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

Shanggar Kuppusamy1,2, Kia Fatt Quek3, Retnagowri Rajandram1, Azad Hassan Abdul Razack1,2, Norman Dublin1,4

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

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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
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

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.
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,  

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

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

| PSA-prostate specific antigen, PV-prostate volume, PSAD-prostate specific antigen density, DRE-digital rectal examination, aANOVA, bChi-square test, *p < 0.01. |

<table>
<thead>
<tr>
<th>Cancer (n=33)</th>
<th>Non-cancer (n=253)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>70.30±8.35</td>
<td>67.72±6.65</td>
</tr>
<tr>
<td>PSA</td>
<td>12.05±6.78</td>
<td>9.35±5.26</td>
</tr>
<tr>
<td>PV</td>
<td>34.21±14.60</td>
<td>45.97±20.05</td>
</tr>
<tr>
<td>PSAD</td>
<td>0.40±0.25</td>
<td>0.23±0.15</td>
</tr>
<tr>
<td>Abnormal DRE</td>
<td>36.4% (n=12)</td>
<td>24.5% (n=62)</td>
</tr>
</tbody>
</table>

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

- PSA-prostate specific antigen, PV-prostate volume, PSAD-prostate specific antigen density, DRE-digital rectal examination, t-test, cChi-square test, Fisher exact test, "p < 0.01 ‘p < 0.05.**
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 PCas [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].
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.

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

<table>
<thead>
<tr>
<th>Combination</th>
<th>Cancers missed</th>
<th>Biopsies spared</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSAD &gt; 0.19 and/or PSA &gt; 7.0</td>
<td>6</td>
<td>92</td>
</tr>
<tr>
<td>PSAD &gt; 0.19 and/or PSA &gt; 7.0</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>PSAD &gt; 0.19 and/or DRE +</td>
<td>3</td>
<td>91</td>
</tr>
<tr>
<td>PSAD &gt; 0.19 and/or PSA &gt; 7.0 and DRE +</td>
<td>3</td>
<td>70</td>
</tr>
</tbody>
</table>

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

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**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

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PSA density in prostate cancer

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