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Diagnostic accuracy of MRI-based PSA density for detection of prostate cancer among the Thai population

Chalida Aphinives*, Supajit Nawapun and Chutima Tungnithiboon

Abstract

Background The PSAD calculating by the serum PSA level divided by prostate volume had more specificity and accuracy than the serum PSA level for detection of prostate cancer.

Methods MRI examinations of 319 patients who had suspected prostate cancer between January 2014 and December 2019 were retrospectively reviewed. Prostate volumes were measured by MRI images and PSAD values were calculated. The accuracy and optimal cutoff points of MRI-based PSAD were evaluated using receiver operating characteristic curves (ROC curves). Correlations between the MRI-based PSAD and Gleason scores were also analyzed to predict prognosis of prostate cancer.

Results Overall, of 154 patients were included in this study, 59 patients (38.31%) were diagnosed with prostate cancer. The optimal cutoff point of PSAD was 0.16 (81.40% sensitivity, 54.70% specificity, 52.70% PPV, 82.50% NPV), and the AUC was 0.680 (95% CI: 0.609–0.751). In subgroup analyses, the optimal cutoff point of PSAD in patients with serum PSA 4–10 ng/ml was 0.16 (61.10% sensitivity, 76.00% specificity) and for > 10 ng/ml was 0.30 (68.30% sensitivity, 64.30% specificity). Furthermore, there was a statistically significant correlation between PSAD and Gleason scores (*p*-value 0.014).

Conclusions The optimal cutoff point of MRI-based PSAD was 0.16 which was relatively different from international consensus.

Keywords PSAD, PSA density, MRI-based PSAD, Prostate cancer

1 Background

Prostate cancer is the 4th most common cancer in Thai men with 6467 new cases in 2018 or 7.6% of all new cancer cases in Thai men [1]. Early treatments of the prostate cancer can improve survival rates and quality of life of the patients, thus the screening tools have an important role in improving quality of life of the patients [2]. Nowadays, Prostate-Specific-Antigen (PSA) is among the best screening tools for early detection due to high sensitivity. The limitation of PSA is its relative lack of specificity. Other conditions could elevate PSA level, such as benign prostatic hypertrophy (BPH), and prostatitis [3, 4].

The PSA density (PSAD) which is calculated from the PSA level (ng/ml) divided by prostate volume (ml) is more accurate and has more specificity than the PSA level alone for detection of prostate cancer [5–9]. The optimal cutoff point of PSAD for detection of prostate cancer was different among races [10–13].

This study was aimed to investigate the accuracy and optimal cutoff point of the MRI-based PSAD among Thai population. Ibrahim et al. reported there was a significant relationship between the PSAD and the

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Gleason score in prostate cancer patients [14]. Thus, this study was also aimed to investigate the correlation between the PSAD and Gleason score for predicting prognosis of prostate cancer patients.

2 Methods

2.1 Patient population

This retrospective study was approved by the Ethics Committee for Human Research. The MRIs of the prostate gland of patients who were suspected of prostate cancer between January 2014 and December 2019 were retrospectively reviewed.

2.1.1 Inclusion criteria

1. Patients who underwent MRI of the prostate gland.
2. Patients who underwent biopsy of the prostate gland and were pathologically confirmed, regardless of systemic or targeted biopsy, TRUS alone or MRI-fusion and number of core biopsy.
3. Serum PSA levels of patients who were investigated within 3 months from MRIs of their prostates, prior to biopsy.

2.1.2 Exclusion criteria

1. Patients who were treated before undergoing MRI of prostate gland, including surgery, radiation therapy, chemotherapy, or hormonal treatment.

2.2 MRI techniques and evaluation

All patients were imaged with the MRI technique using the 3-T MRI scanner (Achieva, Philips Heath Care) or 1.5-T MRI scanner (Aera, Siemens AG 2012), without an endorectal coil.

Width was measured in the axial T2W image; length and height were measured in the mid-sagittal T2W image, as shown in Fig. 1. Three dimensions of prostate gland were measured by two radiologists (one genitourinary radiologist, and a body imaging radiologist) for calculating prostate volume. The prostate volume was calculated using the ellipsoid formula:

$$\begin{aligned} &Prostate\ volume(ml) \\ &= width\ (cm) \times length\ (cm) \\ &\quad \times height\ (cm) \times \frac{\pi}{6} \end{aligned}$$

Two radiologists independently reviewed images and blinded to patient information. The interrater reliability was also assessed.

2.3 PSAD calculation

The PSAD was calculated by

$$PSAD = \frac{PSA\ level\ (ng/ml)}{prostate\ volume(ml)}$$

2.4 Statistical analyses

Categorical variables were demonstrated as numbers (percentage). Continuous variables were demonstrated as mean (±standard deviation) or median

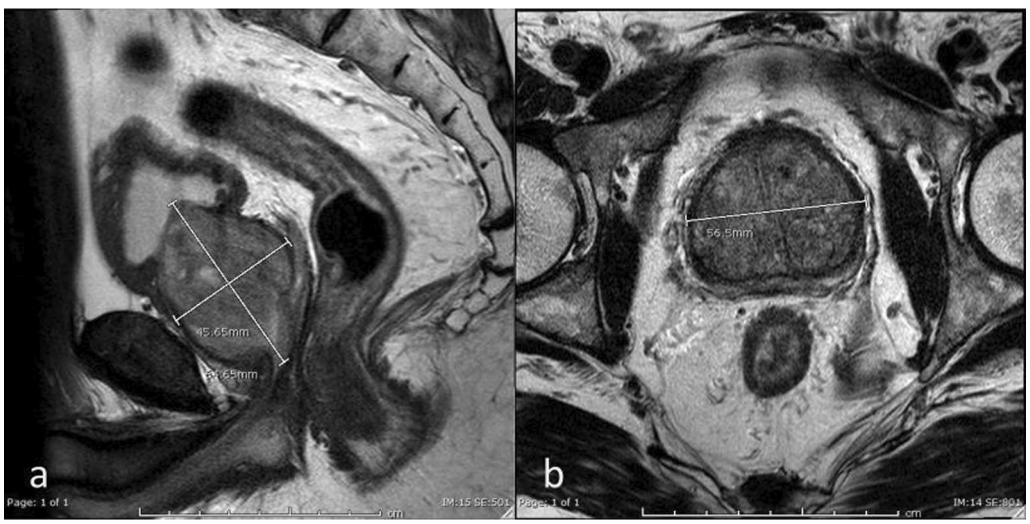

Fig. 1 Measurement of prostate gland size in three dimensions. **a** Mid-sagittal image using for measurement of length and height. **b** Axial T2W using for measurement of width

(± interquartile range), as appropriate. Comparison of categorical variables was done using Fisher's exact test or Chi-square test, as appropriate. Comparison of continuous variables using the independent Student *t*-test or Mann–Whitney U test, as appropriate.

Subgroup analyses of PSAD were also performed and categorized in three groups; patients with serum PSA levels < 4 ng/ml, 4–10 ng/ml, and > 10 ng/ml. Comparisons of categorical and continuous variables of subgroups were performed using the Chi-square test and one-way ANOVA or Kruskal-Walis test, as appropriate.

The receiver operating characteristic curves (ROC curves) were used to evaluate the accuracy of PSAD for detection of prostate cancer and optimal cutoff points. Correlation between PSAD and the Gleason score was analyzed using the Kruskal-Walis test.

Inter-rater reliability was also performed using the Intraclass Correlation Coefficient (ICC).

All analyses were performed using RelSTATA version 10. A p-value < 0.05 was considered statistically significant.

3 Results

3.1 Patient population

MRI examinations of 319 patients who had suspected prostate cancer between January 2014 and December 2019 were retrospectively reviewed. Among these patients, 165 were excluded due to incomplete data (92) and prior treatments (73). Therefore, 154 patients were included in analyses.

Patient ages ranged from 50 to 90 years (mean 66.70 ± 7.15). Fifty-nine of the 154 patients (38.31%) were positive for prostate cancer.

The median serum PSA level and median prostate volume of prostate cancer patients was 14.00 ng/ml (IQR, 9.58–45.13) and 46.99 ml (IQR, 32.68–63.92). The median serum PSA level of 9.30 ng/ml (IQR, 6.49–13.79) and median prostate volume of patients without prostate cancer was 62.41 ml (40.60–79.79). Patients with prostate cancer had significantly higher serum PSA levels, and PSADs than patients without prostate cancer, p-values < 0.001, and 0.017. Demographic data of all patients are shown in Table 1. The patients were categorized into

Table 1 Demographic data of all patients

Variables	Value			
	Total (n = 154)	**Cancer (n = 59)**	**No cancer (n = 95)**	***p*-value**
Age at MRI (years), mean (SD)	66.70 (7.15)	68.61 (7.25)	65.50 (6.86)	0.008
Comorbidities, *n* (%)	81 (52.60)	30 (50.85)	51 (53.68)	0.732
Diabetic mellitus	20 (12.99)	12 (20.34)	8 (8.42)	0.032
Hypertension	28 (18.18)	15 (25.42)	13 (13.68)	0.066
Heart disease	7 (4.55)	4 (6.78)	3 (3.16)	0.429
Dyslipidemia	19 (12.34)	8 (13.56)	11 (11.58)	0.716
Cerebrovascular disease	12 (7.79)	4 (6.78)	8 (8.42)	> 0.999
Others	42 (27.27)	17 (28.81)	25 (26.32)	0.735
Serum PSA levels (ng/ml)				
Median, IQR	10.46 (7.10–20.07)	14.00 (9.58–45.13)	9.30 (6.49–13.79)	< 0.001
< 4 ng/ml, n (%)	3 (1.95)	0 (0.00)	3 (3.16)	
4–10 ng/ml, n (%)	68 (44.16)	18 (30.51)	50 (52.63)	
> 10 ng/ml, n (%)	83 (53.90)	41 (69.49)	42 (44.21)	
Prostate volume (cm^3)				
Median (IQR)	56.98 (37.49–76.40)	46.99 (32.28–63.92)	62.41 (40.60–79.79)	0.016
PSAD, median (IQR)	0.21 (0.12–0.42)	0.31 (0.19–0.94)	0.16 (0.10–0.26)	< 0.001
Gleason score, *n* (%)				
2 + 3 = 5		2 (3.64)		
3 + 3 = 6		16 (29.09)		
3 + 4 = 7		16 (29.09)		
4 + 3 = 7		8 (14.55)		
4 + 4 = 8		4 (7.27)		
4 + 5 = 9		4 (7.27)		
5 + 4 = 9		4 (7.27)		
5 + 5 = 10		1 (1.82)		

3 subgroups with serum PSA levels of < 4 ng/ml, 4–10 ng/ml, and > 10 ng/ml. There were only 3 patients (1.95%) with serum PSA levels < 4 ng/ml, and none of these patients was diagnosed with prostate cancer. There were 68 patients (44.16%) with serum PSA levels 4–10 ng/ml, and 83 patients (53.90%) with serum PSA > 10 ng/ml. Eighteen patients (30.51%) with serum PSA levels 4–10 ng/ml and 41 patients (69.49%) with serum PSA levels > 10 ng/ml were diagnosed with prostate cancer, (*p*-value 0.006). PSAD among these subgroups were those with serum PSA levels < 4, 0.04 (0.015–0.065), 4–10, 0.13 (0.09–0.22), and > 10 ng/ml, 0.32 (0.19–0.79) among patients with significant differences (*p*-value < 0.001). Demographic data of these subgroups are shown in Table 2.

3.2 ROC curves of PSAD were analyzed for detection of prostate cancer

The optimal cutoff point was 0.16 (81.40% sensitivity, 54.70% specificity, 52.70% positive predictive value, 82.50% negative predictive value) as shown in Table 3, and the area under the curve was 0.680 (95%CI: 0.609–0.751).

In subgroup analyses, the optimal cutoff point of patients with serum PSA levels 4–10 ng/ml, and > 10 ng/ml was 0.16 (61.10% sensitivity, 76.00% specificity) and 0.30 (68.30% sensitivity, 64.30% specificity) as shown in Table 4. The receiver operating characteristic (ROC) curves of PSAD in identification of prostate cancer are shown in Fig. 2.

3.3 Correlation between PSAD and gleason score

The median PSADs were 0.27, 0.19, 0.27, 0.23, 0.23, 1.62, 0.86, 2.42 in patients with Gleason scores of 2 + 3, 3 + 3, 3 + 4, 4 + 3, 4 + 4, 4 + 5, 5 + 4, 5 + 5. A statistically significant correlation between PSAD and Gleason scores (*p*-value 0.014) was found. Box plots of PSADs stratified by the Gleason score are shown in Fig. 3.

3.4 Interobserver agreement

Intraclass Correlation Coefficient (ICC) between two radiologists was 0.9894 (95%CI 0.9855–0.9922), indicating good reliability.

4 Discussion

Serum PSA levels are currently used as screening tools for detection of prostate cancer, however, there is a relative lack of specificity. The current study found the median serum PSA level in patients with prostate cancer was significantly higher than its patients without prostate cancer (14.00 ng/ml of serum PSA in patients with prostate cancer, and 9.30 ng/ml of patients without prostate cancer), *p*-value < 0.001. Furthermore, the median prostate volume in patients with prostate cancer was significantly lower than its patients without prostate cancer (46.99 ml of volume in patients with prostate cancer and 62.41 ml of volume in patients without prostate cancer), *p*-value = 0.016. These findings were concordant with previous studies that revealed benign prostate hypertrophy could elevate serum PSA levels. [3, 4, 7]

Table 2 Demographic data of patients with serum PSA levels < 4 ng/ml, 4–10 ng/ml, and > 10 ng/ml

Variables	Serum PSA levels (ng/ml)			
	< 4 (*n* = 3)	**4–10 (*n* = 68)**	**> 10 (*n* = 83)**	***p*-value**
Age at MRI (years), mean (SD)	68.67 (4.73)	65.53 (6.69)	67.60 (7.51)	0.189
Prostate volume (cm^3)				
Median (IQR)	29.88 (21.79–31.32)	55.57 (37.77–77.20)	59.71 (38.97–76.90)	0.049
PSAD Median (IQR)	0.05 (0.03–0.08)	0.13 (0.09–0.22)	0.32 (0.19–0.79)	< 0.001
Pathology, *n* (%)				
Cancer	0 (0.00)	18 (30.51)	41 (69.49)	0.006
No cancer	3 (3.16)	50 (52.63)	42 (44.21)	
Gleason score, *n* (%)				
2 + 3 = 5		1 (5.88)	1 (2.63)	
3 + 3 = 6		6 (35.29)	10 (26.32)	
3 + 4 = 7		8 (47.06)	8 (21.05)	
4 + 3 = 7	–	0 (0.00)	8 (21.05)	
4 + 4 = 8		2 (11.76)	2 (5.26)	
4 + 5 = 9		0 (0.00)	4 (10.53)	
5 + 4 = 9		0 (0.00)	4 (10.53)	
5 + 5 = 10		0 (0.00)	1 (2.63)	

Table 3 Cutoff point for PSAD in the discrimination of prostate cancer of all patients

Cutoff	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	ROC (95% CI)	Accuracy (95% CI)
≥0.10	94.90 (85.90–98.90)	21.10 (13.40–30.60)	42.70 (34.10–54.70)	87.00 (66.40–97.20)	58.00 (53.00–63.00)	49.35 (41.21–57.51)
≥0.11	91.50 (81.30–91.20)	34.70 (25.30–45.20)	46.60 (37.20–56.00)	86.80 (71.90–95.60)	63.10 (57.10–69.10)	56.49 (48.28–64.45)
≥0.12	89.80 (79.20–96.20)	36.80 (27.20–47.40)	46.90 (37.50–56.50)	85.40 (70.80–90.40)	63.30 (57.10–69.60)	57.14 (48.93–65.08)
≥0.13	88.10 (77.10–95.10)	40.00 (30.10–50.60)	47.70 (38.10–57.50)	84.40 (70.50–93.50)	64.10 (57.60–70.50)	58.44 (50.23–66.32)
≥0.14	88.10 (77.10–95.10)	40.00 (30.10–50.60)	47.70 (38.10–57.50)	84.40 (70.50–93.50)	64.10 (57.60–70.50)	58.44 (50.23–66.32)
≥0.15	84.70 (73.00–92.80)	45.30 (35.00–55.80)	49.00 (39.00–59.10)	82.70 (69.70–91.80)	65.00 (58.20–71.80)	60.39 (52.20–68.17)
≥0.16	81.40 (69.10–90.30)	54.70 (44.20–65.00)	52.70 (42.00–63.30)	82.50 (70.90–90.90)	68.00 (60.90–75.10)	64.94 (56.84–72.44)
≥0.17	81.40 (69.10–90.30)	54.70 (44.20–65.00)	52.70 (42.00–63.30)	82.50 (70.90–90.90)	68.00 (60.90–75.10)	64.94 (56.84–72.44)
≥0.18	76.30 (63.40–86.40)	56.80 (46.30–67.00)	52.30 (41.30–63.20)	79.40 (67.90–88.30)	66.60 (59.10–74.00)	64.29 (56.18–71.84)
≥0.19	72.90 (59.70–83.60)	60.00 (49.40–69.90)	53.10 (41.70–64.30)	78.10 (66.90–86.90)	66.40 (58.90–74.00)	64.94 (56.84–72.44)
≥0.20	72.90 (59.70–83.60)	60.00 (49.40–69.90)	53.10 (41.70–64.30)	78.10 (66.90–86.90)	66.40 (58.90–74.00)	64.94 (56.84–72.44)

Table 4 Cutoff point for PSAD in the discrimination of prostate cancer among patients with PSA levels 4–10 and > 10 ng/ml

PSA level (ng/ml)	Cutoff	Sensitivity (%) (95%CI)	Specificity (%) (95%CI)	PPV (%) (95%CI)	NPV (%) (95%CI)	Accuracy (%) (95%CI)
4–10	0.16	61.10 (35.70–82.70)	76.00 (61.80–86.90)	47.80 (26.80–69.40)	84.40 (70.50–93.50)	72.06 (59–86-82.27)
> 10	0.30	68.30 (51.90–81.90)	64.30 (48.00–78.40)	65.10 (49.10–79.00)	67.50 (50.90–80.40)	66.27 (55.05–76.28)

Many studies reported PSA density (PSAD) which calculated from the PSA level (ng/ml) divided by prostate volume (ml) had more accuracy and more specificity than PSA level alone for detection of prostate cancer [5–9]. Most studies used TRUS determined the prostate volume, which differed from MRI in our study. The previous studies suggested PSAD cut-off ranged from 0.15 to 0.2, our study suggested the optimal cut-off at 0.16 which was also within that range.

Previous studies reported the PSA level was different among Asians and Caucasians, therefore, the PSAD and cutoff points were also different. Saema et al. reported the optimal cutoff point was 0.15 (sensitivity 78%, specificity 43%) in the Thai population with PSA levels between 4 and 10 ng/ml [15]. Sathean et al. investigated the optimal cutoff point within the Thai population with different BMI and PSA levels between 4 and 10 ng/ml. This study reported the optimal cutoff points were 0.15 in normal weight patients (BMI < 23), and overweight patients (BMI 23–24.9), and 0.06 in obese patients (BMI ≥ 25) [16]. These studies, however, used the prostate volume by measuring transrectal ultrasonography (TRUS). Previous studies reported prostate volume measuring by MRI to be more accurate than measuring by TRUS [17–21].

In the current study, the optimal cutoff point of PSAD for discrimination of prostate cancer was 0.16 (81.40% sensitivity, 54.70% specificity, 52.70% positive predictive value, 82.50% negative predictive value), and the area under the curve was 0.680 (95%CI: 0.609–0.751). Although the PSAD level of 0.17 demonstrated no difference in terms of sensitivity and specificity, the lower the better, especially for decreasing the unnecessary biopsy. Thai ethnic may make these results different from a few previous studies that reported the optimal cutoff points of PSAD in Brazilian, Iranian, and Indonesian patients were 0.11, 0.11, and 0.70 [8–10] .

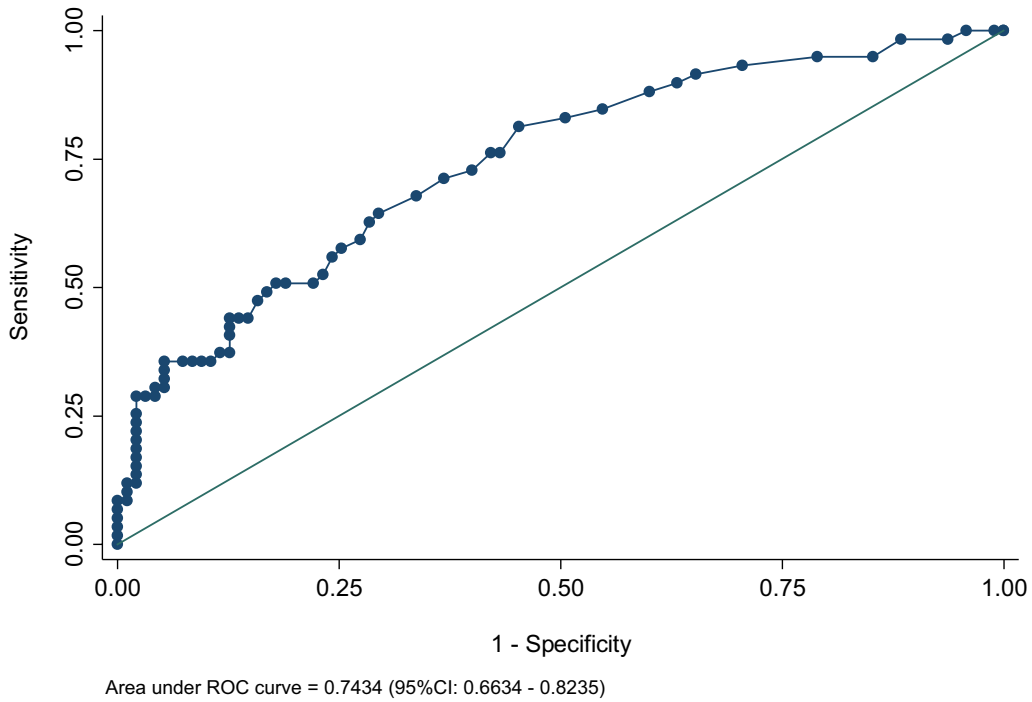

Fig. 2 Receiver operating characteristic (ROC) curves of PSAD in discrimination of prostate cancer

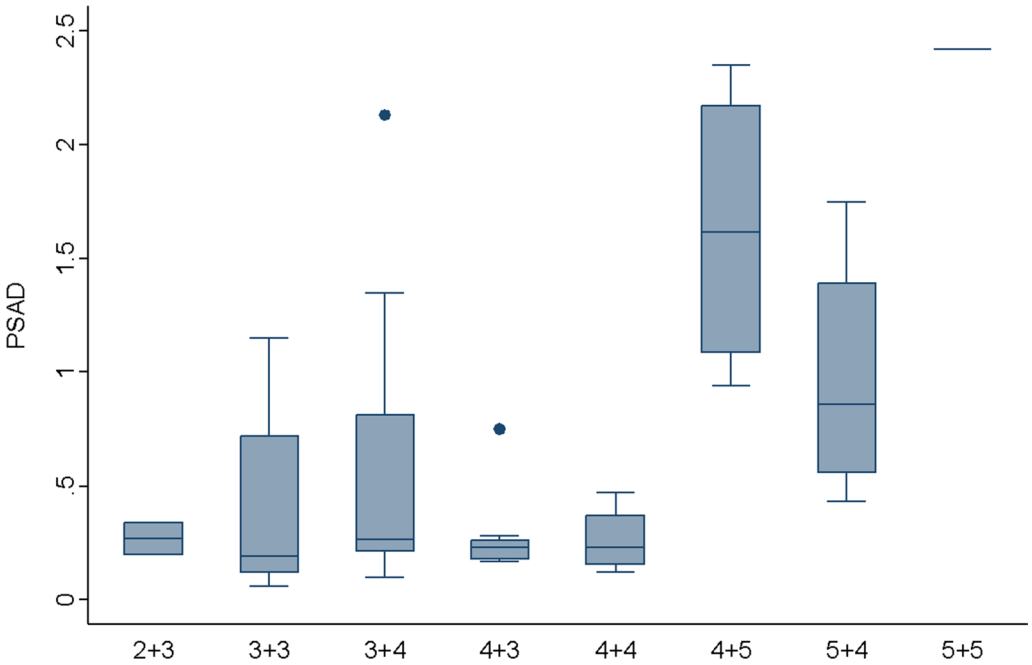

Fig. 3 Correlation between PSAD and gleason score

In subgroup analyses of patients with serum PSA < 4 ng/ml, 4–10 ng/ml, and > 10 ng/ml, it was found that none of patients with serum PSA < 4 ng/ml was diagnosed with prostate cancer. These results could be supported that the patients with serum PSA < 4 ng/ml were low risk groups for cancer. Thus, follow-up of these patients could be more beneficial than biopsies taken. This current study also reported optimal cutoff

points of PSAD in patients with serum PSA 4–10 ng/ml, and > 10 ng/ml were 0.16 (61.10% sensitivity, 76.00% specificity) and 0.30 (68.30% sensitivity, 64.30% specificity). These results were similar to those in previous studies. Lin et al. reported the optimal cutoff points in patients with serum PSA 2.5–10 ng/ml, and 10–20 ng/ml were 0.15, and 0.33 [11].

Karademir et al. reported there was a significant relationship between the PSAD and the Gleason score in prostate cancer patients [14]. The current study also found statistically significant correlations between PSAD and Gleason scores (p-value 0.014) that supported their results. These findings would help to predict the prognosis of prostate cancer patients.

We had several limitations in this study. First, this was the retrospective study. Second, we tried our best to recruit all available prostate cancer patients examined by MRI during the study period; however, there were a small number.

5 Conclusions

The optimal cutoff point of PSAD was 0.16 which was relatively different from the international consensus (81.40% sensitivity, 54.70% specificity, 52.70% PPV, 82.50% NPV), and the AUC was 0.680 (95%CI: 0.609–0.751).

In subgroup analyses, the optimal cutoff points of PSAD in patients with serum PSA 4–10 ng/ml, and > 10 ng/ml were 0.16 (61.10% sensitivity, 76.00% specificity) and 0.30 (68.30% sensitivity, 64.30% specificity). Furthermore, there were statistically significant correlations between the PSAD and Gleason scores (*p*-value 0.014).

Abbreviations

AUC	Area under curve
BPH	Benign prostatic hyperplasia
ICC	Interclass correlation coefficient
IQR	Interquartile range
MRI	Magnetic resonance imaging
PSA	Prostatic specific antigen
PSAD	PSA density
ROC	Receiver operating characteristic

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Author contributions

CA conceptualization, methodology, validation, resources, writing review & editing, project administration. SN conceptualization, methodology, investigation, data curation, writing review & editing. CT methodology, investigation, writing original draft. All authors have read and approved the manuscript.

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Availability of data and materials

All data and material in this study are available to your request.

Declarations

Ethics approval and consent to participate

This study was approved by the Khon Kaen University Ethics Committee for Human Research based on the Declaration of Helsinki and the ICH Good Clinical Practice Guidelines with Reference No. HE621384. Consent to participate is not applicable as it is a retrospective study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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