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# Significant Diagnostic Value of Free-Serum PSA (FPSA)/Prostate-Specific Antigen Density (PSAD) and (F/T)/PSAD for Prostate Cancer of the Chinese Population in a Single Institution

Authors' Contribution:  
Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
Funds Collection G

AE **Li-Bin Nan**  
CF **Xiao-Tao Yin**  
G **Jiang-Ping Gao**

Department of Urology, Chinese People's Liberation Army General Hospital, Beijing, P.R. China

**Corresponding Author:** Jiang-Ping Gao, e-mail: jpgao@163.com  
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**Background:** The aim of this study was to investigate the diagnostic value of (F/T)/PSAD for prostate cancer detection in the Chinese population.

**Material/Methods:** Data were collected retrospectively from patients with prostate cancer or benign prostatic hyperplasia from July 2009 to September 2014. SPSS 19.0 software was used for the receiver operating characteristic curve (ROC), and calculating sensitivity, specificity, and positive predictive values (PPV) and negative predictive values (NPV), respectively. Comparison of the area under ROC (AUC) was performed using the MedCalc v. 10.4.7.0 software.

**Results:** A total of 660 patients (including 251 patients with prostate cancer and 409 patients with prostatic hyperplasia) were included. Prostate volume (PV), prostate-specific antigen density (PSAD), free-serum PSA (FPSA)/PSAD, and free-to-total PSA (F/T)/PSAD had similar AUC ( $P>0.05$ ), and had significantly higher AUC ( $P<0.001$ ) than F/T, total-serum PSA (TPSA), and free-serum PSA (FPSA). Based on the optimal cutoff value, the sensitivity of (F/T)/PSAD and FPSA/PSAD was similar ( $P>0.05$ ), and significantly higher than the PV and PSAD ( $P<0.05$ ). The logistic regression model using a combination of age, FPSA, PV, PSAD, FPSA/PSAD, and (F/T)/PSAD showed higher AUC than each one alone ( $P<0.001$ ).

**Conclusions:** (F/T)/PSAD can be used as a predictor for prostate cancer in the Chinese population aged  $>50$  years and has a significantly lower false negative rate than PSAD and PV with a cutoff value of  $\leq 0.731$ . A new parameter, FPSA/PSAD, has similar diagnostic accuracy comparable to (F/T)/PSAD. The diagnostic value of a combination of age, FPSA, PV, PSAD, FPSA/PSAD, and (F/T)/PSAD needs further investigation.

**MeSH Keywords:** **Diagnosis • Prostate-Specific Antigen • Prostatic Neoplasms**

**Abbreviations:** **PSA** – prostate-specific antigen; **FPSA** – free-PSA; **TPSA** – total-PSA; **F/T** – FPSA/TPSA; **PSAD** – prostate-specific antigen density; **PV** – prostate volume

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## Background

Prostate-specific antigen (PSA) is an essential marker for the screening of prostate cancer with high tissue specificity but has rates for missed diagnosis and misdiagnosis [1–4]. The elevated PSA level is due to a variety of factors [5]. Many benign prostate diseases are also associated with PSA levels ranging from 4 to 10 ng/mL [6–8], resulting in unnecessary prostate biopsies. Some studies have shown a high incidence of prostate cancer when the PSA level is lower than 4.0 ng/mL [9,10].

Moreover, many studies focused their attention on other related parameters, such as free-to-total PSA (F/T) values and prostate-specific antigen density (PSAD), showing higher diagnostic accuracy than that with PSA itself [11–13]. Two parameters, PSAD, and F/T are most commonly used to improve the diagnostic accuracy of PSA. Veneziano et al. [14] combined these 2 parameters and proposed a new parameter (F/T)/PSAD, which was superior to F/T or PSAD alone for the diagnosis of prostate cancer in the Italian population. A previous study in the Chinese population with PSA of 4–10 ng/mL also showed significantly higher specificity with (F/T)/PSAD than F/T and PSAD alone [15]. However, sensitivity and specificity are still not satisfactory. In addition, Lee et al. reported that combination of age, PSA, prostate volume (PV), and digital rectal examination (DRE) status had better prediction ability for prostate cancer than PSA alone [16].

Thus, we further evaluated the diagnostic accuracy of (F/T)/PSAD in 660 Chinese patients with PSA values ranging from 2.5–20 ng/mL and obtained additional evidence for the use of (F/T)/PSAD values in clinical practice for prostate cancer diagnosis. An appropriate new diagnostic parameter FPSA/PSAD was also calculated and analyzed in this study. In addition, the optimal risk prediction model was constructed to increase the diagnostic accuracy of (F/T)/PSAD for prostate cancer diagnosis.

## Material and Methods

### Baseline data

Approval for this study was from the Ethics Committee of the Chinese People's Liberation Army General Hospital, and data collected retrospectively from patients with prostate cancer or benign prostatic hyperplasia who underwent systematic prostate puncture in our hospital from July 2009 to September 2014. Prostate biopsy was by following the guidelines of the Urology Branch of Chinese Medical Association (CUA). Biopsied patients had: 1) hard prostate or irregular shape by DRE; 2) presence of low echo nodules in the periphery of the prostate by transrectal ultrasound; 3) serum-total PSA (TPSA) concentration

>10 ng/mL without limitation on F/T and PSAD; 4) 4 ng/mL <serum TPSA concentration ≤10 ng/mL with the limitation of F/T <0.16 or PSAD >0.15. Biopsy results diagnosed patients with prostate cancer or benign prostatic hyperplasia.

The patients enrolled in this study met the following criteria. Inclusion criteria were: 1) patient age ≥50 years; 2) first prostate puncture (12+X needle); 3) PSA 2.5–20 ng/mL. Exclusion criteria were: 1) history of prostate cancer, prostate surgery, or taking 5- $\alpha$ -reductase inhibitor/drug for treating endocrine dyscrasia in prostate cancer; 2) urinary tract infection or obstruction; 3) diagnosed prostatitis; and 4) undergone prostate massage, DRE, transrectal ultrasound, or cystoscopy within 2 weeks before PSA detection, which might affect serum PSA level.

### Prostate puncture

Informed consent was obtained before performing prostate puncture. Oral antibiotics and cleansing enema were used to prevent infection. With the guidance of color ultrasound, total 12 plus 1–3 needle punctures performed on several sites, including midline of prostate glands, the tip, middle, and bottom of both sides of sagittal and the tip, middle, and bottom of both sides of the peripheral zone of the prostate gland. After a prostate puncture, oral antibiotics were continued for 3 days.

### Transrectal ultrasound

Examination of the prostate was by the transrectal ultrasound using Acuson Sequoia512 (Siemens Medical Solutions USA). PV was calculated according to the formula:  $PV=0.52 \times \text{anterior/posterior diameter (cm)} \times \text{left/right diameter (cm)} \times \text{upper/lower diameter (cm)}$ .

### PSA detection

Venous blood was collected before DRE, transrectal ultrasound, or cystoscopy which might affect the serum PSA level. The TPSA and FPSA levels were determined by the chemiluminescence assay using a fully automated chemiluminescent immunoassay analyzer (Sorin Company, Italy, Liaison-XL). The following parameters were calculated:

$$PSAD=TPSA/(PV)$$

$$F/T=FPSA/TPSA$$

$$(F/T)/PSAD=(FPSA/TPSA)/(TPSA/PV)=(FPSA \times PV)/TPSA^2 [14].$$

In addition, a new parameter was also calculated and analyzed in this study:  $FPSA/PSAD=(FPSA \times PV)/TPSA$

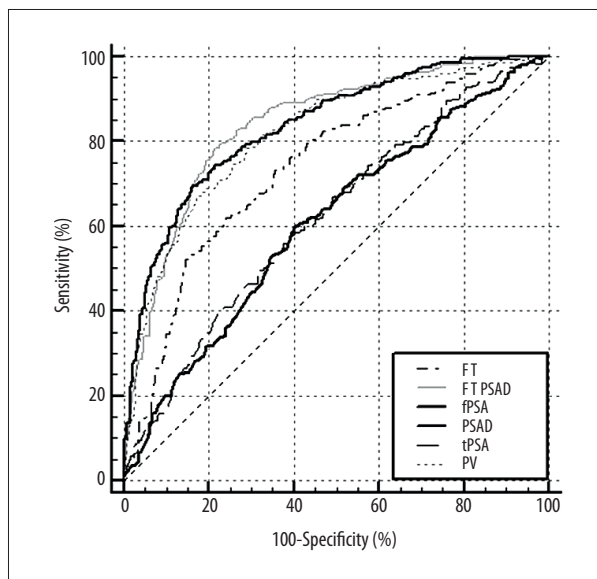
### Statistical analysis

SPSS 19.0 software was used for statistical analysis (SPSS Inc., Chicago, IL, USA) unless otherwise specified. A *P* value <0.05

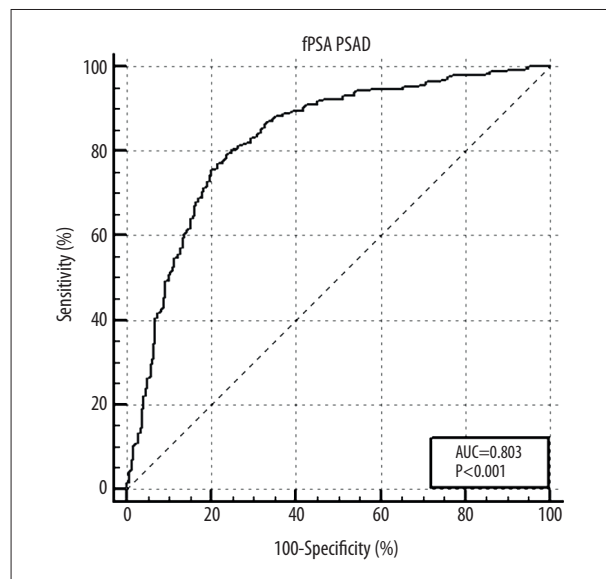
**Table 1.** Comparison of baseline data between 2 groups.

Group	Age (year)	tPSA (ng/mL)	fPSA (ng/mL)	PV (cm <sup>3</sup> )	F/T	PSAD (ng/mL/cm <sup>3</sup> )	(F/T)/PSAD	fPSA/PSAD
Prostate cancer (n=251)	70 (63, 75)	9.64 (6.11, 13.8)	0.9 (0.5, 1.53)	31.12 (23.20, 46.70)	0.095 (0.064, 0.151)	0.281 (0.168, 0.421)	0.327 (0.166, 0.646)	2.885 (1.738, 5.818)
Prostatic hyperplasia (n=409)	74 (71, 77)	8.83 (8.14, 9.52)	2.35 (1.56, 3.04)	93.51 (63.53, 119.22)	0.221 (0.130, 0.302)	0.025 (-0.124, 0.151)	1.612 (0.821, 2.394)	11.177 (6.888, 18.607)
Z	-1.011	-5.317	-4.690	-13.800	-10.388	-14.487	-14.672	-14.244
P	0.312	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Median (interquartile range) was used to show the data and nonparametric test (Mann-Whitney U test) was used to compare data between prostate cancer group and prostatic hyperplasia group because of non-normal distribution. PSA – prostate specific antigen; fPSA – free PSA; tPSA – total PSA; PV – prostate volume; F/T – the ratio of fPSA to tPSA; PSAD – prostate specific antigen density.



**Figure 1.** ROC of (F/T)/PSAD, PSAD, F/T, TPSA, FPSA, and PV for prostate cancer diagnosis. ROC – receiver operating characteristic curves; (F/T) – free-to-total PSA; PSAD – prostate-specific antigen density; TPSA – serum-total PSA; FPSA – serum-free PSA; PV – prostate volume.



**Figure 2.** ROC of fPSA/PSAD for prostate cancer diagnosis. ROC – receiver operating characteristic curves; FPSA – serum-free prostate specific antigen; PSAD – prostate-specific antigen density.

was considered statistically significant. The continuous variables were described by the mean ± standard deviation (SD). Two independent tests, *t*-test and analysis of variance (ANOVA) were used to compare data between groups when the data met the normal distribution. Otherwise, a nonparametric test was used, and the median (interquartile range) was used to show the data. Comparison of percentages was by chi-square test. The receiver operating characteristic curves (ROC) evaluated the diagnostic value of TPSA, FPSA, PV, F/T, PSAD, FPSA/PSAD, and (F/T)/PSAD in patients to determine prostate cancer or exclude prostatic hyperplasia with a prostate biopsy. Youden index was used to determine the optimal cutoff value. The area

under the curve (AUC) was calculated and evaluated using a nonparametric test. The comparison between the AUC of 2 ROC curves was performed by the method of DeLong et al. 1988 [17] using MedCalc v. 10.4.7.0 software (MedCalc Software bvba, Mariakerke, Belgium). Based on the optimal cutoff value, the diagnostic accuracy was assessed using sensitivity, specificity, and positive predictive value (PPV) and negative predictive value (NPV). A stepwise logistic regression analysis was used to find an optimal risk prediction model. The goodness-of-fit of the model ( $\chi^2$ ) was evaluated by the Hosmer-Lemeshow test with  $P>0.05$  as a threshold, with higher *P*-value indicating a better fit.

**Table 2.** Comparison results of ROC curves (*P*-values).

Parameter	tPSA	fPSA	PV	F/T	PSAD	(F/T)/PSAD	fPSA/PSAD
tPSA	NA	NA	NA	NA	NA	NA	NA
fPSA	0.718	NA	NA	NA	NA	NA	NA
PV	<0.001	<0.001	NA	NA	NA	NA	NA
F/T	<0.001	<0.001	<0.001	NA	NA	NA	NA
PSAD	<0.001	<0.001	0.306	<0.001	NA	NA	NA
(F/T)/PSAD	<0.001	<0.001	0.199	<0.001	0.684	NA	NA
fPSA/PSAD	<0.001	<0.001	0.376	<0.001	0.720	0.274	NA

ROC – receiver operating characteristic curves; PSA – prostate specific antigen; fPSA – free PSA; tPSA – total PSA; PV – prostate volume; F/T – the ratio of fPSA to tPSA; PSAD – prostate specific antigen density; PPV – positive predictive value; NPV – negative predictive value; NA – not applicable.

**Table 3.** Comparison of diagnostic accuracy among tPSA, fPSA, F/T, PSAD, and (F/T)/PSAD using the diagnostic parameters.

Parameter	AUC	Optimal cutoff value	Sensitivity	Specificity	PPV	NPV
tPSA	0.623	8.505 (ng/mL)*	0.582	0.606	0.475	0.703
fPSA	0.609	1.075 (ng/mL)#	0.547	0.739	0.547	0.739
PV	0.820	39.226 (cm <sup>3</sup> )#	0.673	0.826	0.703	0.805
F/T	0.741	0.120#	0.622	0.760	0.614	0.766
PSAD	0.836	0.198 (ng/mL/cm <sup>3</sup> )*	0.697	0.836	0.723	0.818
fPSA/PSAD	0.830	6.263 (cm <sup>3</sup> )#	0.773	0.785	0.688	0.850
(F/T)/PSAD	0.840	0.731#	0.785	0.785	0.691	0.856

\* If the data was greater than or equal to this value, the patients can be diagnosed with prostate cancer when using this parameter for predicting prostate cancer; # If the data was lower than or equal to this value, the patients can be diagnosed with prostate cancer when using this parameter for predicting prostate cancer. PSA – prostate specific antigen; fPSA – free PSA; tPSA – total PSA; PV – prostate volume; F/T – the ratio of fPSA to tPSA; PSAD – prostate specific antigen density; PPV – positive predictive value; NPV – negative predictive value.

## Results

### Characteristics of included patients

A total of 660 patients were in this study, including 251 patients with prostate cancer (38%) and 409 patients with prostatic hyperplasia (62%). Nonparametric test (Mann-Whitney U test) compared the data between the prostate cancer group and prostatic hyperplasia group because of non-normal distribution. Table 1 shows no significant difference in age between patients with prostate cancer and prostatic hyperplasia. A significant difference ( $P<0.001$ ) was present in tPSA, fPSA, PV, F/T, PSAD, fPSA/PSAD, and (F/T)/PSAD.

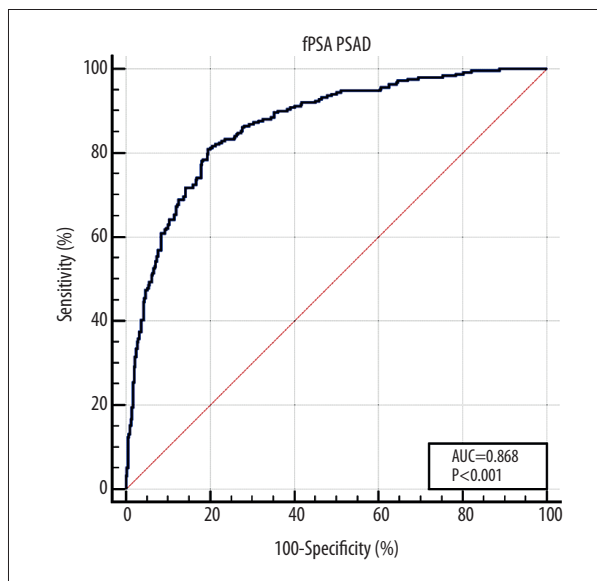
### Diagnostic value of tPSA, fPSA, PV, F/T, PSAD, fPSA/PSAD, and (F/T)/PSAD

The ROC curves of tPSA, fPSA, PV, F/T, PSAD, and (F/T)/PSAD for diagnosis of prostate cancer are shown in Figure 1. The ROC curves of equal to or lower than 6 parameters can be drawn together by MedCalc v. 10.4.7.0 software, thus, the ROC curve of the new parameter fPSA/PSAD are shown in Figure 2. The AUCs of tPSA, fPSA, PV, F/T, PSAD, fPSA/PSAD, and (F/T)/PSAD were 0.623, 0.609, 0.820, 0.741, 0.836, 0.830, and 0.840, respectively. All these parameters had significant diagnostic value based on the nonparametric test ( $P<0.001$ ). Table 2 shows a comparison of results between the AUC of ROC curves. The results showed that PV, PSAD, fPSA/PSAD, and (F/T)/PSAD had similar AUC ( $P>0.05$ ), and they had significantly higher AUC ( $P<0.001$ ) than F/T, tPSA, and fPSA.

**Table 4.** Results of logistic regression analysis.

	Coefficient	SE of coefficient	P-value	OR	95% CI of OR		
					Lower limit	Upper limit	
Age	0.040	0.014	0.004	1.041	1.013	1.069	
fPSA	-0.647	0.260	0.013	0.523	0.315	0.871	
PV	-0.023	0.007	0.002	0.977	0.963	0.992	
Model	PSAD	5.606	1.319	0.000	272.056	20.492	3611.858
	(F/T)/PSAD	-1.059	0.292	0.000	0.347	0.196	0.615
	fPSA/PSAD	0.120	0.063	0.055	1.128	0.997	1.275
	Constant	-2.224	1.075	0.039	0.108	NA	NA

Model equation:  $\log P/1-P = -2.224 + 0.040 \cdot \text{Age} - 0.647 \cdot \text{fPSA} - 0.023 \cdot \text{PV} + 5.606 \cdot \text{PSAD} - 1.059 \cdot ((\text{F/T})/\text{PSAD}) + 0.120 \cdot (\text{fPSA}/\text{PSAD})$ ,  
P=probability of prostatic cancer. PSA – prostate specific antigen; fPSA, – free PSA; tPSA – total PSA; PV – prostate volume;  
F/T – the ratio of fPSA to tPSA; PSAD – prostate specific antigen density; SE – standard error; OR – odds ratio; CI – confidence interval.



**Figure 3.** ROC of logistic regression model for prostate cancer diagnosis. ROC – receiver operating characteristic curve.

Table 3 shows the optimal cutoff values for PV, PSAD, fPSA/PSAD, and (F/T)/PSAD of  $\leq 39.226$  (cm),  $\geq 0.198$  (ng/mL/cm<sup>3</sup>),  $\leq 6.263$  cm<sup>3</sup>, and  $\leq 0.731$ , respectively for predicting prostate cancer. Based on these cutoff values, sensitivity, specificity,

PPV, and NPV were calculated. Among them, the sensitivity of (F/T)/PSAD and fPSA/PSAD was similar between each other ( $P > 0.05$ ), and it was significantly higher than PV and PSAD ( $P < 0.05$ ). There was no significant difference in the specificity, PPV, and NPV among PV, PSAD, fPSA/PSAD, and (F/T)/PSAD ( $P > 0.05$ ).

#### Determination of optimal risk prediction model

All the parameters (including age, tPSA, fPSA, PV, F/T, PSAD, and (F/T)/PSAD) were analyzed using multiple regression analysis. The results showed that fPSA (OR=0.523, 95% CI=0.315–0.871,  $P=0.013$ ), PV (OR=0.977, 95% CI=0.963–0.992,  $P=0.002$ ), PSAD (OR=272.056, 95% CI=20.492–3611.858,  $P < 0.001$ ), and (F/T)/PSAD (OR=0.347, 95% CI=0.196–0.615,  $P < 0.001$ ) were independent predictors of prostate cancer regardless of age (Table 4). Hosmer-Lemeshow test showed good regression model fitting ( $P=0.890$ ). Thus, the diagnostic value of the model was evaluated. The ROC curve was shown in Figure 3. The AUC for this model was 0.868, which was significantly higher ( $P < 0.001$ ) than that of tPSA, fPSA, PV, F/T, PSAD, fPSA/PSAD, and (F/T)/PSAD (Table 5). In addition, based on the Yuden index of 0.613, the sensitivity, specificity, PPV, and NPV of this model were 0.809, 0.804, 0.717, and 0.873, respectively, which were similar ( $P > 0.05$ ) to fPSA/PSAD and (F/T)/PSAD. However, the NPV of this model was significantly higher ( $P=0.044$ ) than that of PSAD.

**Table 5.** Comparison results of ROC curves between the regression model and tPSA, fPSA, PV, F/T, PSAD and (F/T)/PSAD (P-values).

Parameter	tPSA	fPSA	PV	F/T	PSAD	fPSA/PSAD	(F/T)/PSAD
Model	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

ROC – receiver operating characteristic curves; PSA – prostate specific antigen; tPSA – total PSA; fPSA – free PSA; PV – prostate volume; F/T – the ratio of fPSA to tPSA; PSAD – prostate specific antigen density.

## Discussion

Results from this study share similarity with an earlier study by Yan et al. (2007) [15], which showed significantly higher specificity of (F/T)/PSAD than F/T. Although the specificity of (F/T)/PSAD appeared higher than that of PSAD, it was not statistically significant. Moreover, the sensitivity of (F/T)/PSAD was significantly higher than F/T and PSAD. An earlier study showed different diagnostic accuracy of PSAD in patients with different PSA values [18], and these conflicting results could be due to different PSA values and other confounding factors (e.g., region, sample size, and age). Further studies are needed to investigate the factors affecting the diagnostic accuracy of PSA parameters for prostate cancer detection.

In addition, compared to an earlier study, this study has some advantages. Firstly, we analyzed the diagnostic accuracy of PV for prostate cancer. Based on the results of this study, we conclude that patients with  $PV \leq 39.226 \text{ cm}^3$  had a higher risk of prostate cancer. Moreover, the diagnostic accuracy of PV for prostate cancer was significantly higher than TPSA, FPSA, and F/T. Earlier studies showed that PV might influence the diagnostic accuracy of PSA [16,19], and an increase in the detection rate of prostate cancer along with a decrease in PV [20]. No study to date reported the diagnostic accuracy of PV for prostate cancer previously, hence, this is the first study comparing the diagnostic accuracy of PV with the PSA parameters (TPSA, FPSA, F/T, PSAD, and (F/T)/PSAD). Secondly, age is a prominent factor leading to an increase in prostate cancer risk [21–23], and multiple regression analysis performed in this study showed PV, PSAD, and (F/T)/PSAD as independent predictors of prostate cancer regardless of age. Thirdly, the sample size in this study was higher than in the study of Yan et al. [15]. In addition, a newly calculated parameter FPSA/PSAD analyzed in this study showed similar diagnostic accuracy with (F/T)/PSAD. Further studies are necessary to validate this new parameter.

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In this study, the optimal cutoff value for PSAD was 0.198, similar to the one reported (0.20) by Xie et al. (2016) [24], and Matsuyama et al. [11]. Xie et al. (2016) [24] analyzed the PSAD variation rate (PSADVR) and showed significantly higher diagnostic accuracy than PSAD. PSADVR may also be a potential parameter that increases the predictive accuracy of PSA. Further studies are required to compare the diagnostic accuracy of PSADVR and (F/T)/PSAD for prostate cancer detection. Furthermore, some limitations of this study should be noted. Firstly, due to the CUA guidance in China, men with PSA between 4 and 10 ng/mL received biopsy only if  $F/T < 0.16$  or  $PSAD > 0.15$ , so there was bias in this study. Secondly, being a retrospective study, some data (such as voiding symptoms, family history, and cancer grades) could not be analyzed due to lack of availability.

## Conclusions

Within a PSA range of 2.5–20 ng/mL, the diagnostic value of (F/T)/PSAD, FPSA/PSAD, PV, or PSAD is significantly higher compared than F/T, FPSA, and TPSA. Moreover, (F/T)/PSAD has higher sensitivity than PV, F/T, or PSAD alone, with the cutoff values for (F/T)/PSAD  $\leq 0.731$ . Being a new parameter, FPSA/PSAD has similar diagnostic accuracy of (F/T)/PSAD. The combined diagnostic value using age, FPSA, PV, PSAD, FPSA/PSAD, and (F/T)/PSAD needs further investigation, as it had a significantly higher AUC and increased NPV when analyzed using a logistic regression model.

## Conflicts of interest

None.

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