Int J Clin Exp Med 2018;11(4):3873-3879
www.ijcem.com /ISSN:1940-5901/IJCEM0063171

Original Article

Revisiting prostate specific antigen density (PSAD): a prospective analysis in predicting the histology of prostate biopsy

Shanggar Kuppusamy[1,2], Kia Fatt Quek[3], Retnagowri Rajandram[1], Azad Hassan Abdul Razack[1,2], Norman Dublin[1,4]

[1]Department of Surgery, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia; [2]University Malaya Medical Centre, Kuala Lumpur, Malaysia; [3]Jeffrey Cheah School of Medicine & Health Sciences, Monash University Malaysia, Bandar Sunway, Selangor, Malaysia; [4]KPJ Tawakkal Specialist Hospital, Kuala Lumpur, Malaysia

Received May 2, 2017; Accepted January 25, 2018; Epub April 15, 2018; Published April 30, 2018

Abstract: This investigation evaluated use of prostate specific antigen density (PSAD) prior to prostatic biopsy to predict prostate cancer (PCa) diagnosis and enables enhanced patient selection for prostatic biopsy. A total of 286 consecutive patients who underwent transrectal ultrasound (TRUS) biopsy of the prostate for prostate specific antigen (PSA) between 4.01 and 30.0 ng/ml were recruited to this study. Histology reports were correlated with the digital rectal examination (DRE) findings, TRUS volume, PSA levels and PSAD. In this study population, only 33 cases (11.5%) had PCa. Detection rates were 8.6%, 16.2% and 23.8% in the PSA range of 4.01-10.00 ng/ml, 10.01-20.00 ng/ml and 20.01-30.00 ng/ml, respectively. The best sensitivity (78.8%) and specificity (51.0%) for PSAD were obtained at a cut-off of 0.19 at which 136 biopsies were potentially avoidable (significant at p=0.005) and 7 may have been missed. In combination with abnormal DRE, it was possible to reduce the number of missed cancers to 3 by sparing 91 biopsies. PSA levels give the best statistical parameters at 7.00 ng/ml. Prostate volume and abnormal DRE were poor independent tests for PCa histology. A PSAD level > 0.19 in combination with an abnormal DRE improves patient selection for TRUS biopsy.

Keywords: Prostate cancer, prostate specific antigen, prostate specific antigen density, prostate cancer screening, prostate volume

Introduction

Prostate cancer (PCa) is the sixth most common cancer in Asia and ranks fourth in Malaysia [1, 2]. The age-standardised incidence rate (ASR) varies widely between regions with highest ASR per 100,000 populations in Australia and New Zealand (111.6) followed by Northern America (97.2). In comparison, Asian regions range from 10 to 30 with highest incidence in the Western Asian population [1]. In Malaysia, the ASR is only 6.2 and, hence, the use of prostate specific antigen (PSA) as a tool for patient selection to undergo a prostate biopsy using the standard PSA cut-off level of 4.0 ng/ml [3] may not be relevant. This may give rise to a large number of unnecessary prostate biopsies which overburdens the clinical services in a particular hospital.

Various methods of improving the diagnostic capability of total PSA are available, namely, complex PSA, free PSA, free-to-total PSA [4] but all these tests are costly and not routinely offered in many hospitals. Other methods also include reduction of PSA threshold to 2.5 ng/ml [5, 6] and use of an age-specific PSA range although these methods may not be applicable in a community with low PCa incidence [7, 8].

Although not very widely used nowadays, the prostate specific antigen density (PSAD) is simpler and may possibly improve the selection of patients for prostate biopsy. PSAD assessment has been described, especially in the indeterminate PSA range of 4.1 to 10.0 ng/ml to serve the purpose of supplementing the PSA level [9].

For the above reasons, this study explored the use of PSAD to improve prediction of histology

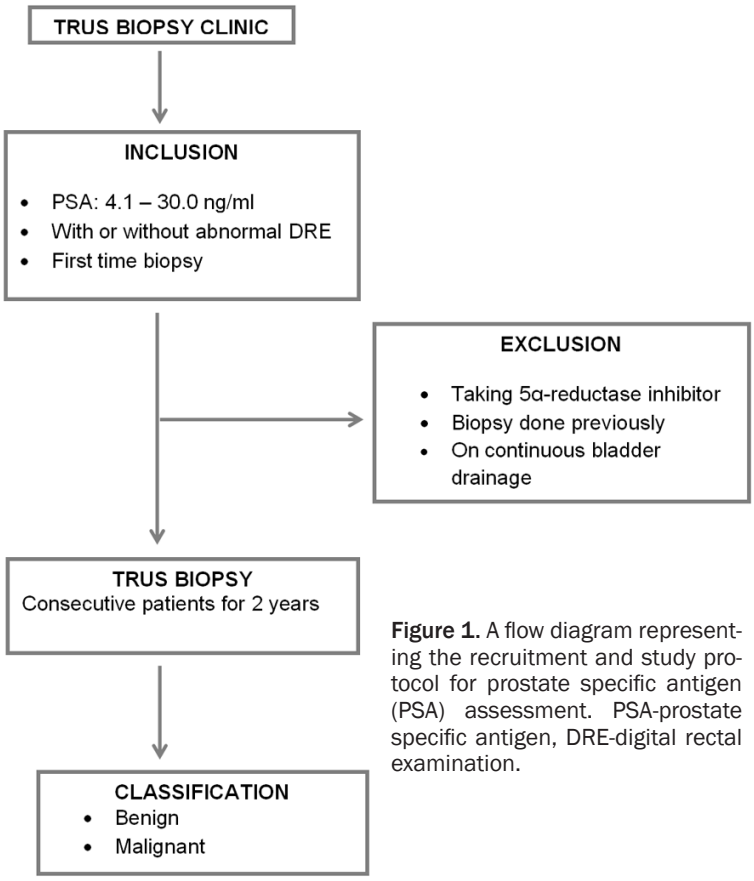

Figure 1. A flow diagram representing the recruitment and study protocol for prostate specific antigen (PSA) assessment. PSA-prostate specific antigen, DRE-digital rectal examination.

which may lead to better patient selection, especially in those undergoing a repeat biopsy. This, in turn could reduce the number of unnecessary negative biopsies.

Materials and methods

All patients who underwent transrectal ultrasound (TRUS) guided biopsy of the prostate at the University Malaya Medical Centre, Kuala Lumpur were prospectively included in this study over a period of two years, based on inclusion and exclusion criteria as well as study protocol shown in **Figure 1**. In view of the low incidence of PCa in our centre, we increased the threshold to include all patients with a total PSA value of 4.01 to 30.0 ng/ml, irrespective of their digital rectal examination (DRE) findings. These patients had presented to the Urological Outpatient Clinic for assessment of lower urinary tract symptoms or with raised PSA levels with or without an abnormal DRE based on the standard PSA cut-off values outlined by the standard protocol. The study protocol was approved by the hospital Medical Ethics Committee prior to the commencement of this project. Upon commencement, the blood samples from all selected individuals were collected and sent for total PSA level assessment using the ADVIA Centaur PSA assay (Siemens Healthcare Diagnostic Inc, Muenchen, Germany). Based on the manufacturer protocol, this detection kit reliably reports a total PSA value from 0.1 ng/ml to 100 ng/ml [10, 11]. The prostate volume (PV) was measured using the prostatic ellipse formula during TRUS and the number of biopsy cores was determined based on the Vienna nomogram [12]. PSAD was calculated using the formula: PSAD= Total PSA/PV

The biopsy was performed with adequate prophylactic antibiotics, for example, 400 mg Norfloxacin p.o given prior to the procedure and continued twice daily for 3 days. Stool evacuation was also carried out using phosphate enema the morning of the procedure. The results of the biopsy were classified as malignant or benign.

Statistical analysis was performed to evaluate the sensitivity, specificity and the positive predictive values at various PSAD cut-off levels. A receiver operating characteristic (ROC) curve was constructed to assess the performance of PSA, PSAD and PV in detecting PCa. For comparisons between groups, independent t-test or analysis of variance (ANOVA) were used to compare means. Pearson chi-square test or Fisher's exact test used to compare percentages. The analysis was performed using SPSS Statistics for Windows, Version 21.0. Armonk, NY; IBM Corp. For all analyses, $p < 0.05$ was considered statistically significant.

Results

Cancer detection rates

A total of 286 consecutive patients who underwent TRUS biopsy of the prostate gland during the selected period were recruited into this

Table 1. Descriptive statistic of age, prostate volume, PSAD, PSA and abnormal DRE according to PSA category

	Total PSA (ng/ml)			*p* value
	4.01-10.00 (n=197)	10.01-20.00 (n=68)	20.01-30.00 (n=21)	
Age	67.63±6.71	69.15±7.16	68.00±7.69	0.295[a]
PV	41.97±16.67	48.07±23.34	57.41±24.91	0.001[a,*]
PSAD	0.19±0.10	0.35±0.18	0.51±0.25	0.000[a,*]
Abnormal DRE (n)	24.4% (48)	26.5% (18)	38.1% (8)	0.390[b]
Cancer detection rate (negative biopsy)	8.6% (91.4%)	16.2% (83.8%)	23.8% (76.2%)	-

PSA-prostate specific antigen, PV-prostate volume, PSAD-prostate specific antigen density, DRE-digital rectal examination, [a]ANOVA, [b]Chi-square test, [*]$p < 0.01$.

Table 2. Association between age, PSA, PSAD, PV and abnormal DRE and disease status

	Cancer (n=33)	Non-cancer (n=253)	*p* value
Age	70.30±8.35	67.72±6.65	0.043[a,*]
PSA	12.05±6.78	9.35±5.26	0.037[a,*]
PV	34.21±14.60	45.97±20.05	0.001[a,**]
PSAD	0.40±0.25	0.23±0.15	0.000[a,**]
Abnormal DRE	36.4% (n=12)	24.5% (n=62)	0.143[b] or 0.107[c]

PSA-prostate specific antigen, PV-prostate volume, PSAD-prostate specific antigen density, DRE-digital rectal examination, [a]t-test, [b]Chi-square test, [c]Fisher exact test, [**]$p < 0.01$ [*]$p < 0.05$.

study. Their PSA levels were in the range of 4.01 to 30.00 ng/ml. The subjects were grouped into three PSA ranges (4.01-10.00, 10.01-20.00 and 20.01-30.00 ng/ml) as shown in **Table 1**. Parameters analysed were age distribution, PV, PSAD and the DRE findings. We noted that age distribution did not differ significantly among the three groups. The cancer detection rates in each group were 8.6%, 16.2% and 23.8%, respectively. An alarming number of negative biopsies in all the three groups were noted, ranging from 76% to 91%. The mean PV and PSAD were found to be significantly different among the three PSA range groups ($p < 0.01$ and $p < 0.001$, respectively). The DRE findings were not significantly indicative within the three groups analysed in this study (**Table 1**).

The above parameters were assessed to differentiate between PCa and non-PCa subjects as shown in **Table 2**. The mean age between cancer and non-cancer subjects has shown weakly significant results, with the cancer group showing a slightly higher value. Furthermore, PSA testing of the particular population using the specified PSA range of 4.01 to 30.00 ng/ml has also yielded weak significance only. Besides, utilisation of abnormal DRE as the sole determinant for cancer and non-cancer cases was not significant in this study too. However, a statistically significant result was obtained when PV and PSAD used to differentiate between the cancer and non-cancer patients, as seen in **Table 2**. The mean value for PSAD was 0.40 in the cancer vs 0.23 in the non-cancer group. The difference in mean PV was 34.16 ± 14.68 and 45.91 ± 20.05 between the cancer and non-cancer groups respectively.

Diagnostic performance

The area under the curve (AUC) was compared after constructing the ROC for the total PSA, PV and PSAD (**Figure 2A-C**). It has been noted that the AUC was best for PSAD at 72.4% in comparison with total PSA (61.2%) and PV (29.5%). It can be inferred that the sensitivity and specificity of PV was not as high as PSA and PSAD, therefore an independent use of PV revealed a large number of missed cancers (n=18-25). Moreover, the number of biopsies that could be spared at various cut-off levels for PV was also high (n=69-150) (**Table 3**). The sensitivity and specificity for PSA and PSAD were best observed at 7.00 ng/ml and > 0.19 respectively based on calculation from the ROC curve using various cut-off levels for these parameters (**Table 3**). In patients with PSA values > 7.00 ng/ml, the number of biopsy spared and cancers missed was projected to be 129 and 12 respectively. A total of 136 prostate biopsies could have been spared with PSAD > 0.19,

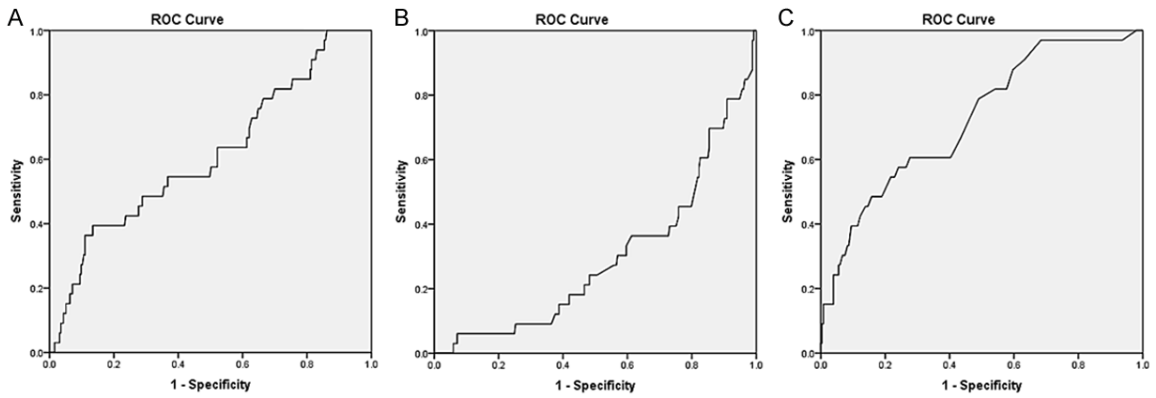

Figure 2. Receiver operating characteristic (ROC) curve showing sensitivity and specificity of PSA (A), PV (B) and PSAD (C) for diagnosis of prostate cancer. PSA: Prostate Specific Antigen; PV: Prostate Volume; PSAD: Prostate Specific Antigen Density.

Table 3. Diagnostic performance of PSA, PSAD and PV

	Sensitivity (%)	Specificity (%)	Cancers missed	Biopsies spared
PV (cc)				
> 30.0	45.5	20.2	18	69
> 36.0	36.4	35.6	21	111
> 40.0	24.2	49.4	25	150
PSA (ng/ml)				
> 6.0	81.8	29.2	6	82
> 7.0	63.6	46.2	12	129
> 8.0	54.5	54.5	15	182
> 9.0	51.5	63.2	16	176
PSAD				
> 0.15	90.9	36.8	3	96
> 0.19	78.8	51.0	7	136
> 0.22	60.6	59.7	13	164
> 0.27	57.6	73.5	14	200

PSA-prostate specific antigen, PV-prostate volume, PSAD-prostate specific antigen density.

missing 7 cancers (**Table 3**). A combination of DRE with parameters like PSA and PSAD, showed better outcome. The best result was achieved when DRE findings were combined with PSAD > 0.19 (**Table 4**), projecting a total of 91 biopsies could be spared and only 3 subjects would have been missed.

Discussion

PCa detection rates at PSA 4-10 ng/ml or 4-20 ng/ml are very low in Asian countries when compared to the West [13, 14]. Being based on a Malaysian hospital based cohort, this study has also shown much lower cancer detection rate compared to other Asian countries despite utilising the PSA range of 4-30 ng/ml [15, 16]. This gives rise to an increased number of unnecessary prostate biopsies, thus overburdening our clinical service. The reason for this finding could be multifactorial such as ethnicity, lifestyle and dietary habits of our community [16].

PSA values are known to be superior to an abnormal DRE for prostate biopsy patient selection, but it is recommended that both are used in combination in order to improve the detection of PCa [17, 18]. The problem arises with a large number of unnecessary prostate biopsies especially in the indeterminate range of 4.01 to 30.0 ng/ml with normal DRE, in our centre as well as in other centres with low PCa incidence. A clear indication for patient selection is still lacking. In our series, we found that PSA is a good test to differentiate between malignant and non-malignant prostate especially in a higher PSA value. It has been well described that PSA has varying sensitivity and specificity in relation to an increasing trend i.e the higher the PSA, the more likely that cancer will be found [15, 19]. Various PSA cut-off levels have been recommended depending on various parameters like age and ethnicity [8, 15, 17, 20]. The same could not be said about the DRE findings. The same perspective is not applicable regarding DRE findings, which may be caused by its inter-variability among clinicians of varying levels of expertise [21]. The value of DRE alone in predicting PCa is limited [22].

Table 4. Results of the use of combinations to reduce the number of unnecessary biopsies

Combination	Cancers missed	Biopsies spared
PSAD > 0.19 and/or PSA > 7.0	6	92
PSAD > 0.19 and/or PSA > 7.0	2	18
PSAD > 0.19 and/or DRE +	3	91
PSAD > 0.19 and/or PSA > 7.0 and DRE +	3	70

PSA-prostate specific antigen, PSAD-prostate specific antigen density, DRE-digital rectal examination.

A simple and practical method of assessing the PV and PSAD could be performed to supplement PSA and DRE. This project assessed the diagnostic capability of PSAD. The use of PSAD in determining PCa and non-cancer was first described in 1992, however, there was no significant evidence derived to aid cancer detection [9]. The current recommended cut-off value for PSAD is > 0.15 [23]. One particular study, has proven the benefit of this cut-off value in reducing the number of negative biopsies [24]. In our study, it was noted that the mean PSAD level of > 0.19 was highly significant in differentiating between cancer and non-cancer patients. In fact, this significance was found to be superior to PSA and PV. This cut-off value was similar to that reported in a study in Japan [18] but was different compared to a report from Taiwan (> 0.20) [13]. A recent multi-centre study in a Chinese cohort also proved that a higher PSAD value is recommended for better cancer detection in patients with PSA range of 2.5 to 20.0 ng/ml. However, a study of western population have described the best sensitivity and specificity with cut-off value > 0.11 instead [25]. It has been demonstrated that the PSAD cut-off of 0.15 is a good determinant of PCa diagnosis [26]. Hence, a clear difference can be observed between western and Asian populations, with higher PSAD values being more predictive of PCa in Asia.

In this study, a significant number of prostate biopsies could have been spared by using this higher PSAD cut-off value with an acceptable number of missed cancer cases. In contrast, it has been shown that among patients with PSA values between 4.1 and 9.9 ng/ml and normal DRE findings, a PSAD cut-off value of > 0.15 has resulted in almost 50% of missed cancer cases [18]. Therefore, it was suggested that all patients in the intermediate range should undergo a biopsy [18] due to a differences when comparing populations with varying incidences [27]. In another Spanish report, the PSAD cut-off of 0.19 had a significant number of missed cancer cases of almost 50% [28] which may be the reason for lack of importance given to PSAD for patient selection for prostatic biopsy. However the data obtained from this study has suggested otherwise; a higher cut-off for PSAD at a value of 0.19 may result in only 5% of missed PCa cases. A combination of PSAD cut-off of 0.19 and DRE findings could have further reduced the number of missed cancer cases to just 3 in our setting. Therefore, this study is in favour of the beneficial effect of PSAD in reducing the amount of unnecessary biopsy being conducted without compromising on number of missed PCa cases. This is in comparison with western studies, which have displayed significant numbers of missed cases (approximately 50%) despite combining PSAD with DRE [29]. It was noted in our report that the patients who would have been missed using the above criteria had PCa of Gleason 6 and 7 with a PSA of less than 10 ng/ml. As per active surveillance protocols, close monitoring of these patients would suffice until they show evidence of progression of disease [27, 30].

In summary, the group of patients who are most likely to benefit from the revised cut-off value of PSAD in our centre are those whose PSA value ranges between 4.01 to 30.00 ng/ml and a normal DRE. A patient with an abnormal DRE finding will be recommended for prostate biopsy regardless of his PSA level [30, 31]. In addition, the patients who had a negative prior biopsy could avoid an unnecessary repeat biopsy [27, 30]. PSAD and PSA cut-off values should be tailored to the local population especially in communities with low PCa incidence, as suggested by Shahab and colleagues [32].

Our study is limited by the fact that the participants were based on a single centre experience and not representative of the entire nation. Therefore, a multicentre focus involving low volume centres for PCa is essential to validate the findings obtained. This work is also limited by the possible need to analyse the aggressiveness of the missed cancer patients

so as to assess whether surveillance alone is sufficient in these cases.

Conclusion

It has been found that the PSAD value improves the diagnostic performance of total PSA level, especially in the range of 4.01 to 30.00 ng/ml in Malaysia as the incidence and cancer detection rates are quite low. An increased cut-off value for PSAD (i.e. > 0.19) in combination with DRE findings suggests better capability in significantly reducing the number of performing unnecessary biopsy, without a significant number of missed cancer patients. This fact may be confirmed by undertaking a larger multicentre study within the population.

Acknowledgements

We would like to acknowledge Rebecca Anthony Dass and nursing team of the Urology Daycare unit at University Malaya Medical Centre for their help in patient counselling, data collection and administrative duties.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Shanggar Kuppusamy, Department of Surgery, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia. Tel: (603) 79492070; Fax: (603) 79586360; E-mail: shanggar@ummc.edu.my

References

[1] Chen R, Ren S, Yiu MK, Fai NC, Cheng WS, Ian LH, Naito S, Matsuda T, Kehinde E, Kural A, Chiu JY, Umbas R, Wei Q, Shi X, Zhou L, Huang J, Huang Y, Xie L, Ma L, Yin C, Xu D, Xu K, Ye Z, Liu C, Ye D, Gao X, Fu Q, Hou J, Yuan J, He D, Pan T, Ding Q, Jin F, Shi B, Wang G, Liu X, Wang D, Shen Z, Kong X, Xu W, Deng Y, Xia H, Cohen AN, Gao X, Xu C and Sun Y. Prostate cancer in Asia: a collaborative report. Asian J Uro 2014; 1: 15-29.

[2] Zainal Ariffin Omar and Nor Saleha Ibrahim Tamin. National Cancer Registry Malaysia Cancer Statistics-Data and Figure 2007.

[3] Chang CC, Lee YC, Tsai HW, Yii SC, Yen TH, Chu FY. Diagnostic role of serum free-to-total prostate specific antigen (PSA) ratio in prostate cancer with serum total concentration of PSA below 4 ng/mL. Asian Pac J Cancer Prev 2015; 16: 5261-5264.

[4] Tonry CL, Leacy E, Raso C, Finn SP, Armstrong J and Pennington SR. The role of proteomics in biomarker development for improved patient diagnosis and clinical decision making in prostate cancer. Diagnostics (Basel) 2016; 6.

[5] Lin YR, Wei XH, Uhlman M, Lin XT, Wu SF, Diao PF, Xie HQ, Xie KJ and Tang P. PSA density improves the rate of prostate cancer detection in Chinese men with a PSA between 2.5-10.0 ng ml (-1) and 10.1-20.0 ng ml (-1): a multicenter study. Asian J Androl 2015; 17: 503-507.

[6] Muntener M, Kunz U, Eichler K, Puhan M, Schmid DM, Sulser T and Strebel RT. Lowering the PSA threshold for prostate biopsy from 4 to 2.5 ng/ml: influence on cancer characteristics and number of men needed to biopt. Urol Int 2010; 84: 141-146.

[7] Anderson JR, Strickland D, Corbin D, Byrnes JA and Zweiback E. Age-specific reference ranges for serum prostate-specific antigen. Urology 1995; 46: 54-57.

[8] Chen R, Huang Y, Cai X, Xie L, He D, Zhou L, Xu C, Gao X, Ren S, Wang F, Ma L, Wei Q, Yin C, Tian Y, Sun Z, Fu Q, Ding Q, Zheng J, Ye Z, Ye D, Xu D, Hou J, Xu K, Yuan J, Gao X, Liu C, Pan T, Sun Y; Chinese Prostate Cancer Consortium. Age-specific cutoff value for the application of percent free prostate-specific antigen (PSA) in Chinese men with serum PSA levels of 4.0-10.0 ng/ml. PLoS One 2015; 10: e0130308.

[9] Benson MC, Whang IS, Pantuck A, Ring K, Kaplan SA, Olsson CA and Cooner WH. Prostate specific antigen density: a means of distinguishing benign prostatic hypertrophy and prostate cancer. J Urol 1992; 147: 815-816.

[10] Barnett JM, Wraith P, Kiely J, Persad R, Hurley K, Hawkins P and Luxton R. An inexpensive, fast and sensitive quantitative lateral flow magneto-immunoassay for total prostate specific antigen. Biosensors (Basel) 2014; 4: 204-220.

[11] Kort SA, Martens F, Vanpoucke H, van Duijnhoven HL and Blankenstein MA. Comparison of 6 automated assays for total and free prostate-specific antigen with special reference to their reactivity toward the WHO 96/670 reference preparation. Clin Chem 2006; 52: 1568-1574.

[12] Djavan B. Prostate biopsies and the Vienna nomograms. Eur Urol Suppl 2006; 5: 500-510.

[13] Yu HJ and Lai MK. The usefulness of prostate-specific antigen (PSA) density in patients with intermediate serum PSA level in a country with low incidence of prostate cancer. Urology 1998; 51: 125-130.

[14] Kobayashi T, Nishizawa K, Ogura K, Mitsumori K and Ide Y. Detection of prostate cancer in men with prostate-specific antigen levels of

2.0 to 4.0 ng/mL equivalent to that in men with 4.1 to 10.0 ng/mL in a Japanese population. Urology 2004; 63: 727-731.
[15] Mochtar CA and Andika RS. The value of prostate-specific antigen in Asia. Ther Adv Urol 2010; 2: 77-83.
[16] Zhu Y, Wang HK, Qu YY and Ye DW. Prostate cancer in East Asia: evolving trend over the last decade. Asian J Androl 2015; 17: 48-57.
[17] Lucca I and Shariat SF. Re: Prostate cancer incidence and PSA testing patterns in relation to USPSTF screening recommendations. Eur Urol 2016; 70: 205-206.
[18] Catalona WJ, Richie JP, deKernion JB, Ahmann FR, Ratliff TL, Dalkin BL, Kavoussi LR, MacFarlane MT and Southwick PC. Comparison of prostate specific antigen concentration versus prostate specific antigen density in the early detection of prostate cancer: receiver operating characteristic curves. J Urol 1994; 152: 2031-2036.
[19] Lichtensztajn DY, Gomez SL, Sieh W, Chung BI, Cheng I and Brooks JD. Prostate cancer risk profiles of Asian-American men: disentangling the effects of immigration status and race/ethnicity. J Urol 2014; 191: 952-956.
[20] Hailan M and Rifat UN. Age-specific reference ranges of serum prostate-specific antigen in Iraqi men. Arab J Urol 2011; 9: 273-277.
[21] Ojewola RW, Jeje EA, Tijani KH, Ogunjimi MA and Anunobi CC. Clinico-pathological correlation of digital rectal examination findings amongst nigerian men with prostatic diseases: a prospective study of 236 cases. Niger J Surg 2013; 19: 26-31.
[22] Bosch JL, Bohnen AM and Groeneveld FP. Validity of digital rectal examination and serum prostate specific antigen in the estimation of prostate volume in community-based men aged 50 to 78 years: the Krimpen Study. Eur Urol 2004; 46: 753-759.
[23] Adhyam M and Gupta AK. A review on the clinical utility of PSA in cancer prostate. Indian J Surg Oncol 2012; 3: 120-129.
[24] Bazinet M, Meshref AW, Trudel C, Aronson S, Peloquin F, Nachabe M, Begin LR and Elhilali MM. Prospective evaluation of prostate-specific antigen density and systematic biopsies for early detection of prostatic carcinoma. Urology 1994; 43: 44-51.
[25] Gregorio EP, Grando JP, Saqueti EE, Almeida SH, Moreira HA and Rodrigues MA. Comparison between PSA density, free PSA percentage and PSA density in the transition zone in the detection of prostate cancer in patients with serum PSA between 4 and 10 ng/mL. Int Braz J Urol 2007; 33: 151-160.
[26] Verma A, St Onge J, Dhillon K and Chorneyko A. PSA density improves prediction of prostate cancer. Can J Urol 2014; 21: 7312-7321.
[27] Rosenberg MT, Spring AC and David Crawford E. Prostate cancer and the PCP: the screening dilemma. Int J Clin Pract 2015; 69: 1438-1447.
[28] Lujan M, Paez A, Llanes L, Miravalles E and Berenguer A. Prostate specific antigen density. Is there a role for this parameter when screening for prostate cancer? Prostate Cancer Prostatic Dis 2001; 4: 146-149.
[29] Ciatto S, Bonardi R, Lombardi C, Cappelli G, Castagnoli A, D'Agata A, Zappa M and Gervasi G. Predicting prostate biopsy outcome by findings at digital rectal examination, transrectal ultrasonography, PSA, PSA density and free-to-total PSA ratio in a population-based screening setting. Int J Biol Markers 2001; 16: 179-182.
[30] Heidenreich A, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V, Mottet N, Schmid HP, van der Kwast T, Wiegel T, Zattoni F and European Association of U. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and treatment of clinically localised disease. Eur Urol 2011; 59: 61-71.
[31] Mistry K and Cable G. Meta-analysis of prostate-specific antigen and digital rectal examination as screening tests for prostate carcinoma. J Am Board Fam Pract 2003; 16: 95-101.
[32] Shahab AA, Soebadi DM, Djatisoesanto W, Hardjowijoto S, Soetojo S and Hakim L. Prostate-specific antigen and prostate-specific antigen density cutoff points among Indonesian population suspected for prostate cancer. Prostate Int 2013; 1: 23-30.