this was a retrospective study with single-center samples, with drawbacks inherent in the study design. Furthermore, adding more clinical parameters perhaps augment the accuracy of the prediction model, some scholars considered some PCa genomic biomarkers could improve the diagnostic value and avoid unnecessary biopsy [39]. Selvi et al reported that arginine and its metabolites, including plasma arginine, ornithine, arginine to ornithine ratio, and urinary diacetylspermine, could be used as molecular markers to predict PCa when the PSA level is in the gray area, and these biomarkers could be an important research focus in diagnosing PCa [40]. Third, active surveillance (AS), a strategy of management of patients with low-risk prostate cancer, could reduce unnecessary over-treatment [41]. A meta-analysis found the mpMRI-targeted biopsy is a useful addition to systematic confirmation in patients on AS with low-risk PCa [42]. However, the present research has not follow-up this field because AS was carried out late in our hospital. We may consider performing more relevant studies in the future. Nonetheless, the models we built are convenient, and the required parameters are accessible and valuable.

Conclusions

We developed 2 models to predict PCa and CS-PCa. When the best cut-off value is 0.36 in the regression model for the PCa group and 0.50 for the CS-PCa group, the 2 prediction models had satisfactory diagnostic value for PCa and CS-PCa among

patients with PSA in the gray area, which could provide an important reference value for clinical treatment. Prospective studies are needed for further confirmation.

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Conflict of Interest

None.