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ORIGINAL ARTICLE

Prostate Cancer

# Peripheral zone PSA density: a predominant variable to improve prostate cancer detection efficiency in men with PSA higher than 4 ng ml<sup>-1</sup>

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To improve the diagnostic efficiency of prostate cancer (PCa) and reduce unnecessary biopsies, we defined and analyzed the diagnostic efficiency of peripheral zone prostate-specific antigen (PSA) density (PZ-PSAD). Patients who underwent systematic 12-core prostate biopsies in Shanghai General Hospital (Shanghai, China) between January 2012 and January 2018 were retrospectively identified ( $n = 529$ ). Another group of patients with benign prostatic hyperplasia ( $n = 100$ ) were randomly preselected to obtain the PSA density of the non-PCa cohort (N-PSAD). Prostate volumes and transition zone volumes were measured using multiparameter magnetic resonance imaging (mpMRI) and were combined with PSA and N-PSAD to obtain the PZ-PSAD from a specific algorithm. Receiver operating characteristic (ROC) curve analysis was used to assess the PCa detection efficiency in patients stratified by PSA level, and the area under the ROC curve (AUC) of PZ-PSAD was higher than that of PSA, PSA density (PSAD), and transition zone PSA density (TZ-PSAD). PZ-PSAD could amend the diagnosis for more than half of the patients with inaccurate transrectal ultrasonography (TRUS) and mpMRI results. When TRUS and mpMRI findings were ambiguous to predict PCa (PIRADS score  $\leq 3$ ), PZ-PSAD could increase the positive rate of biopsy from 21.7% to 54.7%, and help 63.8% (150/235) of patients avoid unnecessary prostate biopsy. In patients whose PSA was 4.0–10.0 ng ml<sup>-1</sup>, 10.1–20.0 ng ml<sup>-1</sup>, and >20.0 ng ml<sup>-1</sup>, the ideal PZ-PSAD cut-off value for predicting clinically significant PCa was 0.019 ng ml<sup>-2</sup>, 0.297 ng ml<sup>-2</sup>, and 1.180 ng ml<sup>-2</sup>, respectively (sensitivity >90%). Compared with PSA, PSAD, and TZ-PSAD, the efficiency of PZ-PSAD for predicting PCa is the highest, leading to fewer missed diagnoses and unnecessary biopsies.

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**Keywords:** benign prostate hyperplasia; detection efficiency; peripheral zone prostate-specific antigen density; prostate biopsy; prostate-specific antigen; prostatic neoplasm

## INTRODUCTION

Prostate cancer (PCa) is one of the most common malignancies among men worldwide.<sup>1,2</sup> With the aging of populations and changes in dietary and environmental factors, the incidence of prostate cancer has significantly increased.<sup>3</sup> PCa patients in which the disease is detected late and those with a high degree of malignancy have a poor prognosis. Despite the effectiveness of androgen deprivation therapy (ADT) in the early stages of the disease, almost all patients deteriorate to castration-resistant prostate cancer (CRPC), which eventually leads to death.<sup>4</sup> Therefore, early effective prostate cancer screening strategies are urgently needed to enable the identification of patients with PCa.

Prostate-specific antigen (PSA) has been an important screening indicator for prostate cancer in clinical practice.<sup>5</sup> However, its main drawback is the lack of specificity and low diagnostic efficacy.<sup>6</sup> Age-related benign prostatic hyperplasia (BPH) and prostatitis may also alter PSA values.<sup>7</sup> Prostate volume (PV) is another strong predictor, and research into a volume-based prostate cancer identification strategy

is worth exploring.<sup>8</sup> One study reported that PSA density (PSAD), the ratio of PSA to PV, could increase the detection efficiency of PCa.<sup>9</sup> Furthermore, another study extracted transition zone volume (TZV) from the PV and defined the ratio of total prostate-specific antigen (tPSA) to TZV as the transition zone of PSA density (TZ-PSAD), which improved the PCa detection efficiency for the PSA “gray zone”.<sup>10</sup> However, these indicators preliminarily combine volume with PSA and require further precise quantification.

It is generally known that PCa mainly originates from the peripheral zone (PZ). Although a small portion of PCa originates from the transition zone (TZ), the degree of cell differentiation and disease prognosis are significantly better than those of prostate cancer originating from the PZ.<sup>11</sup> This suggests that peripheral zone PSA density (PZ-PSAD) is more representative and targeted in predicting PCa. In order to define and calculate PZ-PSAD, we extracted the volume of the PZ (PZV) and the PSA values corresponding to the PZ and proposed a precise formula for PZ-PSAD. We compared the

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diagnostic efficacies of PZ-PSAD, PSA, PSAD, and TZ-PSAD and sought a better indicator to provide guidance for the diagnosis and screening of PCa.

## PATIENTS AND METHODS

### Patients

From January 2012 to January 2018, 529 males with suspected PCa underwent transrectal ultrasound-guided 12-core systematic prostatic biopsy in Shanghai General Hospital (Shanghai, China). The criteria for prostate biopsy were PSA level  $>4$  ng ml<sup>-1</sup> and/or abnormal findings on digital rectal examination (DRE), transrectal ultrasound (TRUS), or prostatic multiparameter magnetic resonance imaging (mpMRI). Those with an unclear history of prior medications and those with a history of 5 $\alpha$ -reductase inhibitor treatment were excluded from the study cohort. After biopsy, patients with a pathological diagnosis of prostatic intraepithelial neoplasia or atypical small acinar proliferation were also excluded. Another 100 patients with BPH, who underwent prostatic hyperplasia surgery in Shanghai General Hospital and who had benign pathology with no malignant tumors, were randomly preselected. Their average PSA density served as the prostate-specific antigen density of the non-PCa cohort (N-PSAD), a parameter in the range of PSA density in the non-PCa cohort. This study was approved by the Ethics Committees of Shanghai General Hospital (2014KY054). All patients enrolled in the study provided informed consent and demonstrated good compliance.

### Clinical data

Patients' baseline data, including age, PSA value, PV, TZV, and DRE; and TRUS and mpMRI findings, were collected. For patients with PCa, we obtained the Gleason score of the biopsy specimen, the number of positive cores after biopsy, and clinical tumor stage after radical surgery for PCa. In the mpMRI results, those with abnormal heterogeneous nodules in the mpMRI images and a Prostate Imaging Reporting and Data System (PIRADS) score  $>3$  were registered as "positive," and those without suspicious nodules or a PIRADS score  $\leq 3$  were registered as "negative." The mpMRI was also used to measure the length, width, and height of the entire prostate and TZ by a radiologist. In the mpMRI image (**Supplementary Figure 1**), the transverse diameter (A), anteroposterior diameter (B) of the transition zone and the transverse diameter (C), and anteroposterior diameter (D) of the entire prostate are measured on a horizontal section. The superoinferior diameter of the transition zone (E) and that of the entire prostate (F) were measured on the sagittal plane. The PV was measured at the boundary of the prostate capsule, and the TZV was measured at the boundary of the fibrous layer of the TZ. The PV and TZV were calculated using the following ellipsoid volume formula: volume (ml) =  $(\pi/6) \times$  anteroposterior diameter (cm)  $\times$  transverse diameter (cm)  $\times$  superoinferior diameter (cm).

The PZ-PSAD was calculated using the following formula: 
$$\text{PZ-PSAD} = \frac{\text{PSA} - (\text{N-PSAD} \times \text{TZV})}{\text{PV} - \text{TZV}}$$
 The numerator "PSA - (N - PSAD  $\times$  TZV)" is the PSA value corresponding to the PZ, which was obtained by subtracting the PSA corresponding to the TZ from the total PSA. The denominator "PV-TZV" is the volume of the PZ. N-PSAD is the average PSA density obtained from the standardized BPH patients ( $n = 100$ ).

### Biopsy procedure and pathological diagnosis

The transrectal systematic 12-core prostate biopsy was performed in patients with left lateral decubitus and local infiltration of mucosa; lidocaine gel (Kangye, Handan, China) was administered. Two

experienced urologists performed the TRUS-guided biopsies and used the tips of the BARD MAGNUM instrument (Bard, Covington, GA, USA) with a penetration depth of 22 mm. Oral antibiotics, such as cephalosporin, quinolone, or metronidazole (Xinyi, Shanghai, China), and hemostatic agents, such as amino cyclic acid (Tiancheng, Changchun, China) or hemocoagulase (Aohong, Jinzhou, China), were administered immediately after the transrectal prostate biopsy for 3 days. After formalin fixation and paraffin embedding, the pathological sections were examined by two independent pathologists. The final pathological report included a gross description, site localization, pathological diagnosis, the number of positive cores, and Gleason score.

### Statistical analyses

Mann-Whitney *U* test was used to compare the differences in age, PSA, PV, PSAD, TZ-PSAD, and PZ-PSAD between the PCa and non-PCa groups. Pearson's Chi-square ( $\chi^2$ ) test or Fisher's exact test was used to compare DRE, TRUS, and mpMRI findings and the PCa detection rates between the groups. The Kruskal-Wallis test was used to compare Gleason scores and clinical tumor stages between the groups with PSA levels of 4.0–10.0 ng ml<sup>-1</sup>, 10.1–20.0 ng ml<sup>-1</sup>, and  $>20.0$  ng ml<sup>-1</sup>. Analysis of variance (ANOVA) was used to compare differences in age, PSA, PV, PSAD, TZ-PSAD, PZ-PSAD, and the number of positive cores between the groups with PSA levels of 4.0–10.0 ng ml<sup>-1</sup>, 10.1–20.0 ng ml<sup>-1</sup>, and  $>20.0$  ng ml<sup>-1</sup>. Area under the receiver operating characteristic (ROC) curves (AUCs) were used to calculate the efficacy of PZ-PSAD, PSA, PSAD, and TZ-PSAD for detecting PCa. The diagnostic efficacy for PCa was also assessed using different PZ-PSAD, PSA, PSAD, and TZ-PSAD cutoff values in men with PSA levels of 4.0–10.0 ng ml<sup>-1</sup>, 10.1–20.0 ng ml<sup>-1</sup>, 4.0–20.0 ng ml<sup>-1</sup>, and  $>20.0$  ng ml<sup>-1</sup>. The following formula can be used to evaluate the efficiency of PCa diagnosis at different cutoff points for each volume-adjusted PSA parameter: total efficiency = sensitivity  $\times$  specificity. The cutoff point with the greatest efficiency is considered the optimal threshold for diagnosing PCa.

All statistical analyses were performed using IBM SPSS version 23.0 (IBM Co., Armonk, NY, USA) and MedCalc version 11.6 (MedCalc software, Acaciaaan, Ostend, Belgium). Data were presented as mean  $\pm$  standard deviation (s.d.) or median (interquartile range [IQR]) for continuous proportional and categorical variables, respectively. All statistical tests were two sided, and statistical significance was set at  $P < 0.05$ .

## RESULTS

Comparisons of the clinical characteristics between PCa and non-PCa patients in the study cohort are shown in **Table 1**. Overall, 44.6% (236/529) of the patients were histologically diagnosed with PCa. The differences in age, PSA, PV, PSAD, TZ-PSAD, and PZ-PSAD and DRE, TRUS, and mpMRI findings in patients with and without PCa were all significantly different (all  $P < 0.01$ ). Patients with PCa were older and had higher values of PZ-PSAD, PSA, PSAD, and TZ-PSAD and positive findings on DRE, TRUS, and mpMRI than did patients with benign pathology. The mean value of PZ-PSAD between PCa and non-PCa groups differed the most (29.10 times), compared with PSA (5.24 times), PSAD (6.23 times), and TZ-PSAD (4.84 times). Similarly, the median value of PZ-PSAD between the two groups differed the most (7.08 times) among the four parameters, and the quartile interval of PZ-PSAD did not overlap between the two groups. This indicates that PCa and non-PCa patients have different ranges of PZ-PSAD data sets, and that PZ-PSAD best reflects the difference between the PCa and non-PCa groups.

**Table 1: Comparison of clinical characteristics between prostate cancer and nonprostate cancer patients in the study cohort**

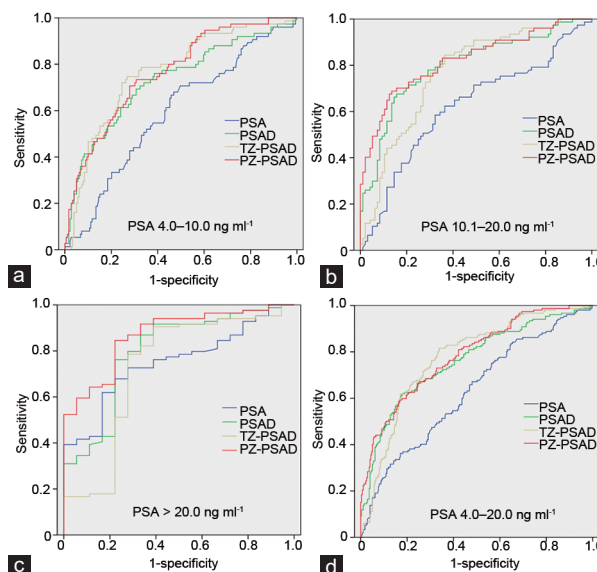
Group	PCa	Non-PCa	P
Cases, n (%)	236 (44.6)	293 (55.4)	
Age (year)			
Median (IQR)	70 (66–77)	66 (62–70)	
Mean±s.d.	71.26±7.46	66.71±6.72	<0.001 <sup>a</sup>
PSA value (ng ml <sup>-1</sup> )			
Median (IQR)	15.68 (8.49–36.79)	8.32 (5.82–12.41)	
Mean±s.d.	56.51±158.17	10.79±9.75	<0.001 <sup>a</sup>
Prostate volume (ml)			
Median (IQR)	40.13 (30.99–61.77)	45.79 (61.78–82.00)	
Mean±s.d.	49.64±28.56	67.09±32.96	<0.001 <sup>a</sup>
PSAD (ng ml <sup>-2</sup> )			
Median (IQR)	0.389 (0.198–0.987)	0.141 (0.098–0.198)	
Mean±s.d.	1.209±3.243	0.194±0.233	<0.001 <sup>a</sup>
TZ-PSAD (ng ml <sup>-2</sup> )			
Median (IQR)	0.716 (0.394–1.659)	0.255 (0.149–0.385)	
Mean±s.d.	1.853±4.258	0.383±0.523	<0.001 <sup>a</sup>
PZ-PSAD (ng ml <sup>-2</sup> )			
Median (IQR)	0.659 (0.235–2.274)	0.093 (-0.044–0.228)	
Mean±s.d.	6.053±31.264	0.208±0.984	<0.001 <sup>a</sup>
DRE (n)			
Normal	112	265	
Positive	124	28	<0.001 <sup>b</sup>
TRUS findings (n)			
Normal	87	252	
Positive	149	41	<0.001 <sup>b</sup>
mpMRI findings (n)			
Normal	57	215	
Positive	179	78	<0.001 <sup>b</sup>

<sup>a</sup>Mann-Whitney *U* test; <sup>b</sup> $\chi^2$  analysis. PCa: prostate cancer; IQR: interquartile range; s.d.: standard deviation; PSA: prostate-specific antigen; PSAD: prostate-specific antigen density; TZ-PSAD: transition zone prostate-specific antigen density; PZ-PSAD: peripheral zone prostate-specific antigen density; DRE: digital rectal examination; TRUS: transrectal ultrasound; mpMRI: multiparameter magnetic resonance imaging

The clinical characteristics of patients stratified according to different PSA levels are compared in **Supplementary Table 1**. In all, 254, 173, and 102 patients had PSA values of 4.0–10.0 ng ml<sup>-1</sup>, 10.1–20.0 ng ml<sup>-1</sup>, and >20.0 ng ml<sup>-1</sup>, respectively. The rates of PCa detection were significantly different in men with PSA values of 4.0–10.0 ng ml<sup>-1</sup>, 10.1–20.0 ng ml<sup>-1</sup>, and >20.0 ng ml<sup>-1</sup> (29.5%, 44.5%, and 82.4%, respectively; *P* < 0.01). The age, PZ-PSAD, PSAD, and TZ-PSAD and DRE, TRUS, and mpMRI findings of patients stratified according to the three different PSA levels were significantly different (all *P* < 0.01). Compared with patients with lower levels of PSA, those with higher levels of PSA were older and had higher PZ-PSAD, PSAD, and TZ-PSAD values and rates of positive findings on DRE, TRUS, and mpMRI (all *P* < 0.01).

The clinical tumor characteristics, such as the Gleason score, clinical tumor stage, number of positive cores, and the DRE and TRUS findings in PCa patients with different PSA levels were significantly different, as shown in **Table 2** (all *P* < 0.05). The clinical characteristics of the 100 patients with BPH are shown in **Supplementary Table 2**. The average PSA density of these standardized BPH patients was 0.182 ± 0.177 ng ml<sup>-2</sup> (N-PSAD).

The ROC analyses of parameters for the detection of PCa are shown in **Supplementary Table 3** and **Figure 1**. Clearly, PZ-PSAD had the largest AUC and the greatest accuracy for discriminating PCa from non-PCa, followed by TZ-PSAD, PSAD, and PSA. In men with PSA levels of 4.0–10.0 ng ml<sup>-1</sup>, 10.1–20.0 ng ml<sup>-1</sup>, and >20.0 ng ml<sup>-1</sup>, the ideal PZ-PSAD cutoff values for predicting PCa were 0.105 ng ml<sup>-2</sup>,



**Figure 1:** Receiver operating characteristic curve analyses of PSA, PSAD, TZ-PSAD, and PZ-PSAD in detecting prostate cancer in patients with PSA levels of (a) 4.0–10.0 ng ml<sup>-1</sup>, (b) 10.1–20.0 ng ml<sup>-1</sup>, (c) >20.0 ng ml<sup>-1</sup>, and (d) 4.0–20.0 ng ml<sup>-1</sup>. PSA: prostate-specific antigen; PSAD: PSA density; TZ-PSAD: transition zone PSAD; PZ-PSAD: peripheral zone PSAD.

0.436 ng ml<sup>-2</sup>, and 1.803 ng ml<sup>-2</sup>, respectively. Among the PCa patients, 197 patients had a Gleason score ≥ 7 or a pathological grade ≥ T2b,

**Table 2: Clinical tumor characteristics in men with prostate-specific antigen levels of 4.0–10.0 ng ml<sup>-1</sup>, 10.1–20.0 ng ml<sup>-1</sup>, and >20 ng ml<sup>-1</sup>**

Group	PSA 4.0–10.0 ng ml <sup>-1</sup>	PSA 10.1–20.0 ng ml <sup>-1</sup>	PSA >20.0 ng ml <sup>-1</sup>	P
Case, n (%)	75 (29.5)	77 (44.5)	84 (82.4)	
Gleason score, n (%)				
≤6	35 (46.7)	30 (39.0)	19 (22.6)	<0.001 <sup>a</sup>
7	36 (48.0)	32 (41.6)	31 (36.9)	
≥8	4 (5.3)	15 (19.5)	34 (40.5)	
Clinical tumor stage, n (%)				
T1c–T2a	37 (49.3)	23 (29.9)	16 (19.0)	<0.001 <sup>a</sup>
T2b	24 (32.0)	30 (39.0)	38 (45.2)	
T2c–T4	14 (18.7)	24 (31.2)	30 (35.7)	
Number of positive cores, mean±s.d.	4.32±2.78	5.51±3.39	7.06±3.30	<0.001 <sup>b</sup>
DRE (+), n (%)	31 (41.3)	33 (42.9)	60 (71.4)	<0.001 <sup>c</sup>
TRUS findings (+), n (%)	40 (53.3)	44 (57.1)	65 (77.4)	0.003 <sup>c</sup>
mpMRI (+), n (%)	52 (69.3)	57 (74.0)	70 (83.3)	0.108 <sup>c</sup>

<sup>a</sup>Kruskal-Wallis test; <sup>b</sup>ANOVA; <sup>c</sup>χ<sup>2</sup> analysis. PSA: prostate-specific antigen; DRE: digital rectal examination; TRUS: transrectal ultrasound; mpMRI: multiparameter magnetic resonance imaging; s.d.: standard deviation; ANOVA: analysis of variance; DRE (+): touch hard or suspicious nodules in the prostate; TRUS findings (+): find suspicious nodules in the image; mpMRI (+): with a PIRADS score > 3

and we designated these patients to have clinically significant PCa. When a sensitivity of at least 90% is required, in men with PSA levels of 4.0–10.0 ng ml<sup>-1</sup>, 10.1–20.0 ng ml<sup>-1</sup>, and >20.0 ng ml<sup>-1</sup>, the ideal PZ-PSAD cutoff values for predicting clinically significant PCa were 0.019 ng ml<sup>-2</sup>, 0.297 ng ml<sup>-2</sup>, and 1.180 ng ml<sup>-2</sup>, respectively (Table 3).

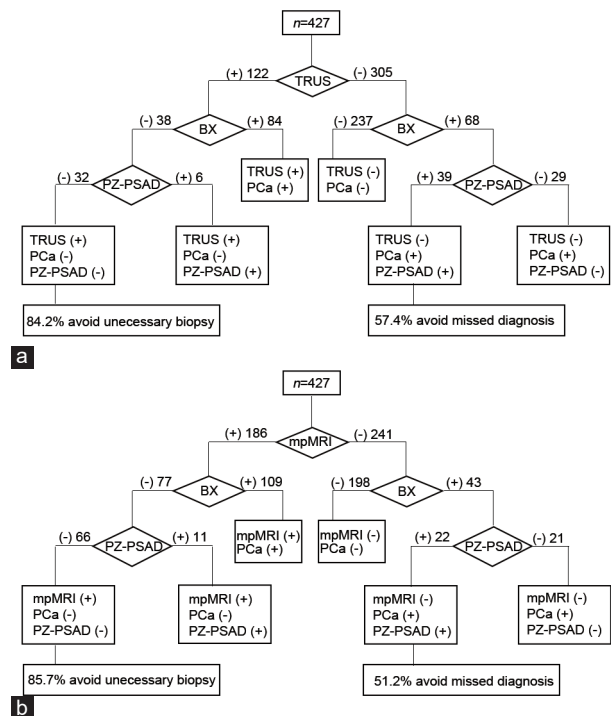
We further compared the diagnostic efficiency between PSA and PZ-PSAD in the group with PSA levels that ranged from 4.0 ng ml<sup>-1</sup> to 20.0 ng ml<sup>-1</sup>. The optimal cutoff values of PSA and PZ-PSAD to predict PCa were 7.895 ng ml<sup>-1</sup> and 0.258 ng ml<sup>-2</sup>, respectively. Compared with PSA, PZ-PSAD could increase the positive rate of biopsy from 43.5% to 65.7%, and help 68.9% (91/132) of the patients avoid unnecessary prostate biopsy.

We evaluated the efficacy of PZ-PSAD as a diagnostic aid in patients with inaccurate TRUS and mpMRI results (Figure 2). In 427 patients with PSA levels that ranged from 4.0 ng ml<sup>-1</sup> to 20.0 ng ml<sup>-1</sup>, 77 patients in the non-PCa group had positive mpMRI findings (Figure 2b). Among them, 66 (85.7%) patients with PZ-PSAD values <0.258 ng ml<sup>-2</sup> (diagnostic cutoff value) could avoid unnecessary biopsies by screening of PZ-PSAD. Similarly, 43 PCa patients had negative mpMRI findings, of which 22 (51.2%) with PZ-PSAD values ≥0.258 ng ml<sup>-2</sup> could avoid a missed diagnosis by screening of PZ-PSAD. On TRUS examination (Figure 2a), it was found that PZ-PSAD could help 32 (84.2%) patients avoid unnecessary biopsies and 39 (57.4%) patients avoid a missed diagnosis.

We further evaluated the efficacy of PZ-PSAD to diagnose PCa when TRUS and mpMRI findings were ambiguous to diagnose PCa (Table 4). Among 235 patients with negative mpMRI and TRUS findings, 51 (21.7%) patients were histologically diagnosed with PCa. The optimal cutoff value of PZ-PSAD obtained by ROC curve analysis was used to screen patients. Only 31.9% (75/235) of the patients with PZ-PSAD (+) required a biopsy and 80.4% (41/51) of the PCa patients could be detected. Among the 10 PCa patients with PZ-PSAD (-), three patients had a Gleason score of 7 and seven patients had a Gleason score of 6; all patients were medium- and low-risk PCa patients. PZ-PSAD could increase the positive rate of biopsy from 21.7% to 54.7% and help 63.8% (150/235) of the patients avoid unnecessary prostate biopsy.

## DISCUSSION

This project was undertaken to propose a “rigorous,” “efficient,” and “practical” index to diagnose PCa. We designed a “rigorous” formula for PZ-PSAD by combining the PSA value with TZV, PZV, and the baseline N-PSAD. Our findings indicate that PZ-PSAD is “efficient” and



**Figure 2:** Combined with PZ-PSAD, (a) TRUS and (b) mpMRI can be more efficient in PCa diagnosis and help patients avoid unnecessary prostate biopsy and missed diagnosis. TRUS: transrectal ultrasound; mpMRI: multiparameter magnetic resonance imaging; PZ-PSAD: peripheral zone prostate-specific antigen density; PCa: prostate cancer; Bx: transrectal systematic 12-core prostate biopsy; (-): negative; (+): positive; PZ-PSAD (-): PZ-PSAD <0.258 ng ml<sup>-2</sup>; PZ-PSAD (+): PZ-PSAD ≥0.258 ng ml<sup>-2</sup>.

has a diagnostic efficacy superior to that of PSA, PSAD, and TZ-PSAD for predicting PCa. PZ-PSAD is “practical” in that we can improve the diagnostic accuracy of mpMRI and TRUS, and indicate the need for a prostate biopsy when TRUS and mpMRI findings are ambiguous to diagnose PCa (PIRADS score ≤3). Subsequently, through the ROC curve analysis of a large dataset, this study recommended individual PZ-PSAD screening criteria for men to improve the diagnostic efficiency for PCa.

As a “rigorous” parameter, PZ-PSAD is calculated according to a comprehensive formula that includes the PSA, TZV, PZV, and baseline

N-PSAD. In contrast, previous volume-adjusted PSA densities, such as PSAD and TZ-PSAD, are the ratio of PSA to PV or TZV and require precise quantification. This formula divides the tPSA into two parts, with PZ and TZ each taking part. The PSA of TZ is calculated by the product of N-PSAD and TZV, and the PSA of PZ is divided by PZV to obtain PZ-PSAD. This method is concise, and the data needed are economical and easy to obtain in clinical practice. To obtain the N-PSAD, we preselected 100 standardized BPH patients from our center rather than extracting this information from a database. These BPH patients are similar in age, diet, ethnicity, and living environment to the patients with suspected PCa who were enrolled in this study, which can reduce the experimental error and heterogeneity in different populations. Subsequently, the mean PSAD of 0.18 ng ml<sup>-2</sup> in the standardized BPH patients was defined as the N-PSAD. Bazinet *et al.*<sup>12</sup> reported that the optimal cutoff value of PSAD in early prostate cancer was 0.15 ng ml<sup>-2</sup>. Yue<sup>13</sup> reported that the value of PSAD in patients with BPH was 0.17 ng ml<sup>-2</sup>. Zhao *et al.*<sup>14</sup> reported that PSAD in the negative prostate puncture group was 0.19 ng ml<sup>-2</sup>. The value of N-PSAD in this study is representative and similar to the data reported above in Asian and Western cohorts.

PZ-PSAD is “efficient” and has higher diagnostic efficiency than PSA, PSAD, and TZ-PSAD. In recent years, PSA has been the most commonly utilized tool for the diagnosis of PCa. But in the PSA “gray zone” (4.0–10.0 ng ml<sup>-1</sup>), the diagnostic specificity of PSA is relatively low and without effective threshold values.<sup>15</sup> So the Chinese Urological Association recommends that men with PSA levels >10 ng ml<sup>-1</sup> undergo prostate biopsy.<sup>16</sup> The American Urological Association (AUA) guidelines recommend not merely using the PSA threshold to

indicate the need for a prostate biopsy, and that multiple factors should be considered, including PSA density, free PSA/total PSA, molecular subtype, PSA kinetics, patient age, PSA doubling speed, and family history.<sup>17–19</sup> PSAD and TZ-PSAD have been reported to improve the prostate cancer detection rate with PSA levels of 2.5–20.0 ng ml<sup>-1</sup> and 4.0–20.0 ng ml<sup>-1</sup>, respectively.<sup>20,21</sup> Our study attempted to enhance the predictive performance of PSA utilizing capacity-adjusted parameters and defined a new parameter, PZ-PSAD. Clearly, PZ-PSAD had the largest AUC and total efficiency for discriminating PCa, followed by TZ-PSAD, PSAD, and PSA. PZ-PSAD is efficient for PCa screening and has high specificity to identify confounding factors that affect PSA values, such as BPH and prostatitis.

PZ-PSAD is “practical” to aid mpMRI and TRUS in predicting PCa and indicating the need for a prostate biopsy in clinical practice (Figure 2 and Table 4). The results show that in 427 patients with PSA levels of 4.0–20.0 ng ml<sup>-1</sup>, PZ-PSAD can amend the diagnosis in patients with inaccurate TRUS and mpMRI results and help more than half of the patients avoid unnecessary biopsies and missed diagnosis. Therefore, we can combine the results of TRUS and mpMRI with PZ-PSAD to assess the need for a prostate biopsy. Furthermore, in the clinical diagnosis strategy, for suspected PCa patients with elevated PSA and abnormal TRUS and mpMRI findings (PIRADS >3), prostate biopsy is recommended; if the TRUS and mpMRI results are negative with PIRADS ≤3, it is difficult to decide whether a prostate biopsy should be performed. Among suspected PCa patients with negative mpMRI and TRUS results, if patients with positive PZ-PSAD result (31.9%) are recommended for a biopsy, 80.4% of PCa patients will be detected. PZ-PSAD increased the positive rate of biopsy from 21.7% to 54.7%, and helped 150 (63.8%) patients avoid unnecessary prostate biopsy. Moreover, ten PCa patients with PZ-PSAD (–) were medium- and low-risk patients, and 7 of them had a Gleason score ≤6. This reveals that PZ-PSAD helps to screen clinically significant PCa effectively when TRUS and mpMRI findings were negative or ambiguous to diagnose PCa.

When using PZ-PSAD for PCa diagnosis, stratified screening for patients with PSA values of different levels is more targeted and efficient. In the current study, we discovered that patients with different PSA levels have different detection rates of PCa and tumor characteristics, as shown in Table 2. Moreover, the detection rate of PCa in Chinese men is much lower than that in other reports.<sup>22,23</sup> We added groups with PSA levels of 10–20 ng ml<sup>-1</sup> and >20 ng ml<sup>-1</sup> to supplement the deficiency of PSA “gray area” coverage and conducted a stratified analysis based on PSA levels. In men with PSA levels that ranged from 4.0–10.0 ng ml<sup>-1</sup>, 10.1–20.0 ng ml<sup>-1</sup>, and >20.0 ng ml<sup>-1</sup>, the ideal PZ-PSAD cutoff values for predicting PCa were 0.105 ng ml<sup>-2</sup>, 0.436 ng ml<sup>-2</sup>, and 1.803 ng ml<sup>-2</sup>, respectively. In clinical practice, there is more demand for the screening of clinically significant PCa (Gleason ≥7 or pathological grade ≥T2b) and, thus, higher sensitivity is required. When a sensitivity of at least 90% is required, in men with

**Table 3: The optimal cutoff value of peripheral zone prostate-specific antigen density, prostate-specific antigen, prostate-specific antigen density, and transition zone prostate-specific antigen density for predicting clinically significant prostate cancer**

PSA (ng ml <sup>-1</sup> )	Variable	Best cutoff	Sensitivity (%)	Specificity (%)	AUC-ROC
4.0–10.0	PZ-PSAD	0.019	92.6	43.5	0.403
	PSA	4.895	90.7	16.0	0.145
	PSAD	0.095	94.4	34.0	0.321
	TZ-PSAD	0.195	92.6	44.0	0.407
10.1–20.0	PZ-PSAD	0.297	90.6	71.6	0.649
	PSA	10.885	90.6	18.3	0.166
	PSAD	0.225	90.6	71.6	0.649
	TZ-PSAD	0.335	92.2	58.7	0.541
>20.0	PZ-PSAD	1.180	92.3	54.2	0.500
	PSA	25.00	91.0	25.0	0.228
	PSAD	0.470	91.0	54.2	0.493
	TZ-PSAD	0.720	91.0	54.2	0.493

PSA: prostate-specific antigen; PSAD: prostate-specific antigen density; TZ-PSAD: transition zone prostate-specific antigen density; PZ-PSAD: peripheral zone prostate-specific antigen density; ROC: receiver operating characteristic; AUC-ROC: area under the ROC curve

**Table 4: The efficacy of peripheral zone prostate-specific antigen density to diagnose prostate cancer in patients with negative multiparameter magnetic resonance imaging and transrectal ultrasound results (prostate imaging reporting and data system ≤3)**

Group	PSA 4.0–10.0 ng ml <sup>-1</sup>	PSA 10.1–20.0 ng ml <sup>-1</sup>	PSA >20.0 ng ml <sup>-1</sup>	Total
TRUS/MRI (–), n	135	78	22	235
Pathology (+), n (%)	22 (16.3)	18 (23.1)	11 (50.0)	51 (21.7)
PZ-PSAD cutoff value (ng ml <sup>-2</sup> )	0.105	0.436	1.803	
PZ-PSAD (+), n (%)	45 (33.3)	19 (24.4)	11 (50.0)	75 (31.9)
PZ-PSAD (+) pathology (+), n	17	14	10	41

PSA: prostate-specific antigen; PZ-PSAD: peripheral zone prostate-specific antigen density; PCa: prostate cancer; TRUS: transrectal ultrasound; mpMRI: multiparameter magnetic resonance imaging; PIRADS: Prostate Imaging Reporting and Data System; TRUS/MRI (–): without suspicious nodules or a PIRADS score ≤3; pathology (+): prostate cancer; PZ-PSAD (+): PZ-PSAD > cut-off value



PSA levels of 4.0–10.0 ng ml<sup>-1</sup>, 10.1–20.0 ng ml<sup>-1</sup>, and >20.0 ng ml<sup>-1</sup>, the ideal PZ-PSAD cutoff values for predicting clinically significant PCa were 0.019 ng ml<sup>-2</sup>, 0.297 ng ml<sup>-2</sup>, and 1.180 ng ml<sup>-2</sup>, respectively. The development of individual screening criteria can increase the efficiency of PZ-PSAD in diagnosing PCa in more scenarios.

In clinical practice, to screen for PCa, the first examinations are PSA detection, DRE, and TRUS. For cases of suspected PCa after the above-mentioned examinations, mpMRI is performed because the cost of MRI is higher than that of TRUS. In this study, the PV and TZV are measured by mpMRI to calculate PZ-PSAD because of its accuracy. It will be more practical to use TRUS for PZ-PSAD calculation in clinical practice. Therefore, this study compared the PZ-PSAD data measured by mpMRI and TRUS. It revealed that the PZ-PSAD data measured by mpMRI and TRUS were not statistically different ( $P = 0.172$ ). This suggests that the PV and TZV measured by TRUS can be used to calculate PZ-PSAD in clinical applications, which improves the convenience and popularity of this index.

In order to advance the application and generalization of these experimental findings, some problems require further investigation. The clinical data were obtained from a single hospital, which leads to a selection bias. In addition, different cores, biopsy schemes, and operating techniques may lead to different detection rates of PCa, and prostate systematic multipoint biopsy may also fail to detect a part of the prostate cancer.<sup>24–26</sup> To confirm our findings, larger prospective randomized studies are needed.

## CONCLUSION

In the diagnosis of PCa, PZ-PSAD, PSA, PSAD, and TZ-PSAD have certain diagnostic value for patients with PSA values of different levels, but the accuracy of PZ-PSAD to predict PCa is the highest, which means a lower missed diagnosis rate and more patients can avoid unnecessary biopsy. PZ-PSAD can amend the diagnosis in patients with inaccurate TRUS and mpMRI results, and indicate the need for a prostate biopsy when TRUS and mpMRI findings were negative or ambiguous to diagnose PCa.

## AUTHOR CONTRIBUTIONS

CW and YYW conceived the study, collected data, performed the statistical analysis, and drafted the manuscript. SYW, JXD, and MD helped to collect data and performed the statistical analysis. YR, XHW, YFJ, BMH, and SJX participated in design and coordination of the study. CYJ and FJZ conceived the study, participated in its design and coordination, and helped to draft the manuscript. All authors read and approved the final manuscript.

## COMPETING INTERESTS

All authors declared no competing interests.

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**Supplementary Table 1: Clinical characteristics in men with prostate-specific antigen levels of 4.0–10.0 ng ml<sup>-1</sup>, 10.1–20.0 ng ml<sup>-1</sup>, and >20 ng ml<sup>-1</sup>**

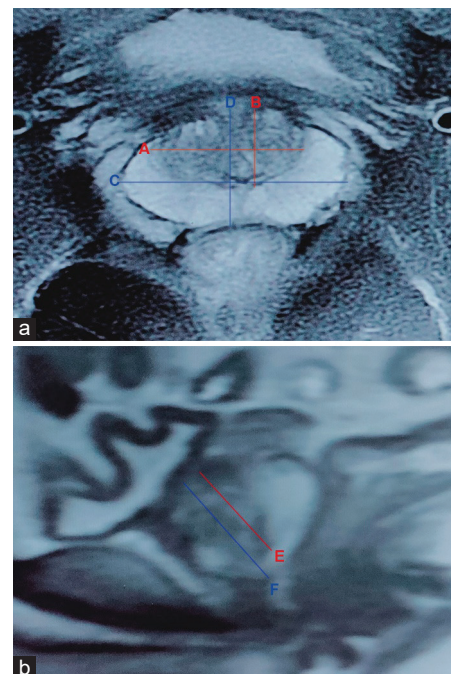
Group	PSA 4.0 – 10.0 ng ml <sup>-1</sup>	PSA 10.1 – 20.0 ng ml <sup>-1</sup>	PSA >20.0 ng ml <sup>-1</sup>	P
Case number, n (%)	254 (48.0)	173 (32.7)	102 (19.3)	
Positive detection rate	75 (29.5%)	77 (44.5%)	84 (82.4%)	<0.001 <sup>a</sup>
Age (year)				
Median (IQR)	67 (62–72)	68 (63.5–72)	73.5 (65–79)	
Mean±s.d.	67.37±7.01	68.40±6.79	72.72±8.00	<0.001 <sup>b</sup>
PSA value (ng ml <sup>-1</sup> )	6.70±1.60	14.02±2.86	121.28±225.74	<0.001 <sup>b</sup>
PV value (ml)	55.99±26.92	63.25±36.25	60.87±36.36	0.063 <sup>b</sup>
PSAD value (ng ml <sup>-2</sup> )	0.150±0.092	0.298±0.192	2.477±4.655	<0.001 <sup>b</sup>
TZ-PSAD value (ng ml <sup>-2</sup> )	0.309±0.226	0.571±0.458	3.706±6.063	<0.001 <sup>b</sup>
PZ-PSAD value (ng ml <sup>-2</sup> )	0.091±0.367	0.455±0.548	13.607±46.633	<0.001 <sup>b</sup>
DRE (+)	50	41	61	<0.001 <sup>a</sup>
TRUS findings (+)	69	53	68	<0.001 <sup>a</sup>
mpMRI (+)	100	86	71	<0.001 <sup>a</sup>

<sup>a</sup>χ<sup>2</sup> analysis; <sup>b</sup>ANOVA. PCa: prostate cancer; IQR: interquartile range; s.d.: standard deviation; PSA: prostate-specific antigen; PSAD: prostate-specific antigen density; TZ-PSAD: transition zone prostate-specific antigen density; PZ-PSAD: peripheral zone prostate-specific antigen density; DRE: digital rectal examination; TRUS: transrectal ultrasound; mpMRI: multiparameter magnetic resonance imaging; ANOVA: analysis of variance

**Supplementary Table 2: Clinical characteristics in 100 patients with benign prostate hyperplasia who were selected to obtain the average prostate-specific antigen density in the nonprostate cancer cohort**

Parameter	BPH
Age (year)	
Median (IQR)	65 (61–73.75)
Mean±s.d.	66.74±8.30
PSA value (ng ml <sup>-1</sup> )	
Median (IQR)	6.15 (2.68–13.89)
Mean±s.d.	9.08±8.25
Prostate volume (ml)	
Median (IQR)	50.30 (36.29–71.99)
Mean±s.d.	57.91±33.95
PZ-PSAD (ng ml <sup>-2</sup> )	
Median (IQR)	0.137 (0.058–0.210)
Mean±s.d.	0.182±0.177

BPH: benign prostate hyperplasia; PSA: prostate-specific antigen; N-PSAD: prostate-specific antigen density in the non-PCa cohort; PZ-PSAD: peripheral zone prostate-specific antigen density; s.d.: standard deviation; IQR: interquartile range



**Supplementary Figure 1: Measurement of the prostate and transition zone volumes. (a)** Measurement of the transverse diameter and anteroposterior diameter on horizontal plane. **(b)** Measurement of the superoinferior diameter on sagittal plane. A: transverse diameter of the transition zone; B: anteroposterior diameter of the transition zone; C: transverse diameter of the entire prostate; D: anteroposterior diameter of the entire prostate; E: superoinferior diameter of the transition zone; F: superoinferior diameter of the entire prostate.

**Supplementary Table 3: Sensitivity, specificity, and area under the receiver operating characteristic curve of peripheral zone prostate-specific antigen density, prostate-specific antigen, prostate-specific antigen density, and transition zone prostate-specific antigen density for predicting prostate cancer**

<i>PSA (ng ml<sup>-1</sup>)</i>	<i>Variable</i>	<i>Best cutoff</i>	<i>Sensitivity (%)</i>	<i>Specificity (%)</i>	<i>AUC-ROC</i>
4.0–10.0	PZ-PSAD	0.105	70.7	72.1	0.770
	PSA	6.455	68.0	53.1	0.592
	PSAD	0.142	69.3	69.3	0.730
	TZ-PSAD	0.289	74.7	73.2	0.766
10.1–20.0	PZ-PSAD	0.436	68.8	86.5	0.823
	PSA	14.05	58.5	67.7	0.621
	PSAD	0.298	67.5	84.4	0.799
4.0–20.0	TZ-PSAD	0.844	84.4	63.5	0.769
	PZ-PSAD	0.258	59.2	83.3	0.785
	PSA	7.895	67.1	52.0	0.630
	PSAD	0.208	61.8	82.2	0.762
>20.0	TZ-PSAD	0.302	81.6	66.2	0.775
	PZ-PSAD	1.803	84.5	77.8	0.870
	PSA	39.21	67.9	77.8	0.750
	PSAD	0.801	76.2	77.8	0.797
	TZ-PSAD	0.685	90.5	61.1	0.728

PSA: prostate-specific antigen; PSAD: prostate-specific antigen density; TZ-PSAD: transition zone prostate-specific antigen density; PZ-PSAD: peripheral zone prostate-specific antigen density; ROC: receiver operating characteristic; AUC-ROC: area under the ROC curve-ROC