Original Article

Diagnostic properties of percent-free PSA as a predictor of prostate cancer in Thai men with total serum PSA level of 4-10 ng/ml

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Abstract

Objective: The percent-free prostate specific antigen (%fPSA) could enhance total PSA (tPSA) with regards to early prostate cancer detection by increasing its specificity. However, due to significant physiologic differences across races, the optimal cut-off level for %fPSA may vary. We aimed to determine optimal %fPSA cut-off level for Thai men aged between 50 to 80 years whose tPSA score ranged from 4-10 ng/mL and to evaluate its corresponding diagnostic properties, specifically sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The secondary endpoint is the relationship between Gleason Grade Group and %fPSA value.

Materials and Methods: A total of 184 male patients from age 50-80 years whose tPSA was between 4-10 ng/ml were enrolled onto the study. Their %fPSA were measured before undergoing trans-rectal ultrasonography (TRUS) guided prostate biopsy, which procured at least 10 cores. All histologic reports were reviewed and confirmed for further analysis.

Results: Out of the 184 patients registered the final diagnoses were 31 (16.84%) were positive for prostate cancer and the other 153 (83.16%) had benign prostate hypertrophy (BPH). At %fPSA cut-off of ≤ 10%, the sensitivity would be 22.6%, specificity 95.4%, PPV 50.0% and NPV 85.9%. However, at a %fPSA cut-off of ≤ 20%, the sensitivity was 77.4%, specificity 32.7%, PPV 18.9%, and NPV 87.7%. The %fPSA value has a direct relationship with sensitivity and NPV whereas it is inversely proportional to specificity and PPV. Lower %fPSA is associated with higher risk of prostate cancer. The area under the curve (AUC) of ROC curve was 0.65. The incidence of prostate cancer among patients with Gleason Grade Groups 1, 2, 3, 4, and 5 were 41.94%, 32.26%, 16.13%, 6.45%, and 3.23% respectively. The mean %fPSA scores among those groups were 14.75%, 17.64%, 10.19% ,13.33%, and 15.65% respectively.

Conclusion: The decision to undergo prostate biopsy in Thai males with a tPSA score between 4-10 ng/ml can be guided by %fPSA, which proved to be an effective and useful predictive tool. The cut-off level of %fPSA ≤ 20% had the highest diagnostic properties in Thai men in our study which yielded a sensitivity of 77.4%, specificity of 32.7%, PPV of 18.9%, and NPV 87.7%. If %fPSA was ≥ 30%, there was no risk of prostate cancer in this cohort. In addition, with regard to disease severity, we found that %fPSA level is not associated with the Gleason Grade Grouping.

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Introduction

Prostate cancer is the second most common malignancy in males worldwide and the fifth highest cause of mortality[1], leading to a significant burden on healthcare systems. This emphasizes the need for early detection, one method of which – namely the process of prostate specific antigen (PSA) screening – contributes to a 21% reduction in the mortality risk.[2] Total serum PSA is currently utilized worldwide as a tumor marker for prostate cancer. Although it has a high degree of sensitivity, it lacks specificity. This is especially important in cases where the total serum PSA lies between 4-10 ng/ml since a mere 25% of incidences of prostate cancer could be identified in this group. As a result, subsequent unnecessary prostate biopsies[3,4] could lead to significant morbidity, overdiagnosis, overtreatment, and anxiety, as well as excessive cost.

The total serum PSA consists of two isoforms, the free unbound PSA and the complex PSA.[5-8] Various studies have shown promise regarding the possibility of using percent-free PSA (%fPSA) in distinguishing benign from malignant prostate disease. Studies have shown that lower %fPSA was associated with greater risk of prostate cancer, aggressive pathologic features, and biochemical recurrence after radical prostatectomy.[5-8]

Compared to the less accessible and more costly multiparametric MRI (mpMRI) of the prostate, laboratory kit for %fPSA proved to be more financially and logistically feasible. Furthermore, mpMRI of prostate has several limitations including the obesity of the patient or the inability to remain immobile, which potentially affect the quality of the images. Other contraindications include foreign implants such as pacemakers, aneurysm clips, ear implants, and other metallic instruments.

Due to its advantaeous cost implications and versatility, %fPSA could play a pivotal role in assisting the diagnosis by the physician and decision making for further management of suspected prostate cancer in the environment where healthcare resources are scarce. Nevertheless, the percent-free PSA values derived from the populations of different races could not be used in their current form[9-11] In addition, the consensus for the cut-off level of %fPSA has not been agreed[8]. One of the popular cut-off levels proposed by Catalona et al. defined significant %fPSA as ≤ 25%, which yielded a sensitivity as high as 95%. They also found that a value of %fPSA between 0 and 10% had the highest incidence of prostate cancer at 55-56%.[12]

This study aimed to determine the most appropriate cut-off level of %fPSA among Thai males whose total serum PSA ranged from 4 to 10 ng/ml, as mpMRI of the prostate are less available and more expensive. Other parameters to be established include sensitivity, specificity, positive predictive value, and negative predictive value. We also assessed the association between Gleason Grade Group and the value of percent-free PSA.

Materials and Methods

Patients

This retrospective study registered data from Thai male patients from 50 to 80 years of age whose serum PSA ranged from 4 to 10 ng/ml who visited Maharaj Nakorn Chiang Mai Hospital from 1 April 2011 to 31 December 2022. Patients with untreated urinary tract infection (UTI), untreated bleeding disorder, prostatitis, history of prior prostate surgery, and history of prior prostate cancer were excluded. The study protocol was approved by the Ethics Committee of Chiang Mai University Hospital with the study number SUR-2564-08360.

Methods

Blood samples of total PSA and free PSA were taken from patients who fulfilled the inclusion criteria and were quantitatively analyzed using a COBAS-e double sandwich electrochemiluminescence immunoassay (ECLIA) analyzer. Percent-free PSA values were then calculated by dividing free PSAs with total serum PSAs and multiplying the results by 100.

A total of 184 patients underwent trans-rectal ultrasonography (TRUS) guided biopsy for the first time during the defined period. Prostate volume was measured by TRUS prior to biopsy. Extended core biopsy was carried out, the process of which had to yield at least 10 cores of prostatic specimens. There were no MRI-guided prostate biopsies carried out in this study. The specimens would then be handled and evaluated by experienced pathologists. The procedure included use of Hematoxylin and Eosin (H&E) dye, formalin fixing, and the procurement of paraffin-embedded blocks.

The diagnosis and grading of adenocarcinoma were reported in line with the Gleason Scoring System in accordance with the definitions provided by the Consensus Conference of International Society of Urological Pathology.

Statistical analysis

The data obtained were analyzed and calculations were carried out to obtain the sensitivity, specificity, PPV, and NPV of each cut-off level. ROC curves were utilized to determine the optimum cut-off level for a screening tool for prostate cancer. Statistically significant differences were defined as $p < 0.05$. All statistical analyses were performed with STATA version 15.0 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

Results

Data from a total of 184 patients with total PSA between 4 to 10 ng/ml were used in the study. Of those, 31 patients (16.84%) were diagnosed with prostate cancer and 153 (83.16%) were diagnosed with benign prostate hyperplasia after the results of TRUS-guided biopsies were confirmed by pathology.

The baseline characteristics significantly differed in terms of mean age between the groups (68.16 years in prostate cancer group vs 65.71 years in benign prostatic hyperplasia (BPH) group; $p = 0.012$). In addition, %fPSA was significantly lower in prostate cancer group in comparison to the BPH group ($p = 0.005$). Average prostate volume among the prostate cancer group was 38.90 ml, which was also significantly lower than the 49.55 ml in the BPH group ($p = 0.014$)(Table 1).

The highest proportion of prostate cancer (50%) was observed in the 0-10% range of %fPSA value. The highest incidence of prostate cancer (11 patients, 35.48%) was in the 10.1-15% range of %fPSA value, whereas the peak incidence of BPH (56 patients, 36.60%) was in the 15.1-20% stratum of %fPSA value. None of the patients with %fPSA ≥ 30% were diagnosed with prostate cancer (Table 2).

At a %fPSA cut-off level of ≤ 10%, the highest specificity of 95.4% and highest PPV of 50% were

Table 1. Demographic and clinical characteristics according to biopsy pathology

Parameters	BPH (n=153)	Prostate cancer (n=31)	P-value
Age (Years), mean (SD)	65.71 (4.95)	68.16 (4.61)	0.012
BMI (kg/m^2), mean (SD)	23.95 (3.25)	23.46 (3.12)	0.440
%Free PSA, mean (SD)	18.44 (6.34)	14.89 (6.50)	0.005
Total PSA (ng/ml), mean (SD)	6.60 (1.60)	6.37 (1.55)	0.472
Prostatic volume (ml), mean (SD)	49.55 (22.96)	38.90 (14.50)	0.014
Numbers of biopsy cores, mean (SD)	10.80 (2.94)	11.16 (1.66)	0.513

BMI = body mass index, SD = standard deviation, PSA = prostate specific antigen, BPH = benign prostatic hyperplasia

Table 2. %Free PSA and pathologic report

%Free PSA	BPH (n=153)	Prostate cancer (n=31)	Total (N=184)	%Ca-p	P-value
0-10	7 (4.58)	7 (22.58)	14	50.00	<0.001
10.1-15	40 (26.14)	11 (35.48)	51	21.57	0.289
15.1-20	56 (36.60)	6 (19.35)	62	9.68	0.064
20.1-25	30 (19.61)	3 (9.68)	33	9.09	0.189
25.1-30	9 (5.88)	4 (12.90)	13	30.77	0.164
30.1-35	7 (4.58)	0	7	0	0.224
35.1-40	4 (2.61)	0	4	0	0.363

PSA = prostate specific antigen, %Ca-p = percentage of patients with prostate cancer, BPH = benign prostatic hyperplasia

Table 3. Diagnostic properties of %fPSA at each cut-off level

%Free PSA	Sensitivity (%)	Specificity (%)	PPV	NPV
≤10	22.6	95.4	50.0	85.9
≤15	58.1	69.3	27.7	89.1
≤20	77.4	32.7	18.9	87.7
≤25	87.1	13.1	16.9	83.3
≤30	100.0	7.2	17.9	100.0
≤35	100.0	2.6	17.2	100.0

PSA = prostate specific antigen, PPV = positive predictive value, NPV = negative predictive value

Table 4. The relationship between Gleason Grade Group and mean %Free PSA

Gleason grade group (score)	Number of patients (n=31), n (%)	Mean %Free PSA (SD)
1 (3+3)	13 (41.94)	14.75 (5.62)
2 (3+4)	10 (32.26)	17.64 (8.48)
3 (4+3)	5 (16.13)	10.19 (3.38)
4 (4+4, 3+5, 5+3)	2 (6.45)	13.33 (1.90)
5 (4+5, 5+4, 5+5)	1 (3.23)	15.65 (0.00)

PSA = prostate specific antigen, SD = standard deviation

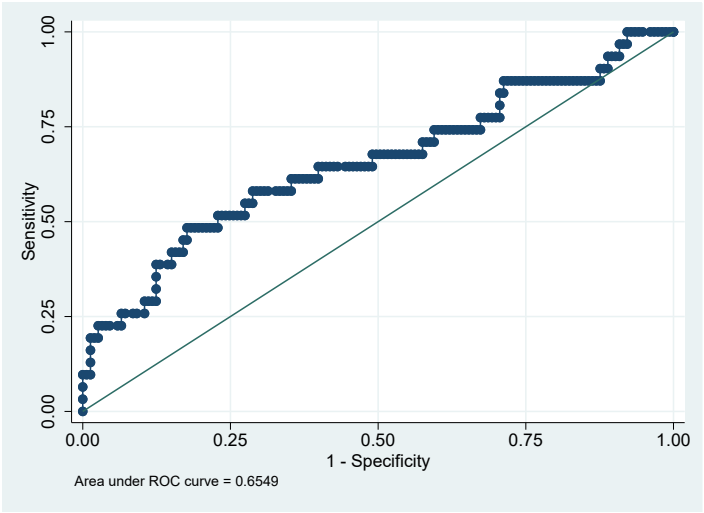

Figure 1. The receiver operating characteristic (ROC) curve

observed, which subsequently lead to a 4.6% rate of unnecessary biopsies. The sensitivity and NPV were 22.6% and 85.7%, respectively. If the %fPSA cut-off level was increased to ≤ 20%, sensitivity and NPV improved to 77.4% and 87.7% respectively. Nevertheless, its specificity and PPV also dramatically dropped to 32.7% and 18.9% respectively. The %fPSA value has a direct relationship with sensitivity and NPV whereas it is inversely proportionate to specificity and PPV (Table 3).

The number of prostate cancer patients classified as Gleason Grade Groups 1, 2, 3, 4, and 5 were 13, 10, 5, 2, and 1 respectively. The mean %fPSA in those groups were 14.75%, 17.64%, 10.19%, 13.33%, and 15.65% respectively. The incidence in each Gleason grade group decreased as the score increased. Moreover, the results revealed no significant association between severity of the disease and either Gleason grade group or mean %fPSA (Table 4).

Figure 1. shows the receiver operating characteristic (ROC) curve plot of sensitivity against 1-specificity. The area under the curve was 0.65, indicating that the %fPSA in this study can

effectively distinguish between prostate cancer and BPH.

Discussion

Analysis of the data from the 184 patients in our study showed an overall cancer detection rate of 16.8%, which is consistent with the 17.3% prevalence of prostate cancer in Thailand.[13] The demographic and characteristic data show that the average age of patients with prostate cancer was significantly higher than those with BPH, a finding which coincided with the results of the study conducted by Matsuyama et al.[14]

Several other studies also found that the average prostatic volume of those with prostate cancer was substantially smaller than those with BPH, which also corresponded with our findings.[5,10,15]

In our study, the prevalence of prostate cancer was highest in the %fPSA ≤ 10% group and dropped to zero in the group with a %fPSA ≥ 30%. In a study by Catalona et al.[12] a universal cut-off level of %fPSA ≤ 25% was proposed however, in that study there was only a minority of Asian patients (2%). Using the same cut-off level in our study, the diagnostic properties were less than the original paper, with a sensitivity of only 87.7%, specificity of 13.3%, PPV 16.9%, and NPV 83.3%. In addition, our study showed an inverse relationship between %free PSA and the detection rate of prostate cancer while total serum PSA was found to have no significant difference, a finding also being reported by Tijani et al.[16]

The concepts of race-specific cut-off level were proposed by Arai et al.[17] and Oesterling et al.[18] This would mean our study should be cross-referenced with other Asian populations rather than Caucasian. A study conducted by Matsuyama et al.[14] found that optimal cut-off level among Japanese people, a specifically Asian population, to be ≤ 17%. This concurred with our finding that the optimal cut-off level among Thai people is ≤ 20%, which yielded a of sensitivity 77.4%, specificity of 32.7%, PPV of 18.9%, and NPV 87.7%.

The ROC curve gave rise to an AUC of 0.65, which was higher than the pre-determined discrimination line. As a result, we concluded that the predictive value of %fPSA shown in our study did not occur by chance. Regarding the relationship between severity of disease and %fPSA, we found none which were significant, which is consistent with other studies by Noldus et al.[19] and Sakai et al.[20] As a result, we suggest adding %fPSA to the total serum PSA to give more information as a screening tool for prostate cancer in Thailand, especially in centers without facilities to carry out mpMRI of the prostate.

There are several limitations in this study. Firstly, it was carried out in a single center which potentially limits the transferability of the findings. Secondly, having different physicians perform TRUS-guided biopsy, due partly to the retrospective nature of the study, might result in variations in cancer detection rate. Thirdly, the relatively small sample size in this study could impact the reliability of the statistical outcomes However, the findings of this pioneering study, conducted solely among a Thai population, warrant further investigation as they highlight inter-racial differences in this field. Lastly, some patients with negative-cancer biopsy results might possibly have had undetected prostate cancers since this random TRUS biopsy procedure could potentially miss a small cancerous area. Further studies with a more accurate biopsy protocol such as MRI-ultrasound-fusion guided biopsy, which is widely acknowledged as being more precise in most recent studies, are recommended in the future.

Conclusions

The decision to undergo prostate biopsy in Thai males with tPSA between 4-10 ng/ml can be guided by %fPSA, which proved to be an effective and useful predictive tool. The cut-off level of %fPSA ≤ 20 % had the highest diagnostic properties in Thai men in our study which yielded a sensitivity of 77.4%, specificity of 32.7%, PPV of 18.9%, and NPV 87.7%. If %fPSA is ≥ 30%, there was no risk of prostate cancer. In addition, with regard to disease severity, we found that %fPSA level is not associated with Gleason grade grouping.

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Conflicts of Interest

The authors declare no conflict of interest.

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