

# Improving the detection rate of prostate cancer in the gray zone of PI-RADS v2 and serum tPSA by using prostate-specific antigen–age volume

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## Abstract

To improve the detection of prostate cancer (PCa) by combining the Prostate Imaging Reporting and Data System version 2 (PI-RADS v2) and prostate-specific antigen–age volume (PSA–AV), especially among those in gray zone with PI-RADS v2 score 3 or serum total prostate-specific antigen (tPSA) 4 to 10 ng/mL.

The 357 patients were enrolled in this study. The PI-RADS v2 scoring system was used to represent characteristics on multiparametric magnetic resonance imaging (mpMRI). PI-RADS v2 score 3 or tPSA 4 to 10 ng/mL were defined as the gray zone in detecting PCa. The formula equates to the patient age multiplied by the prostate volume, which is divided by the tPSA level. Univariate and multivariate analyses were done to ascertain significant predictors of prostate cancer.

In all, 174 (48.7%) were benign prostatic hyperplasia, 183 (51.3%) had PCa. The results showed that PI-RADS v2, tPSA, and PSA–AV were significant independent predictors of prostate cancer. PI-RADS v2 score  $\geq 4$  could detect PCa with rate of 82.1%. Serum tPSA  $\geq 10$  ng/mL could detect PCa with rate of 66.2%, PSA density (PSAD)  $\geq 0.15$  ng/mL/cc with rate of 62.8%, and PSA–AV  $\leq 250$  with rate of 83.5%. Combining with PSA–AV  $\leq 250$ , patients those with tPSA 4 to 10 ng/mL could improve the detection from 36.0% up to 81%, those with PI-RADS v2 score 3 from 28.6% up to 60.0%.

PI-RADS v2 and PSA–AV are faithful variables for detecting PCa. And for patients, those in gray zones of PI-RADS v2 and tPSA, PSA–AV can improve detection rate of PCa.

**Abbreviations:** DWI = diffusion weighted imaging, mpMRI = multiparametric magnetic resonance imaging, PCa = prostate cancer, PI-RADS v2 = The Prostate Imaging Reporting and Data System version 2, PSA–AV = prostate-specific antigen–age volume, PSAD = prostate-specific antigen density, tPSA = total prostate-specific antigen, TRUS = transrectal ultrasound.

**Keywords:** MRI, PI-RADS score, PSA, volume

## 1. Introduction

Prostate cancer (PCa) is the second most common cancer worldwide, and its death rate ranks sixth in males<sup>[1]</sup> and the

number of males diagnosed as PCa in Asia is dramatically increasing.<sup>[2]</sup> Prostate-specific antigen (PSA), as a classical parameter, is widely used to monitor PCa,<sup>[3]</sup> and the cut-off point, 4 ng/mL, indicates the increasing risk of PCa.<sup>[4]</sup> However, it is prone to lead to over diagnosis and overtreatment owing to its lack of accuracy. For people with PSA levels between 4 and 10 ng/mL, which is a gray zone, only a quarter suffer from PCa.<sup>[5]</sup> Thus, reliable parameters are needed to improve the accurate diagnosis of PCa.

Multiparametric magnetic resonance imaging (mpMRI) can identify the presence of PCa and it is suggested that mpMRI is helpful in improving the diagnosis of PCa.<sup>[6]</sup> In 2014, the Prostate Imaging-Reporting and Data System Version 2 (PI-RADS v2) was published to establish a globally agreed upon criterion regarding PCa diagnosis on imaging. It classifies all imaging characteristics into 5 points of diagnosis PCa: 1 point, which indicates very low probability; to 5 points, which indicates very high probability.<sup>[7]</sup> PI-RADS v2 has not provided the follow-up management for lesions of score 3. It is reported in several researches that the PI-RADS v2 score 3 has no connection with clinically significant PCa,<sup>[8]</sup> while some report that score 3 is a characteristic of the indeterminate zone detection of PCa.<sup>[9]</sup>

In order to improve the diagnosis of PCa in these gray zones, this study makes use of prostate-specific antigen–age volume (PSA–AV). PSA–AV is a parameter derived from a simple combination of total prostate-specific antigen (tPSA), age, and prostate volume.<sup>[10]</sup> The formula equates to the patient age multiplied by the prostate volume, which is divided by the tPSA

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level ( $PSA-AV = \text{volume} \times \text{age}/tPSA$ ). PSA-AV scores show its capacity in predicting the absence or presence of PCa. Furthermore, the role of PSA-AV in the Chinese population is proved preliminarily, especially in younger patients.<sup>[11]</sup> Therefore, this study investigates the ability of PSA-AV to detect PCa in the gray zone with PI-RADS v2 score 3 or serum tPSA 4 to 10 ng/mL.

## 2. Materials and methods

### 2.1. Patient population

This is a retrospective study performed at our institution. Institutional review board approval and informed consent were obtained. Between January 2014 and December 2017, a total of 1720 patients underwent prostate MRI at this institution. Excluding cases were based on the following items:

- (1) Prostate mpMRI, patients previously accepted treatment, (drug treatment, biopsies, or surgical therapy);
- (2) Serum examinations were missing or performed after treatment;
- (3) The time interval between MRI and the following transrectal ultrasound (TRUS)-guided 12-core prostate biopsy was more than 2 weeks. Finally, 357 patients were eligible for the study.

### 2.2. MRI

All patients were performed MR examinations on 3.0T GE equipment (DISCOVER MR750 GEHC/GEHC), using a multi-channel vitro coil. Turbo spin-echo T2-weighted imaging (repetition time msec/echo time msec, 4291–4569/95.9–101.2; section thickness, 3 to 4 mm; intersection gap, 0 mm; field of view, 200 × 200 mm; matrix, 352 × 352), diffusion-weighted imaging (DWI, repetition time msec/echo time msec, 4000/57–59; section thickness, 3–4 mm; intersection gap, 0 mm; field of view, 370 × 370 mm; matrix, 128 × 160), apparent diffusion coefficient and dynamic contrast-enhanced (repetition time msec/echo time msec, 4.3/1.9–2.0; section thickness, 3–4 mm; intersection gap, 0 mm; field of view, 320 × 320 mm; matrix, 320 × 224; does 0.1 mmol/kg standard gadolinium-based contrast agent; injection rate: 2–3 cc/sec) were done. The b value of DWI was 1500 s/mm<sup>2</sup>.

### 2.3. Pathology

The prostate biopsies were taken transrectally using an automatic biopsy gun and a 12+X-G needle under ultrasound-guidance (TRUS, 6 in the peripheral zone and 6 in the transitional zone, X in suspicious zone). TRUS-guided biopsy combined TRUS-guided targeted biopsy with cognitive MRI fusion-guided targeted biopsy. Prostate surgery included radical prostatectomy and transurethral resection of the prostate. The specimens which were obtained in ways above were assessed by experienced pathologists.

### 2.4. Statistical analyses

The imaging was read by a senior radiologist who was trained through PI-RADS v2 criterion and blinded to clinical data to decrease bias. T2-weighted imaging and DWI were the dominant determining sequences for transition zone and the peripheral zone, respectively. Prostate volume was measured in T1-weighted imaging and the formula equated to the length multiplied by the

width by height by 0.52. According to PSA level, patients were divided into 3 groups: ≤4 ng/mL as group 1; 4 to 10 ng/mL as group 2; and >10 ng/mL as group 3. All data were analyzed in SPSS 23.0 and  $P < .05$  was thought to have statistical significance. PSA, PSA-AV, age, prostate volume, and PI-RADS v2 were included to predict PCa. Univariate and multivariate analyses were done to ascertain significant predictors of prostate cancer. Detection rate was used to evaluate the diagnostic performance. Receiver operating characteristic analysis was done to find the suitable cut-off point of PSA-AV score to detect PCa.

## 3. Results

Patients characteristics were presented in Table 1. The media and interquartile range relating to age, tPSA, volume, and PAV-AV were 68 (63–74) years, 11.06 (6.79–21.34) ng/mL, 49.18 (30.70–57.62) mL, and 357 (121–453), respectively. According to the tPSA level, 6.4% (23/357) belonged to group 1 (tPSA ≤4 ng/mL), 38.1% (136/357) belonged to group 2 (tPSA between 4 and 10 ng/mL), 55.5% (198/357) belonged to group 3 (tPSA >10 ng/mL). The number of PI-RADS v2 score 1–2 were 154; score 3 was 35; scores 4 to 5 were 168. Moreover, the cut-off line at 250 of PSA-AV was the critical value necessary to reach the maximum Youden index. The number of patients whose PSA-AV ≤250 were 164.

Of the 357 patients involved in the study, 48.7% (174/357) were benign prostatic hyperplasia and 51.3% (183/357) were diagnosed as PCa. Among patients of PCa, 18.6% (34/183) had a Gleason score of 6, 40.4% (74/183) had a Gleason score of 7 and 41.0% (75/183) had a Gleason score of 8 to 10.

The pathologic result stratified by tPSA, prostate-specific antigen density (PSAD), PSA-AV, and PI-RADS v2 are described in Figure 1. The detection rate of PCa among tPSA group 1 to 3 were 13.0% (3/23), 36.0% (49/136), and 82.4% (131/159). The cutoff point at 0.15 ng/mL/cc had detection rate of PCa with 62.8%. When the PSA-AV ≤250 was meant to be positive, the detection rate of PCa was 83.5% (137/164). The detection rate of PCa using the PI-RADS v2 score of 1 to 2, 3, 4 to 5 were 29.4% (35/119), 28.6% (10/35), and 82.1% (138/168), respectively.

**Table 1**  
The patients' characteristics.

Variable	Value	
	Media	IQR
Age, yr	68	63–74
tPSA, ng/mL	11.06	6.79–21.34
PSA-AV	357	121–453
Volume, mL	49.18	30.70–57.62
	frequency	percent
Gleason score		
BPH	174	48.7
Score 6	34	9.5
Score 7	74	20.7
Score 8	47	13.2
Score 9	22	6.2
Score 10	6	1.7
PI-RADSv2 score		
1–2	154	43.1
3	35	9.8
4–5	168	41.1

BPH=benign prostatic hyperplasia, IQR=interquartile range, PI-RADS v2=The Prostate Imaging-Reporting and Data System Version 2, tPSA=total prostate-specific antigen.

	prostate cancer detection rate (%)		
	1-2	3	4-5
PI-RADS v2	29.4	28.6	82.1
	≤4	4-10	>10
PSA (ng/ml)	13.0	36.0	82.4
	13.0	36	82.4
PSAD (ng/ml/cc)	<0.15	≥0.15	
	15.9	62.8	
PSA-AV	>250	≤250	
	23.8	83.5	

**Figure 1.** Prostate cancer detection stratified by PI-RADS v2 score, tPSA and PSA-AV.

PSA-AV, PSAD, tPSA, and PI-RADS v2 were significant predicative parameters for PCa in univariate logistic regression analysis (Table 2). The multivariate logistic regression analysis suggested that PSAD, PI-RADS v2, and PSA-AV were independent predictors of PCa (Table 2).

In the transition zone, PSA-AV ≤250 could detect PCa with rate of 67.3% (33/49), and PSAD ≥0.15 ng/mL/cc with rate of 38.5% (42/109). In the peripheral zone, PSA-AV ≤250 could detect PCa with rate of 90.4% (104/115), and PSAD ≥0.15 ng/mL/cc with rate of 79.4% (127/160) (Tables 3–5).

Figure 2 revealed the detection rate stratified by each subgroup of tPSA, PSA-AV and PI-RADS v2. The study organized the subgroups to detect PCa in the light of the PI-RADS v2 scores of 1 to 2, 3, and 4 to 5. Based on the PI-RADS v2 score 3, a lower PSA-AV and higher PSA showed a stronger connection with positive pathologic outcomes. Among patients of PI-RADS v2 score 3, those with a PSA-AV ≤250 had a detection rate of 60%, compared to the 16.7% detected in those with a PSA-AV >250. Likewise, in this subgroup, group 3 tPSA had a detection rate of 37.5%, compared to the 22.2% of those in group 2. However, combing PSA-AV and tPSA with the PI-RADS v2 score of 4 to 5, the detection rate was not as satisfactory. For patients of PI-RADS v2, 4 to 5, those with a PSA-AV ≤250 had a detection rate

of 92.4%, compared to the 57.1% of PSA-AV >250. Likewise, in this subgroup, group 3 of tPSA had detection rate of 89.8%, compared to the 66.7% of those in group 2 of tPSA (Fig. 2A). The function of PSAD in detecting PCa in subgroups of tPSA and PI-RADS v2 was presented in Figure 2B.

#### 4. Discussion

The study revealed that PI-RADS v2, PSAD, PSA-AV, and tPSA were the significant predictors for PCa. PI-RADS v2 itself was efficient in diagnosing PCa. When the PI-RADS v2 score 4 was supposed to be positive, the detection rate was quite satisfactory, up to 82.1%. This result was similar to previous researches.<sup>[12–14]</sup> PI-RADS v2 score 2 rarely yield to PCa, while the connection between PI-RADS v2 score 3 as well as the presence of PCa was uncertain.<sup>[9,15]</sup> In this situation, other parameters may be needed to decrease false-positives and increase the cancer detection rate.<sup>[16]</sup> Furthermore, the PI-RADS v2 score in subgroups according to tPSA and PSA-AV represent different diagnostic accuracy. Those patients in higher tPSA or lower PSA-AV group, lower PI-RADS v2 score also detected the PCa more effectively (Fig. 2).

The serum tPSA is the most useful cancer marker in predicting PCa.<sup>[17]</sup> However, tPSA has its limitations in clinical experience as it is influenced by a variety of factors, including age, volume, medicine, and others. In previous researches, the specificity of tPSA in 4 to 10 ng/mL was not very high,<sup>[18,19]</sup> which lead to numerous unnecessary biopsies. Some researches confirmed that age was a significant variable associated with serum tPSA.<sup>[20,21]</sup> The baseline serum tPSA for detecting PCa was increasing in parallel with age. Furthermore, the prostate volume, based on MRI, could improve the effectiveness of tPSA for predicting PCa.<sup>[22,23]</sup> PSA-AV, incorporating age, prostate volume and serum tPSA, is a parameter to predict PCa, which was introduced by Patel et al<sup>[10]</sup> Wu YS et al<sup>[11]</sup> had tested the PSA-AV performance in predicting PCa and proved that it was an effective variable in diagnosing PCa, especially in young patients and those with small prostate volumes.

**Table 2**

**Univariate and multivariate logistic regression analyses to detect prostate cancer.**

	Univariate analysis				Multivariate analysis			
	OR	95% confidence interval		P	OR	95% confidence interval		P
		Lower	Upper			Lower	Upper	
PI-RADS v2								
1–2	—	—	—	—	—	—	—	—
3	1.36	0.596	3.102	.485	1.367	0.487	3.836	.552
4–5	15.64	9.061	26.995	<.001	3.046	2.13	4.354	<.001
PSAD								
<0.15	—	—	—	—	—	—	—	—
≥0.15	8.944	4.794	16.646	.044	5.136	2.189	12.053	<.001
PSA-AV								
>250	—	—	—	—	—	—	—	—
≤250	16.215	9.553	27.524	<.001	8.964	3.485	23.055	<.001
tPSA								
group 1	—	—	—	—	—	—	—	—
group 2	3.755	1.062	13.277	.022	4.528	1.053	19.46	.042
group 3	13.035	3.739	45.436	<.001	1.26	0.506	3.134	.062
volume	0.965	0.955	0.976	<.001	0.966	0.95	0.982	<.001
age	1.08	1.05	1.11	<.001	1.134	1.087	1.183	<.001

PI-RADS v2=The Prostate Imaging Reporting and Data System version 2, tPSA=total prostate-specific antigen, PSAD=prostate-specific antigen density, PSA-AV=prostate-specific antigen–age volume.

PI-RADS v2	PSA-AV	prostate cancer detection rate (%)		
		tPSA group		
		1	2	3
1-2	>250	5.9 (1/17)	17.4 (12/69)	3.0 (1/33)
	≤250	0 (0/0)	75 (3/4)	58.1 (18/31)
3	>250	0.0 (0/1)	12.5 (2/16)	25.0 (2/8)
	≤250	0.0 (0/0)	100.0 (2/2)	50.0 (4/8)
4-5	>250	40.0 (2/5)	60.0 (18/30)	57.1 (8/14)
	≤250	0.0 (0/0)	80.0 (12/15)	94.2 (98/104)

PI-RADS v2	PSAD	prostate cancer detection rate (%)		
		tPSA group		
		1	2	3
1-2	<0.15	6.3 (1/16)	13.2 (5/38)	0.0 (0/6)
	≥0.15	0.0 (0/1)	28.6 (10/35)	32.8 (19/58)
3	<0.15	0.0 (0/1)	11.1 (1/9)	50.0 (1/2)
	≥0.15	0.0 (0/0)	33.3 (3/9)	35.7 (5/14)
4-5	<0.15	40.0 (2/5)	42.9 (3/7)	25.0 (1/4)
	≥0.15	0.0 (0/0)	71.1 (27/38)	92.1 (105/114)

**Figure 2.** The detection rate of PCa stratified by each subgroup of PSA-AV (2a) and PSAD (2b) in different groups of PI-RADS v2 and serum tPSA.

To the best of our knowledge, this study is the first research to assess the PSA-AV in the gray zone with PI-RADS v2 score 3 or serum tPSA 4 to 10 ng/mL. The result revealed that of patients in the gray zone, the PSA-AV score was useful in predicting the presence of PCa. Though a PI-RADS v2 score ≤3 suggested lower probabilities of PCa, our study showed that a PSA-AV ≤250 was helpful in raising the detection rate in this range. The same situation in patients of tPSA levels between 4 and 10 ng/mL. By evaluating PSA-AV in the presence of PCa, it could finely improve the problem associated with tPSA: sensitivity in assessing PCa that was relatively low.

Though the PI-RADS v2 is a standard criterion for detecting PCa, it only assesses the appearances on MRI but ignores the capacity of clinical parameters.<sup>[24,25]</sup> In this study, a crosstab was drawn to evaluate the risk of PCa in different subgroups, and detection rates were calculated. Based on our study, we classified

**Table 3** Prostate cancer detection stratified by PI-RADS v2 score, tPSA, or PSA-AV.

	Prostate cancer detection rate (%)		
	1-2	3	4-5
PI-RADS v2	29.4	28.6	82.1
tPSA (ng/mL)	≤4 13.0	4-10 36.0	>10 82.4
PSAD (ng/mL/cc)	<0.15 15.9	≥0.15 62.8	82.4
PSA-AV	>250 23.8	≤250 83.5	

PI-RADS v2 = the Prostate Imaging Reporting and Data System version 2, PSA-AV = prostate-specific antigen-age volume, PSAD = prostate-specific antigen density, tPSA = total prostate-specific antigen.

**Table 4** The detection rate of PCa stratified by each subgroup of tPSA, PSA-AV, and PI-RADS v2.

PI-RADS v2	PSA-AV	prostate cancer detection rate, %		
		tPSA group		
		1	2	3
1-2	>250	5.9 (1/17)	17.4 (12/69)	3.0 (1/33)
	≤250	0 (0/0)	75 (3/4)	58.1 (18/31)
3	>250	0.0 (0/1)	12.5 (2/16)	25.0 (2/8)
	≤250	0.0 (0/0)	100.0 (2/2)	50.0 (4/8)
4-5	>250	40.0 (2/5)	60.0 (18/30)	57.1 (8/14)
	≤250	0.0 (0/0)	80.0 (12/15)	94.2 (98/104)

PCa = Prostate cancer, PI-RADS v2 = The Prostate Imaging Reporting and Data System version 2, PSA-AV = prostate-specific antigen-age volume, tPSA = total prostate-specific antigen.

patients into different risk grades according to their PI-RADS v2 score, serum tPSA and PSA-AV. For patients of PI-RADS v2 scores 1 to 2, if the PSA-AV was ≤250 and the tPSA was >4 ng/mL, it would be favorable to organized follow-up therapeutic measures. Of the PI-RADS v2 score 3, the gray zone is used to detect PCa in clinical experiences, with an associated detection rate of 28.6%. For these patients, the risk of PCa decreases when the PSA-AV is >250 or the PSA-AV is ≤250 and tPSA ≤4 ng/mL simultaneously. When the PI-RADS v2 score exceeds 4, it yields to PCa highly unless the tPSA ≤4 ng/mL. In this way, dividing PI-RADS v2 into more detailed subgroups may be helpful for urologist when making clinical decisions.

The study also discussed the efficiency in detecting PCa of PSAD and PSA-AV. Comparing with PSAD, the variable PSA-AV attached importance to age because the cutoff point of predicting PCa of serum tPSA increased with age.<sup>[26,27]</sup> Both PSAD and PSA-AV showed stronger capacity in assessing PCa in

**Table 5** The detection rate of PCa stratified by each subgroup of tPSA, PSAD, and PI-RADS v2.

PI-RADS v2	PSAD	Prostate cancer detection rate, %		
		tPSA group		
		1	2	3
1-2	<0.15	6.3 (1/16)	13.2 (5/38)	0.0 (0/6)
	≥0.15	0.0 (0/1)	28.6 (10/35)	32.8 (19/58)
3	<0.15	0.0 (0/1)	11.1 (1/9)	50.0 (1/2)
	≥0.15	0.0 (0/0)	33.3 (3/9)	35.7 (5/14)
4-5	<0.15	40.0 (2/5)	42.9 (3/7)	25.0 (1/4)
	≥0.15	0.0 (0/0)	71.1 (27/38)	92.1 (105/114)

PCa = prostate cancer, PI-RADS v2 = The Prostate Imaging Reporting and Data System version 2, PSAD = prostate-specific antigen density, tPSA = total prostate-specific antigen.

peripheral zone than transition zone. In PI-RADS v2 score 3, the PSA-AV was more efficient in predicting PCa than PSAD, and in tPSA between 4 to 10 ng/mL, the performances of PSA-AV were better than PSA, too. However, the superiority was not enormous.

This study had several limitations. First, our study is retrospective and patient selection bias existed. Pay no attention to the role of extreme values of clinical data. Furthermore, the PI-RADS score was evaluated by 1 radiologist, although he did have 10 years of experience in abdominal imaging. Third, the number of cases was still far from satisfactory. In the future, more cases are needed to balance the number of subgroups. Furthermore, the criteria of parameters classification could be made to be more detailed because the level of serum tPSA is influenced by race, body mass index, and other factors.<sup>[28-30]</sup>

## 5. Conclusions

Though PI-RADS v2 performed well in predicting the presence of PCa, in patients of score 3, it needed stricter criteria. Putting serum tPSA and PSA-AV into detecting PCa, patients could be divided into more detailed subgroups of PCa. And in this way, the detection rate of PCa in gray zone may increase.

## Author contributions

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