Original Article

Optimal Prostate-Specific Antigen (PSA) Cut-off Value and Transrectal Ultrasound Guided Prostate Biopsy for the Diagnosis of Prostate Cancer at Ramathibodi Hospital: The First Study in Southeast Asia

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Background: The incidence of prostate cancer (PCa) in Southeast Asia is known to be lower than that of Western countries. Due to the small amount of data from Thailand, however, treatment guidelines have been adopted that were developed for different ethnic groups living in different environments.

Objective: To create an optimum prostate specific antigen (PSA) cut-off level for performing prostate biopsy in the Thai population.

Materials and Methods: Excluding patients with missing data, 1,486 transrectal ultrasound guided prostate biopsies were performed at Ramathibodi Hospital from January 2011 to January 2017. Patient data, such as age, PSA level and prostate biopsy findings, were collected. Sensitivities, specificities, positive predictive value and negative predictive value of the PSA cut-off were assessed by retrospective analysis.

Results: Of the 1,486 transrectal ultrasound guided prostate biopsies evaluated, patients with PCa had a significantly higher mean age (69.34 vs. 67.71 years for PCa and non-PCa, $p<0.001$) and had a higher median PSA level (17.11 vs. 7.89 ng/mL for PCa and non-PCa, $p<0.001$) than non-PCa patients. Sensitivity, specificity and positive predictive value of the PSA cut-off levels of 4 and 10 ng/ml were 97.3%, 8.4% and 33.3% and 68.0%, 66.4% and 48.7%, respectively. While the sensitivity, specificity and positive predictive value of PSA cut-off levels of 5.5 and 11 ng/ml were 91.8%, 23.3% and 33.3% and 64.0%, 72.5% and 52.2%, respectively.

Conclusion: The PSA cut-off should be increased to a level with an optimum trade-off between sensitivities and specificity. New PSA cut-off levels of 5.5 and 11 ng/mL would still detect 91.8% and 64% of cancers and refrain 23.3% and 72.5% of Thai men, respectively, from having unnecessary biopsies. Furthermore, this cut-off may be adopted for use in other Southeast Asian countries since they share similar environmental and genetic factors. More studies need to be performed to validate these findings.

Keywords: Prostate cancer, Prostate-specific antigen (PSA), Screening, Thai, Asia, Transrectal ultrasound guided prostate biopsy, Sensitivity, Specificity

J Med Assoc Thai 2019;102(Suppl.2): S52-5
Website: http://www.jmatonline.com

Prostate cancer is fifth most common cancer among Thai men[1], and the diagnosis of prostate cancer has continued to rise due to the adoption of prostate specific antigen (PSA) screening[2]. Incidence of prostate cancer differs worldwide by region, and the difference can be greater than 25-fold among regions. The highest rate is in Australia/New Zealand (111.6 per 100,000) and the lowest is in Southeast Asia (11.2 per 100,000)[3]. In Thailand, the incidence of prostate cancer is 2.87 per 100,000[1].

The PSA cut-off is the trigger for urologists to perform a transrectal ultrasound (TRUS) guided prostate biopsy. The TRUS guided prostate biopsy has been the gold standard for the diagnosis of prostate cancer since 1990s[4], but there can be complications, such as post biopsy infection[5,6], bleeding[7,8], acute urinary retention[8], discomfort from the endorectal probe[7,9], anxiety and transient erectile dysfunction[8,9]. However, due to a lack of data from Thailand, Thai practice uses the same cut-off as used in Western countries[10], which have a higher incidence of prostate cancer than Thailand. If the cut-off is the same as in the West, it can result in an increased risk of the performance of an unnecessary biopsy.

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How to cite this article: Sirisopana K, Sangkum P, Sirisreetreerux P, Viseshsindh W, Kijvikai K, Kongchareonsombat W, Pacharatakul S, Leenanupun C, Kochakarn W, Jenjitranant P. Optimal Prostate-Specific Antigen (PSA) Cut-off Value and Transrectal Ultrasound Guided Prostate Biopsy for the Diagnosis of Prostate Cancer at Ramathibodi Hospital: The First Study in Southeast Asia. J Med Assoc Thai 2019;102;Suppl.2: S52-5.

This study aimed to create a cut-off value for PSA indicating the need for a TRUS guided prostate biopsy for Thai males in order to decrease the risk of unnecessary biopsies among this population.

Materials and Methods

Between January 2011 to January 2017, 1,577 TRUS guided prostate biopsies were performed in patients with abnormal digital rectal exams (DRE), abnormal PSA screenings or abnormal findings from imaging (prostate MRI or TRUS) at Ramathibodi Hospital, Thailand. Patient data, such as age, PSA level and prostate biopsy findings, were collected, and 91 patients with missing data were excluded.

Serum PSA was obtained by using a fully automated electrochemiluminescence immunoassay (ELCIA) method (Cobas® e 601, Roche).

TRUS prostate guided biopsies were conducted in 12-core biopsy fashion (double sextant biopsy), except for patients with palpable prostate nodules or detectable hypoechoic lesions detected by TRUS, who had an additional 2-4 core biopsies taken. TRUS was performed using a BK medical Flex Focus 400®. The biopsy was performed using a Pro-Mag™ biopsy needle (18 gauge) and a BK medical type 8812® (4-12MHz) end-firing transrectal ultrasound probe.

All specimens were evaluated by experienced uropathologists in accordance with National Comprehensive Cancer Network (NCCN) guidelines and reported as a pathology of the prostate gland, which were categorized as either prostate cancer or as non-prostate cancer, such as benign prostatic hyperplasia, prostatitis, atypical small acinar proliferation, low-grade prostatic intraepithelial neoplasia or high-grade prostatic intraepithelial neoplasia, as well as noting Gleason score and the number of positive cores.

Statistical analysis

A descriptive study was performed. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were analized at various PSA cut-off values, and a receiver operating characteristic (ROC) curve analysis was performed using diagnostic tests. The data were analyzed using a t-test, median regression and Pearson's Chi-square to identify the statistical significance of the difference in means $\pm$ standard deviation and median (interquartile range).

Analysis was performed using Stata version 14 with p-value <0.005 considered as statistically significant.

Results

The demographic data and PSA distribution of the 1,486 patients who underwent TRUS guided prostate biopsies are presented in Table 1. Patients with prostate cancer were significantly older than non-prostate cancer patients (69.34 vs. 67.71 years, p<0.001). Patients with prostate cancer also had a significantly higher median PSA level than non-prostate cancer patients (17.11 vs. 7.89 ng/mL, p<0.001).

The sensitivities, specificity, PPV and NPV for the traditional serum PSA cut-off levels of 4 (ROC area = 0.53) and 10 ng/mL (ROC area = 0.67) were 97.3% and 68.0%, 8.4% and 66.4%, 33.3% and 48.7% and 86.7% and 81.5%, respectively. Considering that all patients had a biopsy based upon PSA level, the ROC curve derived the cut-off levels of 5.5 and 11 ng/mL (ROC area = 0.58 and 0.68 for PSA cut-off levels of 5.5 and 11 ng/mL) with sensitivities of 91.8% and 64.0%, specificity of 23.3% and 72.5%, PPV of 36.0% and 52.2% and NPV of 85.8% and 81.1%, respectively (Table 2).

Discussion

Routine PSA screening can be useful in detecting cancer at an early stage. With available treatments, it has been demonstrated that cancer-specific survival is much better in a localized disease than in a locally advanced or metastatic disease. Although the results of this screening show the age and stage of disease migration, it may lead to over-diagnosis and overtreatment that does not decrease morbidity or mortality sufficiently to justify the potential complications from treatment[11].

In Thailand, the incidence of prostate cancer is

Table 1. Demographic data and distribution corresponding to PSA level

Variable	Prostate cancer	Non-prostate cancer	p-value
No. of patients: n (%)	475 (32.15)	1,011 (67.85)	
Age (years): means (SD)	69.34 (8.07)	67.71 (7.81)	<0.001*
Total PSA (ng/mL): median (max, min)*	17.11 (1.26, 6,383)	7.89 (0.28, 1,825)	<0.001*
PSA distribution (ng/mL): n (%)*			
<4	13 (2.74)	85 (5.72)	
4 to 10	141 (29.68)	591 (58.46)	
>10	321 (67.58)	335 (33.14)	
<5.5	39 (8.21)	236 (23.34)	
5.5 to 11	133 (28.00)	500 (49.46)	
>11	303 (63.79)	275 (27.20)	

PSA = prostate specific antigen
The p-value denotes statistical significance (p<0.05)

Table 2. Sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) of PSA cut-off value

PSA cut-off (ng/mL)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
4	97.3	8.4	33.3	86.7
5.5	91.8	23.3	36.0	85.8
10	68.0	66.4	48.7	81.5
11	64.0	72.5	52.2	81.1

PSA = Prostate specific antigen

lower than in Western countries. Practitioners in Thailand have adopted serum PSA levels as a screening tool, and a cut-off level of 4 ng/mL has been recommend with a sensitivity of 79% and specificity of 59%[12]. In our study, a cut-off level of 4 ng/mL demonstrated a sensitivity of 97.3 %, specificity of 8.4% and ROC area of 0.53 along with a cut-off level of 10 ng/mL that demonstrated a sensitivity of 68.0%, specificity of 66.4% and ROC area of 0.67. Finding patient PSA level is a first step toward performing a TRUS guided prostate biopsy. With a low specificity for this result, there is a risk of doing an unnecessary biopsy at this cut-off. Hence, increasing the PSA cut-off for the Thai population can increase TRUS guided prostate biopsy yield without raising the false negative rate and thus avoid an unnecessary biopsy. Considering that all patients had biopsies based on PSA level, the ROC curve derived cut-off levels that optimally traded off between sensitivity and specificity at 5.5 and 11 ng/mL. A cut-off of 5.5 ng/mL demonstrated a sensitivity of 91.8.0%, specificity of 23.3% and ROC area of 0.58 along with the cut-off level of 11 ng/mL that demonstrated a sensitivity of 64.0%, specificity of 72.5% and ROC area of 0.68.

There are other biomarkers, such as age-specific PSA reference ranges[13,14], PSAV[15], % of PSA[16,17], PSAD[17], PCA3[18], PHI[19] and 4K score®[20] that improve the specificity of detection and decrease the number of unnecessary biopsies. However, these biomarkers are not recommended as a first line test due to their limited value[10,21].

Unfortunately, data regarding biopsy complications could not be collected due to the present study having been retrospectively conducted. For variables such as characteristics of the population, symptomatic or non-symptomatic patients, abnormal findings from DRE or from imaging that could affect identifying prostate cancer[22,23], the author of the present study is assembling this data and will report it in the next study.

The authors would like to highlight that our study has some limitations. First, this is a low volume retrospective study that demonstrated low area under curve (<0.7 to 0.8). Second, there is little data in the Thai literature[24] against which to verify the results of the present study. This can be improved by conducting a prospective randomized study with a higher case volume, which would increase the population of the study and provide much more accurate results.

Conclusion

The PSA cut-off should be increased to an optimum trade-off between sensitivities and specificity. New PSA cut-off levels of 5.5 and 11 ng/mL would still detect 91.8% and 64% of cancers and refrain 23.3% and 72.5% of Thai men, respectively, from having an unnecessary biopsy. Furthermore, this cut-off may be adopted for use in other South East Asia countries since these countries have similar environmental and genetic factors. More studies need to be performed to validate these findings.

What is already known on this topic?

The PSA cut-off need to adjust to optimize its sensitivity and specificity due to the incidence of the prostate cancer is different in each region. This different is contribute from the genetics and environment

What this study adds?

This study demonstrated that PSA cut-off need to be raised in Thai population due to low incidence of prostate cancer in Thailand. This new PSA cut-off will help to decrease the unnecessary biopsy that can cause a morbidity and mortality to the patients. Anyways more studies need to be done to validate these findings.

Key of definitions for abbreviations

ml = Millilitre, ng = Nanogram, NPV = negative predictive value, PCa = Prostate cancer, PPV = positive predictive value, PSA = Prostate-Specific Antigen, PSAD: Prostate-Specific Antigen density, ROC = receiver operating characteristic, TRUS: Transrectal ultrasound guided prostate biopsy

Acknowledgements

This work was supported by Wijittra Matang, Yada Phengsalae and Kornkanok Somboonpun. The authors thank Wijittra Matang, Yada Phengsalae and Kornkanok Somboonpun for continued support and encouragement.

Potential conflicts of interest

The authors declare no conflict of interest.

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