The accuracy of increased blood concentration of prostate-specific antigen to prostate malignancy

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Background: Various controversies arose in the study of Prostate Specific Antigen (PSA) examination as an alternative of biopsy to detect prostate malignancy. Prostate Specific Antigen is a specific protein secreted by the prostate gland and is affected by various conditions. PSA levels will certainly increase at the enlargement of the prostate gland. An accurate cutoff point that can detect prostate cancer is needed.

Objective: To evaluate the PSA diagnostic test against prostate malignancy.

Methods: This study used a diagnostic test method for 91 patients undergoing either prostate gland surgery or open prostatectomy at Bethesda Hospital Yogyakarta in January 2014-January 2016 period. Data were taken from medical records with inclusion criteria as follow: over 50 years of age, preoperative PSA, and PA results. This study was a descriptive analytic study. In the diagnostic test AuROC, cut-off points were determined. Chi-square test was performed to assess sensitivity, specificity, PPV, NPV, LHR -, and LHR +.

Results: We studied 91 patients with a mean age of 70.24 (46-54) and mean PSA level of 27.2 (0.59-101). The results of PA prostate tissue examinations were adenocarcinoma in 15 patients (16.5 %) and BPH in 76 patients (83.5 %). On all PSA levels, AuROC were 0.90. Specificity of PSA with 4 ng/mL cut-off, 10 ng/mL, 20 ng/mL, 50 ng/mL, and 100 ng/mL were 0.53, 35.53, 67.11, 96.05, 98.68. When the cut-offs were reduced to 4.01-10 ng/mL, 10.01-20 ng/mL, 20.01-50 ng/mL, 50.01-100 ng/mL, and > 100 ng/mL, the specificity were 76.32, 68.00, 69.74, 96.05, 100.00. Cut-off value of 50 ng/mL had LHR + >10.00 (15:20).

Conclusion: There is a strong correlation between PSA and prostate malignancy. PSA value> 50 ng / mL has high accuracy to detect prostate malignancy. A biopsy is needed to determine a definitive diagnostic because no cut-off value can be used as a benchmark.
Hasil: Dari 91 pasien rerata usia nya adalah 70.24 (46-54) dan kadar PSA sebesar 27.02 (0.59-101). Hasil PA jaringan prostat adalah 15 pasien adenocarcinoma (16.5%) dan 76 pasien BPH (83.5%). Pada keseluruhan kadar PSA didapatkan AuROC 0.90. Spesifitas pada PSA dengan cut-off 4 ng/mL, 10 ng/mL, 20 ng/mL, 50 ng/mL, dan 100 ng/mL adalah 10.53, 35.53, 67.11, 96.05, 98.68. Apabila rentang cut-off diperkecil menjadi 4.01-10 ng/mL, 10.01-20 ng/mL, 20.01-50 ng/mL, 50.01-100 ng/mL, dan > 100 ng/mL maka spesifitasnya menjadi 76.32, 68.00, 69.74, 96.05, 100.00. Nilai cut-off 50 ng/mL memiliki LHR+ > 10 (15.20).

Kesimpulan: Ada korelasi kuat antara PSA dengan keganasan prostat. Nilai PSA > 50 ng/mL mempunyai akurasi tinggi untuk mendeteksi keganasan prostat. Perlu dilakukan biopsi untuk menentukan diagnostik pasti karena tidak ada nilai cut-off yang dapat dijadikan patokan.

INTRODUCTION

The prostate is one part of the male organ that plays an important role in the process of reproduction. However, this organ became one of the contributors to the emergence of complaints in men generally older population. Complaints of urinary retention are often experienced by men, especially those aged 50 years and above, and it is very closely related to the prostate gland enlargement, either in the form of Benign Prostate Hyperplasia (BPH) or prostate cancer (CaP). Recent decades have shown an increase in the incidence of an enlarged prostate gland. Groves et al. (2013) observed 17.023 men in California USA during 2007-2010 who came to the Emergency Department (IGD) with complaints of urinary retention associated with prostate gland enlargement, they found an increase of 36% incidence of disease from 2007-2010.1 Increasing age also increase the risk of prostate gland enlargement.2,3,4 Haas et al. (2008) with observational methods of Surveillance Epidemiology and End Results (SEER) program of the National Cancer Institute and the International Agency for Research on Cancer (IARC) found that the incidence rate of prostate cancer reached 200 per 100.000 people in almost every part of the world.3

One examination to detect the occurrence of CaP is by measuring the levels of PSA in the blood, although it is still controversial because no definite cut-off value has been found.5,6,7 PSA is a glycoprotein secreted by both the normal gland and neoplastic tissue in the prostate.8 PSA does not always indicate the occurrence of malignancy but is specifically secreted by the prostate gland so it can be used to assess the condition of prostatic gland.

The European randomized study of screening for prostate cancer (ERSPC) showed that early screening and early intervention can reduce mortality by CaP.9,10 Although still controversial, several studies have been conducted to assess the sensitivity and specificity of PSA in detecting the occurrence of CaP. Lojanapiwat et al. (2014) conducted a study of 1,116 people with positive biopsy result, 395 of which was found with cut-off value 4 ng/mL, and the sensitivity and specificity of PSA were 9.3% and 98%.11 CDC’s national program of cancer registries and national cancer institute’s surveillance, epidemiology and end results describes that there are incidence differences between races and ethnic in America.12,13,14 In Asia, the incidence of CaP is lower than western countries.15 This study aimed to evaluate the cut-off point in total PSA level for CaP diagnosis, especially in Indonesia.

METHODS

This study was conducted at Bethesda Hospital Yogyakarta in May until August 2016. The population of this study was all BPH patients under going surgery, either open prostatectomy or TURP at Bethesda Hospital Yogyakarta and were also undergoing PSA examination and biopsy of the prostate gland. Among the 272 subjects who underwent surgical treatment, 91 subjects fulfilled the inclusion criteria, which include age, date of entry, date of surgery, hospital discharge date, surgery type, total PSA lab result and prostate gland biopsy result.
Prostate gland biopsy was performed with a post-operative prostate specimen. Exclusion criteria in this research are incomplete medical record data.

Data were collected through observation from medical records from January 2014 to January 2016. This is a descriptive analytic study with diagnostic test study design, in which the gold standard used was PA results. The sample size was determined using the formula:

\[ n = \frac{Z^2 \times P(1-P)}{\epsilon^2} \]

If we described sensitivity as \( P \), then \( n \) is \( (a+c) \), if we described specificity as \( p \), then \( n \) is \( (b+d) \)

\[ N = \frac{(a+c)}{Prevalence} \]

\[ N = \frac{(b+d)}{(1-Prevalence)} \]

Data analysis was done using Chi-Square and displayed in the form of tables and graphics. Dependent variable was grouped into various cut-off, which were 4.01-10 ng/ml, 10.01-20 ng/ml, 20.01-50 ng/ml, 50.01-100 ng/ml, and more than 100.00 ng/ml. P-value<0.05 was considered statistically significant. This study has been approved by the ethical committee or komisi etik penelitian kedokteran of Fakultas Kedokteran Universitas Kristen Duta Wacana.

RESULT

In this study, PSA levels that were more than 100 ng/mL had no concrete number, thus they were classified as 101 ng/mL. The mean age of subjects was 70.24 (46-54) and the mean of PSA level was 27.02 (0.59-101). From 91 patients examined for biopsy of prostate tissue, 15 patients had adenocarcinoma (16.5%) and 76 patients had BPH (83.5%). By measuring overall level of PSA, AuROC of 86% was obtained. The higher the level of PSA in the blood the lower the sensitivity to prostate malignancy. This can be concluded from the results in which the sensitivity of PSA in the concentration of 4.01-10 ng/ml was 100%, 10.01-20 ng/ml was 100%, 20.01-50 ng/ml was 86.67%, 50.01-100 ng/ml was 60%, and for concentration 100.00 ng/ml was 40% (Table 1). This result is inversely proportional to the specificity of PSA levels in the blood to prostate malignancy. This can be concluded from the results in which the specificity of PSA in the concentration of 4.01-10 ng/ml was 10.53%, 10.01-20 ng/ml was 35.53%, 20.01-50 ng/ml was 67.11%, 50.01-100 ng/ml was 96.05%, an in the concentration of more than 100.00 ng/ml was 98.68%. PPV value in the concentration of more than 4 ng/mL and 10ng/mL were 18.07 and 23.44, and increasing with the increase of PSA level. This is also inversely proportional to NPV value, in which the larger PSA level the smaller NPV value. PSA level above 50 indicates the high accuracy of malignancy incidence (0.78). PSA level above 50ng/ml showed an LHR+ value over 5.0 (15.20). PPV 75,00, and NPV 92,41. Based on the age group, PSA level with 50 ng/ml cut-off point was found mostly in the age group of 60-69 years old.

![Figure 1. ROC curve](image-url)
In this study, the result of the whole area under receiving characteristic curve (AuROC) or ROC is 0.86 (95% Confidence Interval = 0.81-0.99) with mean PSA level 27 (0.59-101 ng/mL). This proves that PSA level is very good for determining the accuracy of the occurrence of a malignancy.\textsuperscript{11} This result is similar with a previous study by Holsmtrom et al. (2009)\textsuperscript{10} in which the AuROC value was 0.84 (95% CI= 0.82-0.86) and another study by Lojanapiwat et al. (2014)\textsuperscript{11} in which the AuROC value was 0.82 (95% CI= 0.79-0.82). In clinical practice, the cut-off point used to predict the presence of malignancy was 4 ng/mL.\textsuperscript{10,11} In this study the sensitivity and specificity for cut-off point 4 ng/mL is 100% and 10,53% and when we increase cut-off point to 20 ng/mL then its sensitivity decreases to 86,67% and specificity increases to 67,11%. In a previous study by Holstrom et al. (2009)\textsuperscript{10} the sensitivity when PSA level 4 ng/mL was only 44%, however, when cut-off point was reduced to 3 ng/mL, its sensitivity increased to 59%. This is because, in a study conducted by Holstrom et al. (2009), the average PSA level at the time of the study was only 3.6 ng/mL. For PPV value 18.07, NPV was 100, LHR+ 1.12, and AuROC was 0.55.\textsuperscript{10,11}

Good specificity is necessary to screen the population with a low prevalence of malignancy.

Table 1. Diagnostic value of PSA with certain cut-off points against prostate malignancy

<table>
<thead>
<tr>
<th>PSA (ng/ml) Cut-off point</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>LHR+</th>
<th>LHR-</th>
<th>DP</th>
<th>PPV</th>
<th>NPV</th>
<th>AuROC</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>100.00</td>
<td>10.53</td>
<td>1.12</td>
<td>0.00</td>
<td>16.48</td>
<td>18.07</td>
<td>100.00</td>
<td>0.55</td>
</tr>
<tr>
<td>10</td>
<td>100.00</td>
<td>35.53</td>
<td>1.55</td>
<td>0.00</td>
<td>16.48</td>
<td>23.44</td>
<td>100.00</td>
<td>0.68</td>
</tr>
<tr>
<td>20</td>
<td>86.67</td>
<td>67.11</td>
<td>2.63</td>
<td>0.20</td>
<td>16.48</td>
<td>34.21</td>
<td>96.23</td>
<td>0.77</td>
</tr>
<tr>
<td>50</td>
<td>60.00</td>
<td>96.05</td>
<td>15.20</td>
<td>0.42</td>
<td>16.48</td>
<td>75.00</td>
<td>92.41</td>
<td>0.78</td>
</tr>
<tr>
<td>100</td>
<td>40.00</td>
<td>98.68</td>
<td>30.40</td>
<td>0.61</td>
<td>17.05</td>
<td>85.71</td>
<td>89.29</td>
<td>0.69</td>
</tr>
</tbody>
</table>

PSA : prostate specific antigen; PPV : positive predictive value; NPV : negative predictive value; DP : diagnose prevalence; LHR+ : positive likelihood ratio; LHR- : negative likelihood ratio; AuROC : arean under the receiver operating characteristic curve.

Table 2. PSA level by cut-off point based on age stratification

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Frequency (n)</th>
<th>PSA Level</th>
<th>cut-off point</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt; 50 ng/mL</td>
<td>≥ 50 ng/mL</td>
</tr>
<tr>
<td>50-59</td>
<td>11</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>60-69</td>
<td>31</td>
<td>24</td>
<td>7</td>
</tr>
<tr>
<td>70-79</td>
<td>34</td>
<td>32</td>
<td>2</td>
</tr>
<tr>
<td>&gt;80</td>
<td>15</td>
<td>13</td>
<td>2</td>
</tr>
</tbody>
</table>

DISCUSSION

In this study, the result of the whole area under receiving characteristic curve (AuROC) or ROC is 0.86 (95% Confidence Interval = 0.81-0.99) with mean PSA level 27 (0.59-101 ng/mL). This proves that PSA level is very good for determining the accuracy of the occurrence of a malignancy.\textsuperscript{11} This result is similar with a previous study by Holsmtrom et al. (2009)\textsuperscript{10} in which the AuROC value was 0.84 (95% CI= 0.82-0.86) and another study by Lojanapiwat et al. (2014)\textsuperscript{11} in which the AuROC value was 0.82 (95% CI= 0.79-0.82). In clinical practice, the cut-off point used to predict the presence of malignancy was 4 ng/mL.\textsuperscript{10,11} In this study the sensitivity and specificity for cut-off point 4 ng/mL is 100% and 10,53% and when we increase cut-off point to 20 ng/mL then its sensitivity decreases to 86,67% and specificity increases to 67,11%. In a previous study by Holstrom et al. (2009)\textsuperscript{10} the sensitivity when PSA level 4 ng/mL was only 44%, however, when cut-off point was reduced to 3 ng/mL, its sensitivity increased to 59%. This is because, in a study conducted by Holstrom et al. (2009), the average PSA level at the time of the study was only 3.6 ng/mL. For PPV value 18.07, NPV was 100, LHR+ 1.12, and AuROC was 0.55.\textsuperscript{10,11}

Good specificity is necessary to screen the population with a low prevalence of malignancy.
Specificity of over 95% is very supportive to avoid any bias that may affect the results of an examination. This will be supported by a sensitivity value approaching 50%. In this study the cut-off value of 50 ng/mL has a specificity of 96% with a sensitivity of 60%. This result was also found in a study conducted by Heyns et al. (2001) in 716 patients with PSA levels greater than 4 ng/mL. Jang and Kim (2012) in his study of 65 patients with PSA levels greater than 100 ng/mL suffering from malignancy. This is reinforced by Gerstenbluth et al. (2002) conclusion that the negative biopsy results in patients with PSA levels greater than 20 ng/mL are often false-negative.

In the 50 ng/mL cut-off LHR + is also obtained at 15.20. Holmstro`rt et al. (2009) based on his research concluded that these cut-off levels could be used to identify men with very low prostate malignancy risk (1.2% incidence at LHR cut-off level less than 0.1). In this study, the 4 ng/mL and 10 ng/mL cut-offs gave LHR values of 0.00, this was because the incidence of prostate cancer at PSA levels below 10 ng/mL was 0 (0%).

The age group 60-69 years old has the most PSA level exceeding cut-off value. Based on various studies the normal value of PSA levels in the age group 60-69 years is 0.0-0.54 ng/mL. This result can be a consideration for screening prostate malignancy in that age group.

The limitation of this study is the tissue used for PA examination was from TURP surgery and open prostatectomy. The recommended biopsy retrieval technique is TRUS-guidance biopsy with sextant core scheme. Biopsy results with TURP specimens may be used but their validity is not as good as TRUS-guidance biopsy. The small sample size also influences the results of this study. To validate the cutoff value obtained from this study, a larger sample size, as well as other research designs are required.

CONCLUSION
There is a very significant correlation to PSA levels in the blood with prostate malignancy. PSA levels over 50 ng/mL have a high specificity for diagnosing prostate malignancy. There is no cut-off value that can be used as a benchmark so that biopsy needs to be done to determine the exact diagnosis of malignancy.

CONFLICT OF INTEREST
We declare there is no conflict of interest

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REFERENCES
Krisna, et al. The Accuracy of Increased...


