Original Article

Prediction of a novel prostate-specific antigen density cutoff value and use of transrectal ultrasound-guided prostate biopsy for diagnosis of prostate cancer in Thailand

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Keywords:
PSAD, prostate-specific antigen density, prostate cancer detection

Abstract

Objective: The measurement of prostate-specific antigen density (PSAD) is a noninvasive and inexpensive practice, which may improve the accurate diagnosis of prostate cancer. The incidence of prostate cancer in Thailand is relatively low compared with that in Western countries. Therefore, a blanket adoption of the Western cutoff value (PSAD 0.15 ng/ml/cm^3) is inapplicable and can lead to unnecessary biopsies. The aim of this study was to determine an optimal PSAD cutoff value for effective diagnosis in Thai men.

Materials and Methods: We retrospectively studied transrectal ultrasound-guided prostate biopsies from 542 men with intermediate PSA concentrations ranging from 4 to 10 ng/ml, carried out from January 2011 to January 2017. The area under the receiver operating characteristic curve (AuROC) was used to evaluate the efficacy of PSAD for the diagnosis of prostate cancer.

Results: In Thai men who had intermediate PSA concentrations, the AuROC was higher for PSAD in comparison to that of PSA (0.692 vs 0.544). The AuROC using the PSAD cutoff value = 0.20 ng/ml/cm^3 was higher than that using the PSAD cutoff value = 0.15 ng/ml/cm^3 (0.652 vs 0.626). The sensitivity, specificity, positive predictive value, and negative predictive values were 67.33%, 62.13%, 29.95%, and 89.15%, respectively.

Conclusion: PSAD improved the diagnosis of prostate cancer in Thai men with intermediate PSA concentrations. The optimal cutoff value was 0.20 ng/ml/cm^3.

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Introduction

The level of prostate-specific antigen (PSA) is used extensively for the detection of prostate cancer.[1] However, the diagnostic power of the PSA test shows an insufficient sensitivity or specificity, particularly at intermediate concentrations (4–10 ng/ml).[2] More recently, prostate-specific antigen density (PSAD) has served as a useful tool for the diagnosis of prostate cancer[3] in patients with a normal digital rectal exam (DRE) and gray-zone (intermediate) PSA concentrations.[4] The PSAD value is easily calculated (PSA concentration divided by the volume of the prostate gland).[4] The most recent clinical practice guidelines support the use of PSAD in combination with other new biomarkers when deciding to avoid a prostate biopsy.[5] The advantages of using PSAD over other tests are its lower cost and simplicity, which enable its use in low-income countries or provincial hospitals.

The prevalence of prostate cancer, which varies worldwide, is relatively low in Asian countries compared with that in Western countries. For example, the incidence of prostate cancer is 2.87 per 100,000 persons in Thailand[6] compared with 109.2 per 100,000 persons in the United States.[7] Furthermore, the PSA cutoff value should be higher for Thai patients compared with that for patients residing in Western countries.[8]

The present study therefore aimed to determine an optimal cutoff value of PSAD for Thai patients with intermediate PSA concentrations and a normal DRE. From the data collected we propose a higher cutoff value than that used in Western countries (0.15 ng/ml/cm^3).[9-11]

Materials and Methods

We collected data from January 2011 to January 2017 retrospectively from Ramathibodi Hospital, Thailand. The inclusion criterion was a prostate biopsy. Exclusion criteria were data from patients with an abnormal DRE with a PSA < 4 ng/ml and >10 ng/ml. Serum PSA concentrations were measured using an automated electrochemiluminescence immunoassay method (Cobase 601, Roche) immediately before biopsy. Prostate volume was measured using transrectal ultrasound (TRUS) (BK Medical Flex Focus 400). PSAD = PSA/prostate volume (ng/ml/cm^3). Prostate tissue biopsies were carried out using a Pro-Mag 18-gauge biopsy needle and a BK Medical Type 8812 equipped with an end-firing TRUS probe and samples were sent for review by pathologists who specialize in urology.

A receiver operating characteristic (ROC) curve was generated to evaluate the performance characteristic of PSAD according to the areas under the ROC curve (AuROC) as a primary outcome. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were evaluated as secondary outcomes.

We analyzed data using a t test median regression and Pearson's chi-square test to evaluate the significance of differences in mean and median values. The research protocol was approved by the Ethical Committee of the Faculty of Medicine Ramathibodi Hospital, Mahidol University (Protocol Number: 06-61-66).

Results

Out of the 1,577 patients who underwent a prostate biopsy at Ramathibodi Hospital from 2011 until 2017, 542 with a normal DRE met the inclusion criteria with PSA concentrations within the gray (intermediate) zone. These patients included 441 without detectable prostate cancer and 101 with histopathologically confirmed prostate cancer (mean ages 66.6 years and 67.4 years, respectively). The mean PSA concentration of those with prostate cancer was 6.91 ng/ml vs 6.68 ng/ml in those without. However, the volume of the prostate glands of patients with prostate cancer, measured by ultrasound during performance of the transrectal prostate biopsy, were significantly smaller in comparison to those of patients without (33.38 ml vs 45.56 ml) (Table 1).

The cutoff value of PSAD with the highest AuROC (0.652) was 0.20 ng/ml/cm^3. The AuROC was 0.626 when we used the cutoff value of PSAD = 0.15 ng/ml/cm^3. When we used the cutoff value of PSAD = 0.20 ng/ml/cm^3, the sensitivity, specificity, positive predictive value, and negative predictive values were 67.33%, 62.13%, 29.95%, and 89.15%, respectively (Table 2). The AuROC of PSAD was higher compared with that of PSA (0.69 and 0.54, respectively) (Figure 1).

Discussion

Benson et al.[3] first reported the advantages of PSAD in differentiating prostate cancer from other benign prostate diseases in patients with a normal DRE patient with serum PSA concentra-

Table 1. Clinical characteristics of DRE-negative patients with intermediate serum PSA concentrations

Data	Total (n = 542)	Non-cancer (n = 441)	Cancer (n = 101)	P-value
Patients (PSA 4–10 ng/ml/cm^3)				
Age (years)				
Mean ± SD	66.72 ± 7.72	66.56 ± 7.88	67.40 ± 6.98	0.344
Median ± (IQR)	67 (62, 72)	67 (62, 72)	67 (62, 71)	
PSA ng/ml				
Mean ± SD	67.2 ± 1.64	6.68 ± 1.64	6.91 ± 1.61	0.202
Median ± (IQR)	6.52 (5.36, 8.12)	6.43 (5.34, 8.00)	6.97 (5.60, 8.12)	
Prostate volume ml				
Mean ± SD	43.29 ± 26.25	45.56 ± 27.46	33.38 ± 16.99	0.001
Median ± (IQR)	39.1 (28.4, 52.0)	41.0 (31.8, 54.0)	28.8 (23.0, 39.1)	

PSA = prostate-specific antigen, SD = standard deviation, IQR = interquartile range

Table 2. Cutoff values and diagnostic variables associated with PSAD

PSAD (ng/ml/cm^3)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AuROC
0.10	94.06	13.15	19.84	90.64	0.5361
0.15	85.15	40.14	24.53	92.20	0.6264
0.20	67.33	62.13	29.95	89.15	0.6521

PSAD = prostate-specific antigen density, PPV = positive predictive value, NPV = negative predictive value

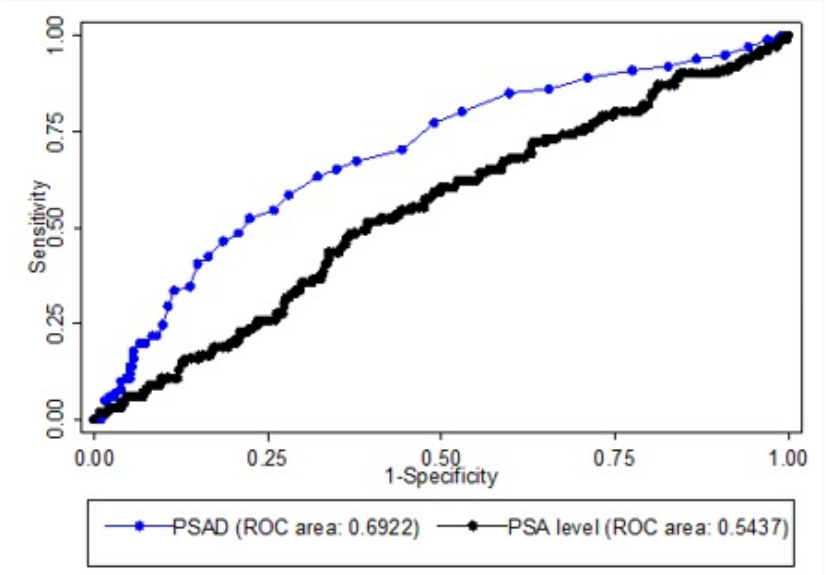

Figure 1. The areas under the receiver operating characteristic curve for prostate-specific antigen (PSA) and PSA density as continuous variables used to predict prostate cancer

tions ranging from 4.0 ng/ml to 10 ng/ml.[3] This concept is supported by the findings of numerous subsequent studies. As in other low-income countries, standard practice in Thailand is to employ a PSAD cutoff value = 0.15 ng/ml/cm^3, which was adopted from the experience of Western countries because of insufficient data available for Thai patients.[12] In this study we determined a new cutoff value for the PSAD of DRE-negative Thai men with intermediate concentrations of serum PSA. This cutoff value = 0.2 ng/ml/cm^3, which is higher in comparison to the Western cutoff value, and is consistent with reports for men from other Asian countries.[13-15] For example, Lin et al.[16] reported PSAD cutoffs as high as 0.35 ng/ml/cm^3 for men of Chinese ethnicity.

A disadvantage of using PSAD is that the procedures of measuring prostate volume and

performing a DRE need to be carried out by skilled technicians or clinicians,[17,18] and these specialists must have sufficient experience in the identification of an abnormal prostate.[19] Other diagnostic methods are available including multiparametric magnetic-resonance imaging for the measurement of prostate volume and a range of practices to facilitate the measurement of biomarkers including the %free PSA,[20] the Prostate Health Index,[21] PCA3,[22] and the 4K score.[23] However the benefits of these practices in routine clinical use in low-income countries have not been realized because of limited availability and high cost. Another Thai study reported using extended 14-core schematic diagram mapping prostate biopsy which also increased the detection rate of prostate cancer and increased the accuracy of the Gleason score from biopsy.[24]

Conclusion

Determining the PSAD in individuals is inexpensive and noninvasive, making it a feasible and efficacious option for use by provincial hospitals. The new cutoff value reported here (0.20 ng/ml/cm^3) may contribute to improving the management of Thai patients with intermediate serum PSA concentrations and a normal DRE.

Conflicts of Interest

The authors declare no conflicts of interest.

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