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ORIGINAL ARTICLE

Prostate Cancer

Evaluation of PSA-age volume score in predicting prostate cancer in Chinese population

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This study was performed to evaluate prostate-specific antigen-age volume (PSA-AV) scores in predicting prostate cancer (PCa) in a Chinese biopsy population. A total of 2355 men who underwent initial prostate biopsy from January 2006 to November 2015 in Huashan Hospital were recruited in the current study. The PSA-AV scores were calculated and assessed together with PSA and PSA density (PSAD) retrospectively. Among 2133 patients included in the analysis, 947 (44.4%) were diagnosed with PCa. The mean age, PSA, and positive rates of digital rectal examination result and transrectal ultrasound result were statistically higher in men diagnosed with PCa (all $P < 0.05$). The values of area under the receiver operating characteristic curves (AUCs) of PSAD and PSA-AV were 0.864 and 0.851, respectively, in predicting PCa in the entire population, both performed better than PSA (AUC = 0.805; $P < 0.05$). The superiority of PSAD and PSA-AV was more obvious in subgroup with PSA ranging from 2.0 ng ml^{-1} to 20.0 ng ml^{-1}. A PSA-AV score of 400 had a sensitivity and specificity of 93.7% and 40.0%, respectively. In conclusion, the PSA-AV score performed equally with PSAD and was better than PSA in predicting PCa. This indicated that PSA-AV score could be a useful tool for predicting PCa in Chinese population.

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INTRODUCTION

Prostate cancer (PCa) is the second most common cancer and a leading cause of death among men in the world, with an estimated incidence of 903 500 cases, causing 258 400 death every year.[1] By the year of 2030, an estimated 500 000 men will die of PCa.[2] The incidence of PCa in China is still relatively low; however, it has risen rapidly over the past decades.[3,4]

Serum prostate-specific antigen (PSA) is the most widely used biomarker for PCa screening since its introduction into clinical practice. It is recommended by the Chinese Urological Association (CUA) guideline that men over 50 years with lower urinary tract symptoms or men over 45 years with a family history of PCa should undergo PSA screening annually.[5] However, since PSA is an organ-specific rather than disease-specific biomarker, the widely application of PSA in PCa screening has revealed its low specificity at its usual cutoff (*e.g.*, 4.0 ng ml^{-1}) and led to overdiagnosis.[6,7] Recently, various strategies were introduced to improve the sensitivity and specificity of PSA.[8–11] Clinical variables including PSA, prostate volume (PV), and age were proved to be independent predictors of positive prostate biopsy findings.[12–17]

In order to combine PSA, PV, and age in a simple and reasonable way, Patel *et al*.[18] developed a novel algorithm that incorporates them into a single score for PCa prediction, called PSA-age volume (PSA-AV) score. This score is calculated by multiplying the age and PV and then dividing the total by the prebiopsy PSA. According to their internal and external validation studies, a lower PSA-AV correlated with a greater cancer risk and a PSA-AV score of 700 was recommended in ruling out cancer in younger patients and patients with small prostates, and in ruling in cancer in older patients and patients with large prostates. This result indicated that PSA-AV could be a more useful tool than PSA in particular groups. Later, in one study, the predictive effect of PSA-AV was similar to PSA density (PSAD) and another study showed that the predictive effect for a PSA-AV score of 700 was similar to a PSA cutoff of 4.0 ng ml^{-1}.[19,20]

Whether PSA-AV could outperform PSAD or PSA was still uncertain based on the previous studies. In addition, according to studies in Chinese population, the clinical feature of Chinese biopsy population differed from that of Caucasians and Africans (normally with higher PSA level and elder age).[21–25] Therefore, it is worth evaluating the predictive utility of PSA-AV and investigating an appropriate cutoff in Chinese population.

PATIENTS AND METHODS

Study population and sample collection

A total of 2355 men who underwent initial prostate biopsy from January 2006 to November 2015 in Huashan Hospital (a Tertiary Health Institutes in Shanghai, China) were retrospectively included in the current study. All the clinical information was collected before biopsy. Two hundred and twenty-two patients were excluded for missing

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information of age, PSA, or PV. The characteristics of tertiary health institutes in China were described in our previous study.[21]

All the patients in the current study underwent an ultrasound-guided transperineal prostate biopsy with 6 cores before October 2007 or 10 cores thereafter. The indications for prostate biopsy at our institute were: (1) total prostate-specific antigen (tPSA) >4.0 ng ml^{-1}; (2) tPSA <4.0 ng ml^{-1}, with a suspicious free prostate-specific antigen (fPSA)/tPSA <0.16 or PSAD >0.15 (PSAD = tPSA/PV, PV [ml] = height [cm] × length [cm] × width [cm] × 0.52); (3) positive findings from a digital rectal examination (DRE) with any level of tPSA; and (4) positive findings from imaging techniques such as transrectal ultrasound (TRUS) and magnetic resonance imaging (MRI), with any level of tPSA. All blood samples were collected prior to biopsy and measured by the Department of Clinical Laboratory in Huashan Hospital for tPSA and fPSA. Prostate specimens were diagnosed by pathologists from the Pathology Department of Huashan Hospital. The current study was approved by the Institutional Review Board of Huashan Hospital, Fudan University, Shanghai, China. Written informed consent was obtained from all patients for their participation in the study.

Statistical analysis

The baseline characteristics of the study cohort and its subgroup with PSA ranging from 2.0 ng ml^{-1} to 20.0 ng ml^{-1} were described as two groups (PCa patients and non-PCa patients). Mann–Whitney U-test was used to compare the distributions of PSA in different groups. Student's *t*-test was used to compare the mean values of other continuous variables (age and PV) and Chi-squared test was used to compare the different proportions of categorical variables (DRE result, TRUS result). Receiver operating characteristic curves were used to evaluate the predictive performance of PSA, PSAD, and PSA-AV. A Z-test was performed to compare the differences among area under the receiver operating characteristic curves (AUCs) of PSA, PSAD, and PSA-AV. Additionally, a PSA cutoff of 10.0 ng ml^{-1}, PSAD cutoff of 0.15, and PSA-AV of 400 were compared with each other in the different age groups and different PV groups. The high-grade PCa was defined as patients with a Gleason score ≥8 according to the CUA guideline. A two-sided test with $P = 0.05$ was used. All statistical analyses were performed using SPSS 19.0 (Statistical Product and Service Solutions, IBM Corporation, Armonk, NY, USA).

RESULTS

A total of 2133 patients were included in the study and 947 (44.4%) were diagnosed with PCa. The characteristics of the study population and the stratified subgroup (PSA ranging from 2.0 ng ml^{-1} to 20.0 ng ml^{-1}) are shown in **Table 1**. In the study cohort and its subgroup with PSA ranging from 2.0 ng ml^{-1} to 20.0 ng ml^{-1}, the mean age, PSA, and positive rates of DRE result and TRUS result were statistically higher in men diagnosed with PCa than that in men without PCa whereas the mean PV was lower in PCa group (all $P < 0.05$).

The discriminative performance of PSA, PSAD, and PSA-AV for predicting PCa and high-grade PCa was evaluated in the study cohort and its subgroup (**Table 2**). When predicting PCa, the AUCs of PSAD and PSA-AV were 0.864 and 0.851, respectively, which indicated that both performed better than PSA (AUC = 0.805; $P < 0.05$). While

Table 1: Characteristics of the study cohort

Variables	*All PSA*				*PSA: 2.0–20.0 ng ml^{-1}*			
	Overall	*PCa*	*Non-PCa*	*P*	*Overall*	*PCa*	*Non-PCa*	*P*
Patients (*n*)	2133	947	1186		1231	322	909	
Age at the time of biopsy (year)								
Mean (s.d.)	70.85 (8.7)	73.0 (8.4)	69.2 (8.6)	$1.8\times10^{-24*}$	69.9 (8.6)	72.5 (8.2)	69.0 (8.5)	$9.0\times10^{-11*}$
Median (IQR)	71.0 (65.0–77.0)	74.0 (68.0–79.0)	69.0 (63.0–76.0)		70.0 (64.0–77.0)	73.0 (67.0–79.0)	69.0 (63.0–76.0)	
tPSA at the time of biopsy (ng ml^{-1})								
Mean (s.d.)	19.9 (3.5)	41.4 (4.0)	11.0 (2.1)	$3.5\times10^{-130**}$	10.0 (1.5)	11.2 (1.5)	9.5 (1.5)	$1.8\times10^{-10**}$
Median (IQR)	14.6 (9.3–33.1)	32.9 (14.7–100.0)	10.9 (7.5–16.3)		10.5 (7.7–13.9)	11.9 (9.1–15.5)	10.1 (7.3–13.1)	
PV (ml)								
Mean (s.d.)	53.4 (26.6)	47.2 (26.0)	58.3 (26.0)	$3.8\times10^{-22*}$	52.6 (23.4)	40.1 (19.1)	57.1 (23.2)	$2.7\times10^{-34*}$
Median (IQR)	48.0 (35.0–65.0)	40.4 (30.0–57.0)	53.6 (40.0–70.9)		49.0 (35.0–64.9)	35.0 (27.0–47.6)	53.8 (40.0–69.0)	
DRE[a], *n* (%)								
Positive	588 (27.6)	483 (51.0)	105 (8.9)	$3.4\times10^{-104†}$	195 (15.8)	116 (36.0)	79 (8.7)	$6.4\times10^{-31†}$
Missing	98 (4.6)	38 (4.0)	60 (5.1)		65 (5.3)	16 (5.0)	49 (5.4)	
TRUS (nodule)[b], *n* (%)								
Positive	1070 (50.2)	661 (69.8)	409 (34.5)	$7.5\times10^{-63†}$	530 (43.1)	205 (63.7)	325 (35.8)	$1.5\times10^{-18†}$
Missing	81 (3.8)	40 (4.2)	41 (3.5)		48 (3.9)	12 (3.7)	36 (4.0)	
Biopsy results, *n* (%)								
Positive	947 (44.4)	/	/		322 (26.2)	/	/	
Gleason score, *n* (%)								
≤6	198 (9.3)	198 (20.9)	/		115 (9.3)	115 (35.7)	/	
7	385 (18.0)	385 (40.7)	/		122 (9.9)	122 (37.9)	/	
≥8	351 (16.5)	351 (37.1)	/		80 (6.5)	80 (24.8)	/	
Missing	13 (0.6)	13 (1.4)	/		5 (0.4)	5 (1.6)	/	

[a]Prostate hardness or nodule detected by DRE was defined as "positive," and other findings were defined as "negative". [b]Nodule detected by transrectal ultrasound was defined as "positive," and other findings were defined as "negative." *The *P* values were calculated by using *t*-test to see whether there is any significant difference between the means of two groups. **The *P* values were calculated using Mann–Whitney U-test to see whether there is any significant difference between the distributions of two groups. †The *P* values were calculated using Chi-square test to test whether there is any significant difference between the different groups. PCa: prostate cancer; PV: prostate volume; s.d.: standard deviation; IQR: interquartile range; tPSA: total prostate-specific antigen; DRE: digital rectal examination; TRUS: transrectal ultrasound

Table 2: Evaluation of the area under the receiver operating curves of prostate-specific antigen and its derivatives

Variables	*PCa (45.33%) in all patients*				*High-grade PCa (16.46%) in all patients*				*PCa (22.71%) in patients with PSA: 2.0–20.0 ng ml^{-1}*				*High-grade PCa (6.26%) in patients with PSA: 2.0–20.0 ng ml^{-1}*			
	AUC	*Lower 95%*	*Upper 95%*	*P*[a]	*AUC*	*Lower 95%*	*Upper 95%*	*P*[a]	*AUC*	*Lower 95%*	*Upper 95%*	*P*[a]	*AUC*	*Lower 95%*	*Upper 95%*	*P*[a]
PSA	0.805	0.786	0.824		0.814	0.789	0.838		0.619	0.584	0.655		0.661	0.602	0.72	/
PSAD[b]	0.864	0.849	0.88	4.0×10^{-6}	0.824	0.802	0.847	0.56	0.768	0.737	0.799	1.0×10^{-7}	0.724	0.669	0.779	0.12
PSA-AV[c]	0.851	0.834	0.867	4.5×10^{-4}	0.819	0.796	0.842	0.78	0.737	0.705	0.769	2.0×10^{-6}	0.704	0.646	0.762	0.31

[a]The *P* value referred to the significance between PSAD or PSA-AV and PSA. [b]PSAD = PSA/PV, PV (ml) = height (cm) × length (cm) × width (cm) × 0.52. [c]PSA-AV = age × PV/PSA. AUC: area under the receiver operating characteristic curves; PSA-AV: prostate-specific antigen-age volume; PCa: prostate cancer; PSA: prostate-specific antigen; PSAD: prostate-specific antigen density; PV: prostate volume

in patients with PSA ranging from 2.0 ng ml^{-1} to 20.0 ng ml^{-1}, the superiority of PSAD and PSA-AV was more obvious (AUC = 0.768 for PSAD and 0.737 for PSA-AV *vs*. 0.619 for PSA; $P < 0.05$). PSAD seemed to perform slightly better than PSA-AV while the difference between their AUCs did not reach statistical significance. When predicting high-grade PCa (Gleason score ≥8), there was no significant difference among the AUCs of PSA, PSAD, and PSA-AV in the study cohort and its subgroup. The ROC curves are shown in **Figure 1**. In addition, the same analysis was also performed in predicting PCa with Gleason score ≥7, which showed that PSAD and PSA-AV both outperformed PSA in the study cohort and its subgroup ($P < 0.05$) (**Supplementary Table 1**).

The sensitivities, specificities, positive predictive values, and negative predictive values of PSA, PSAD, and PSA-AV scores at different cutoffs are shown in **Table 3**. As the PSA-AV cutoff increased, the sensitivity increased from 93.7% to 99.8% and the specificity decreased from 40.0% to 2.1%. Then, we calculated the Youden's indexes of different PSA-AV cutoffs (<400, <500, <700, <800, and <1200) and found that the cutoff of <400 performed best among them. The predictive ability was comparable to the commonly used prostate biopsy indication in Chinese (PSAD ≥0.15) and better than PSA ≥10.0 ng ml^{-1} for its higher positive predictive value (55.5% *vs* 32.2%).

The numbers of PCa patients detected and missed using 3 predictors were calculated and compared. For example, using a PSA-AV cutoff of <400 led to 78 more biopsies and detecting 56 more cancer cases in comparison with PSA ≥10.0 ng ml^{-1}. We also compared the misdetection rate of difference of PSA-AV <400, PSAD ≥0.15, and PSA ≥10.0 ng ml^{-1} and the result (**Table 4**) turned out that both using PSA-AV <400 and PSAD ≥0.15 would have missed fewer PCa patients than using PSA ≥10.0 ng ml^{-1} ($P < 0.05$).

The sensitivity and specificity value changes within different age and PV groups are listed in **Table 5** and **6**. Comparing to PSA cutoff of 10 ng ml^{-1}, A PSA-AV cutoff of 400 had a greater sensitivity in younger patients (age below 70 years) and greater specificity in older patients (age over 70 years). Meanwhile, a PSA-AV cutoff of 400 had a greater sensitivity in patients with small-to-moderate prostate (PV ≤65 ml) and greater specificity in patients with large prostate (PV >65 ml).

DISCUSSION

To the best of our knowledge, this is the first study to evaluate PSA-AV in a Chinese prostate biopsy population. First, we calculated the PSA-AV score of our patients and compared the PCa predictive performance of PSA, PSAD, and PSA-AV. Second, we evaluated the diagnostic parameters of PSA-AV at different cutoffs and found an appropriate cutoff value for the Chinese prostate biopsy population. Finally, we compared the cancer missing rate of PSA, PSAD, and PSA-AV at their certain cutoffs.

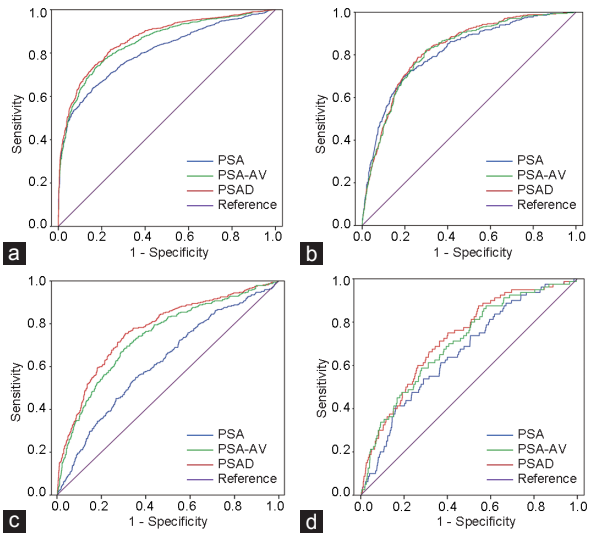

Figure 1: ROCs of PSA, PSAD, and PSA-AV, (**a**) predicting the result of prostate cancer in the entire population, (**b**) predicting the result of high-grade prostate cancer with Gleason Score ≥8 in the entire population, (**c**) predicting the result of prostate cancer in the subgroup with PSA ranging from 2.0 ng ml^{-1} to 20.0 ng ml^{-1}, (**d**) predicting the result of high-grade prostate cancer with Gleason Score ≥8 in the subgroup with PSA ranging from 2.0 ng ml^{-1} to 20.0 ng ml^{-1}. ROC: receiver operating characteristic curve; PSA: total prostate-specific antigen; PSA-AV: prostate-specific antigen-age volume; PSAD: prostate-specific antigen density.

Since PSA is highly organ specific, rather than cancer specific, several benign conditions (elder age, benign prostate hyperplasia, and inflammation of the prostate) may also cause the elevation of serum PSA level.[26] Therefore, PSA had a low specificity ranged from 10% to 30% at its usual cutoff (normally 4.0 ng ml^{-1}) throughout different studies and this would cause overdiagnosis and overbiopsy.[16,27–29] PSAD was applied to bring the influence of PV into consideration while making the decision of prostate biopsy. Although it was not recommended in EAU guideline, PSAD is still recommended as a biopsy indication in Chinese guideline with the cutoff value of 0.15 ng ml^{-2}.[5] Especially for patients with relatively low PSA level (*e.g.*, 2–10 ng ml^{-1} in Caucasians and 2.0–20.0 ng ml^{-1} in Chinese), PSAD had a better performance than PSA in predicting PCa.[9,30–32]

PSA-AV was developed by Patel *et al.*[18] to incorporate PSA, age, and PV into an easily calculated score; in their training and validation study, they noticed that PSA-AV performed better than PSA in predicting PCa. Another study also showed that the predicting performance of PSA-AV was comparable to that of PSAD. In the current study, our results showed the AUCs of PSAD and PSA-AV were 0.864 and 0.851, respectively, both performed better than PSA (AUC = 0.805; $P < 0.05$).

The superiority was more remarkable in patients with PSA ranged from 2.0 to 20.0 ng ml^{-1}. These results were in parallel with the former two studies.[18,19] However, while predicting high-grade PCa, we did not observe difference among PSA, PSAD, and PSA-AV in our study. This might attribute to PSA per tumor volume decreases with increasing tumor grade according to a recent study.[33] Moreover, although there seemed to be no obvious advantage to calculate PSA-AV while we already have PSAD, we performed additional analysis in 509 biopsy patients with PSA 4–10 ng ml^{-1} and showed that an extra 8% of unnecessary biopsies could be spared in this subgroup while combining PSA-AV with PSAD in prebiopsy diagnosis (**Supplementary Figure 1**). The trade-off of combining 3 predictors would be 3 missed cancer cases (missing rate of 0.6%) while TRUS and DRE results are applied together.

Table 3: Predictive values of prostate-specific antigen-age volume, prostate-specific antigen density and prostate-specific antigen

	Sensitivity (%)	*Specificity (%)*	*PPV (%)*	*NPV (%)*
PSA-AV				
<400	93.7	40.0	55.5	88.8
<500	95.8	27.2	51.2	89.0
<700	98.3	12.0	44.1	90.0
<800	99.0	9.53	46.6	92.6
<1200	99.6	3.37	45.1	90.9
<1600	99.8	2.1	44.9	92.6
PSAD				
≥0.10	98.7	11.7	47.2	92.1
≥0.15	95.8	32.0	52.9	90.5
≥0.20	92.1	51.1	60.1	89.0
PSA (ng ml^{-1})				
≥4.00	99.7	4.8	23.6	98.2
≥10.00	93.7	41.6	32.2	95.7

PSA: prostate-specific antigen; PSA-AV: prostate-specific antigen-age volume; PSAD: prostate-specific antigen density; PPV: positive predictive value; NPV: negative predictive value

Table 4: Detection of prostate cancer according to different tests

Cancer missed	*Patients (n)*	*Missed cases (n)*	*P*
PSA-AV ≥400	534	60	3.0×10^{-4}†
PSAD <0.15	418	39	2.2×10^{-5}†
PSA <10.0 ng ml^{-1}	612	116	/

†The *P* values were calculated using Chi-square test to test whether there is any significant difference of the cancer missing rate (or detection rate) between PSA-AV or PSAD and PSA. PSA: prostate-specific antigen; PSAD: prostate-specific antigen density; PSA-AV: prostate-specific antigen-age volume

Another issue that might be of interest was the difference of performance between PSA-AV and logistic regression models combining independent predictors (*e.g.*, PSA, age, PV, DRE, and TRUS findings).[34] In order to illustrate this issue, we divided our cohort into two parts (one with 1067 and another with 1066 patients) and built a logistic model based on PSA, age, and PV in 1067 patients. Then, we validated this logistic model in the other 1066 patients and showed an AUC of 0.855 in predicting PCa in the validation cohort (while PSA-AV had an AUC of 0.851, $P_{\text{AUC compare}} = 0.78$). The model could be improved with an AUC of 0.880 if DRE (normal or abnormal) and TRUS (normal or abnormal) are added, which was better than PSA-AV ($P_{\text{AUC compare}} = 0.02$). The AUC of PSA in our cohort was 0.805, which was relatively high compared with reported Western studies (mostly slightly above 0.5). This finding might be attributable to the fact that the current study was based on a biopsy population at higher risk for PCa (a positive biopsy rate of 44.4%). For example, some of the patients came to the urology department because of elevated PSA while others are seeking help for their urinary symptoms. This reason might also be the explanation of the relatively high AUCs of PSAD, PSA-AV, and the logistic models mentioned above.

In a diagnostic study, Youden's index (sensitivity + specificity−1) is used to determine the cutoff value of a diagnosis test. Briefly, Youden's Index values are larger when both sensitivity and specificity are higher, which indicates that the best cutoff has been identified.[35] In order to compare with former studies, we calculated the Youden's indexes of different PSA-AV cutoffs (<400, <500, <700, <800, and <1200) and found that PSA-AV <400 performed best among them. At this cutoff, the sensitivity was 93.7% and the specificity was 40.0%. In former studies, at the cutoff of 700, the sensitivity ranged from 85% to 95% while the specificity ranged from 35% to 15%. The predictive performance in the current study was better than that of all previous studies; thus, we recommend a PSA-AV cutoff of 400 in Chinese population.[18–20]

Our data showed that in age <70-year group, the sensitivities of PSA-AV cutoff of 400 ranged from 96.2% to 98.6%, which were better than that of PSA cutoff of 10 ng ml^{-1} (ranged from 84.6% to 92.8%). While in age ≥70-year group, the specificity of PSA-AV cutoff of 400 was 47.8%, which was better than that of PSA cutoff of 10 ng ml^{-1} (38.7%). In patients with low-to-moderate PVs (≤65 ml), the sensitivities of PSA-AV ranged from 97.2% to 93.8%, which were better than that of PSA cutoff of 10 ng ml^{-1} (ranged from 82.2% to 89.3%). While in PV ≥ 65 ml group, the specificity of PSA-AV cutoff of 400 was 58.3%, which was better than that of PSA cutoff of

Table 5: Sensitivity and specificity of various cutoff methods in different age groups

Variable	*Total biopsies (n)*	*Cancers detected (n)*	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*
Age <60 years						
PSA ≥10 ng ml^{-1}	151	64	92.8	42.4	42.4	92.8
PSAD ≥0.15	187	68	98.6	21.2	36.4	97.0
PSA-AV <400	194	68	98.6	16.6	35.1	96.2
Age 60–69 years						
PSA ≥10 ng ml^{-1}	443	198	84.6	45.3	44.7	84.9
PSAD ≥0.15	531	227	97.0	32.1	42.2	95.4
PSA-AV <400	505	225	96.2	37.5	44.6	94.9
Age ≥70 years						
PSA ≥10 ng ml^{-1}	923	566	88.3	38.7	61.3	75.0
PSAD ≥0.15	933	611	95.3	34.4	65.5	87.0
PSA-AV <400	896	592	92.4	47.8	66.1	85.0

PSA: prostate-specific antigen; PSA-AV: prostate-specific antigen-age volume; PSAD: prostate-specific antigen density; PPV: positive predictive value; NPV: negative predictive value

Table 6: Sensitivity and specificity of various cutoff methods in different prostate volume groups

Variable	*Total biopsies (n)*	*Cancers detected (n)*	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*
PV <35 ml						
PSA ≥10 ng ml^{-1}	360	268	82.2	49.7	74.4	61.1
PSAD ≥0.15	477	319	97.9	13.7	66.9	78.1
PSA-AV <400	469	317	97.2	16.9	67.6	77.5
PV 35–65 ml						
PSA ≥10 ng ml^{-1}	676	376	89.3	47.6	55.6	85.8
PSAD ≥0.15	821	408	96.9	27.8	49.7	92.4
PSA-AV <400	764	395	93.8	35.5	51.7	88.6
PV >65 ml						
PSA ≥10 ng ml^{-1}	418	149	96.1	26.7	35.6	94.2
PSAD ≥0.15	331	140	90.3	48.0	42.3	92.1
PSA-AV <400	288	135	87.1	58.3	46.9	95.1

PV: prostate volume; PSA: prostate-specific antigen; PSAD: prostate-specific antigen density. PPV: positive predictive value; NPV: negative predictive value; PSA-AV: prostate-specific antigen-age volume

10 ng ml^{-1} (26.7%). Thus, in Chinese population, PSA-AV would be a useful tool in ruling out PCa in younger patients (age <70 years) and in patients with a smaller prostate (PV <65 ml). Results from the current study also supported that using a PSA-AV cutoff of 400 performed more stable across stratified groups (with different age and PV) in Chinese population than the cutoff of 700 in Patel's study in a multi-ethnic population.[18]

In the current study, we chose PSA cutoff of 10 ng ml^{-1} as a comparing cutoff. It was attributed to the difference of PSA "gray zone" in Chinese and Western population as we have mentioned in another study.[36] Evidence from our study and another biopsy cohort from Shanghai showed that the PCa detection rate in patients with PSA at 10–20 ng ml^{-1} ranged from 29.6% to 36.5%. This detection rate was comparable to the PCa detection rate (34%) in patients with PSA at 4–10 ng ml^{-1} in Western populations.[37]

The current study had several strengths: (i) we provided a comprehensive description of the cancer predictive performance of PSA-AV, PSAD, and PSA in a large Chinese biopsy population; (ii) we found a suitable PSA-AV cutoff of 400 in Chinese population; (iii) a contemporary standard 10-core biopsy was used in most of the population. One limitation of our study is that it is a retrospective study from only one health institute. However, as one of the tertiary health institutes in China, patients from all over the country seek for medical service in our institute. Thus, our study population could partially represent the Chinese population.

CONCLUSIONS

According to our data, the PSA-AV score performed equally with PSAD and was better than PSA in predicting PCa. This indicated that PSA-AV score could be a useful tool for predicting PCa in Chinese population. Especially, it was more sensitive in younger patients and patients with small prostates.

AUTHOR CONTRIBUTIONS

YSW, RN, QD conceived and designed the study. XBW, NZ, and RN performed the experiments. YSW, XBW, and RN analyzed the data. GLJ, YY, SJT, HWJ, and SHM contributed materials and analysis tools. YSW, XBW, and QD wrote the manuscript. All authors have read and approved the final version of the manuscript and agreed with the order of presentation of the authors.

COMPETING INTERESTS

All authors declared no competing interests.

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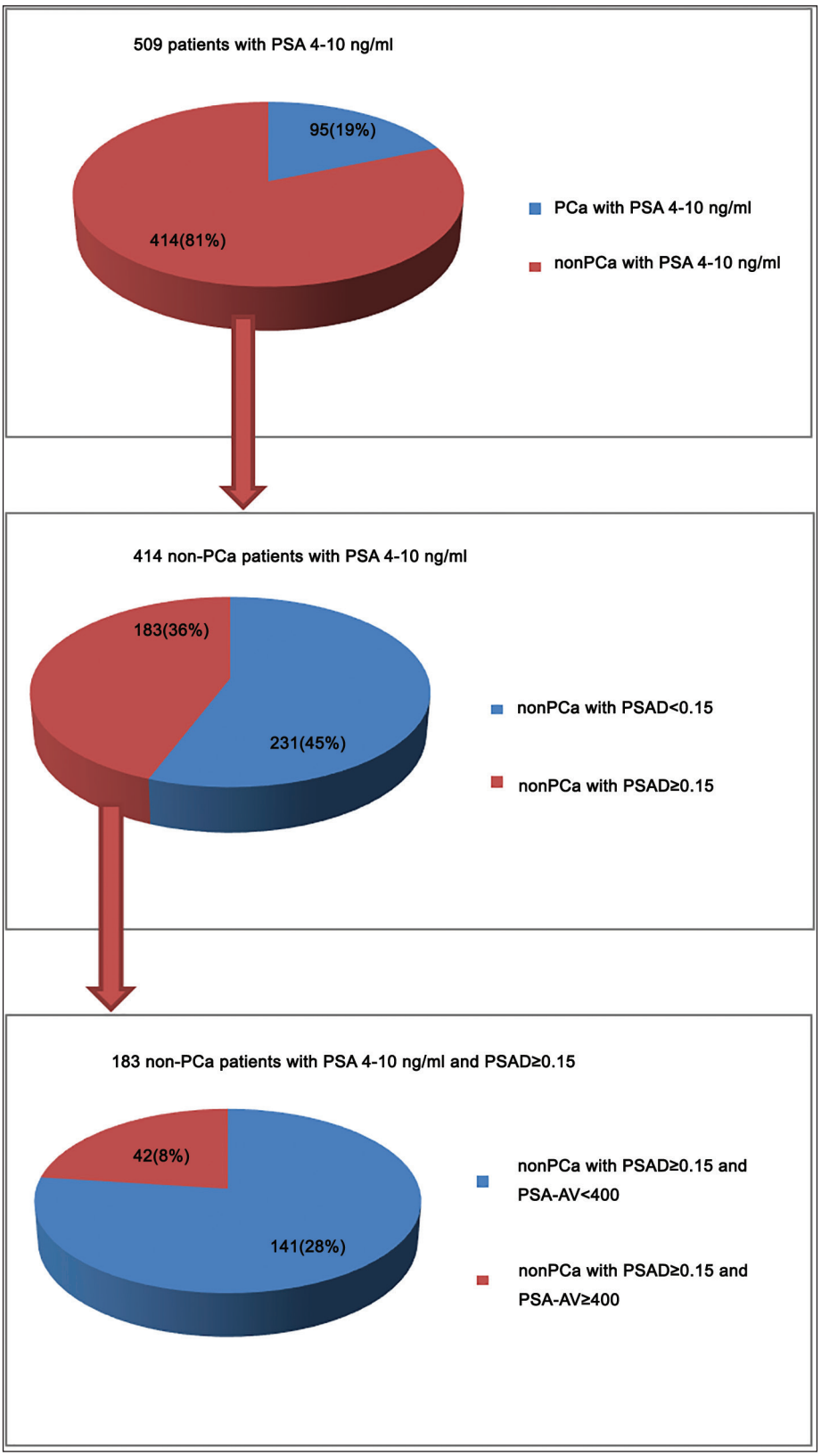
Supplementary Table 1: Evaluation of the area under the receiver operating characteristic curves of prostate-specific antigen and its derivatives in predicting Gleason ≥7 prostate cancer

All PSA	*AUC*	*Gleason ≥7 PCa (34.5%)*		
		Lower 95%	*Upper 95%*	*P*[a]
PSA	0.825	0.806	0.845	
PSAD[b]	0.861	0.844	0.878	7.5×10^{-3}
PSA-AV[c]	0.851	0.834	0.869	4.9×10^{-2}
PSA=2.0–20.0 ng ml^{-1}	*AUC*	*Gleason ≥7 PCa (16.4%)*		
		Lower 95%	*Upper 95%*	*P*[a]
PSA	0.615	0.573	0.657	
PSAD[b]	0.732	0.694	0.771	3.6×10^{-5}
PSA-AV[c]	0.707	0.667	0.746	1.5×10^{-3}

[a]The *P* value referred to the significance between PSAD or PSA-AV and PSA.
[b]PSAD = PSA/PV, PV (ml) = height (cm) × length (cm) × width (cm) × 0.52.
[c]PSA-AV = age × PV/PSA. PCa: prostate cancer; PSA: prostate-specific antigen; PSAD: prostate-specific antigen density; PSA-AV: prostate-specific antigen-age volume; AUC: area under the receiver operating characteristic curve; PV: prostate volume



Supplementary Figure 1: Number of unnecessary biopsies spared by combining PSAD and PSA-AV. ROC: receiver operating characteristic curve; tPSA: total prostate-specific antigen; PSA-AV: prostate-specific antigen-age volume; PSAD: prostate-specific antigen density.