

# Cut-off Point Prostate-Specific Antigen and Prostate-Specific Antigen Density in Prostate Cancer - Suspected Patients in Makassar, Indonesia

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## ABSTRACT

**Background:** Prostate-specific antigen (PSA) is a test performed to detect prostate cancer. Currently, no rational standard exists for its cut-off point, which results in increased patients due to prostate biopsy complications. Therefore, this study aimed to determine the estimated PSA cut-off point and PSA density (PSAD) in patients with suspected prostate cancer (CaP) in Makassar.

**Methods:** The study sample was patients with benign prostatic hyperplasia (BPH) and cancer of the prostate (CaP) in Makassar, Indonesia. Statistical tests were performed with the Mann-Whitney U, Chi-Square, Fisher's Exact, and ROC tests (significance  $p = <0.05$ ) with a retrospective research type.

**Results:** 470 samples were obtained from BPH (88.3%) and CaP (11.7%) patients ranging from 40 to  $\geq 80$  years old. Patients were found at 60-79 years (70.8%) with LUTS symptoms (66%), hematuria (10.6%), urinary retention (42.1%), and US prostate volume ranging from 30-50ml, examination of rectal toucher (RT) BPH 84.3% and CaP 96.4% for assessment of prostate consistency, PSA BPH (14.82 ng/ml) and CaP (48.10 ng/ml), PSAD BPH ( $0.28 \text{ ng/mL}^2$ ) and CaP ( $1.19 \text{ ng/mL}^2$ ). These values can predict histopathology results ( $p < 0.05$ ) on US volume, risk factors for type II DM, hypertension ( $p > 0.05$ ) can predict histopathology results.

**Conclusion:** The average CaP PSA was 48.10 ng/ml with 18.62 ng/ml cut-off point, and PSAD CaP was  $1.99 \text{ ng/mL}^2$  with  $0.53 \text{ ng/mL}^2$  cut-off point, which was higher than in Chinese and American samples.

**Key words:** benign prostatic hyperplasia, prostate cancer, prostate-specific antigen, PSAD

## INTRODUCTION

Prostate cancer is a condition in which the glandular cells grow abnormally and uncontrollably. It is the second most common urinary tract malignancy after bladder (1,2). PSA (prostate-specific antigen) is one of the tests performed to

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detect prostate cancer. At present, its value interpretation is still controversial; there are patients with prostate carcinoma without an increase in PSA, while there are many BPH patients with high PSA density (PSAD) (3).

In Asia, prostate cancer incidence is low; therefore, the higher cut-off point for PSA and PSAD becomes a reference for biopsy. Research from 2000 to 2013 found that 2606 Chinese people had an initial 4.5 ng/ml PSA cut-off point and 0.12 ng/mL<sup>2</sup> PSAD. Furthermore, PSAD above 0.12 ng/mL<sup>2</sup> are significant predictors for prostate cancer detection (4).

At Hasan Sadikin Hospital in Bandung, Indonesia, patient parameters for biopsy are 14.6 ng/ml PSA and 0.23 ng/mL<sup>2</sup> PSAD. However, to date, no rational standard exists for PSA cut-off point. Also, a study conducted in the US reported a significant increase in hospitalized patients due to biopsy complications. Therefore, determining PSA cut-off point and PSAD is very important to avoid unnecessary biopsy (3). This study aimed to determine the estimated PSA cut-off point and PSAD in patients with suspected CaP.

## METHODS

The study was conducted from January 2014 to December 2019. The samples were 470 patients based on secondary data from medical records of benign prostatic hyperplasia (BPH) and cancer patients treated in Makassar from 2014-2019. Furthermore, the age range was 40 to  $\geq 80$  years, and they were divided into BPH and CaP groups. In this study, upheld by the findings of medical records, data collected includes age, clinical, LUTS, hematuria, and urinary retention, consistency in rectal toucher (RT) examination, prostate volume associated with transabdominal ultrasound examination, PSA and PSAD levels, and histopathological examination results of the prostate. Data analysis was performed using SPSS version 22 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp), while statistical analysis was performed using descriptive calculations and frequency distribution, the Mann-Whitney U, Chi-Square, Fisher's Exact and Receiver operator characteristic (ROC) curves. The results are significant when  $p < 0.05$ .

This research is a retrospective with a cross-sectional design.

## RESULTS

The total samples used was 470, and the characteristics are described in *tables 1* and *2*. PSA cut-off

**Table 1 - Patient characteristics**

	Number (n=470)	%
<b>Age Group</b>		
40-49	8	1.7
50-59	83	17
60-69	176	37.4
70-79	157	33.4
$\geq 80$	46	9.8
<b>LUTS Symptoms</b>		
Yes	310	66
No	160	34
<b>Hematuria</b>		
Yes	50	10.6
No	420	89.4
<b>Urinary Retention</b>		
Yes	198	42.1
No	272	57.9
<b>Consistency</b>		
Solid Chewy	352	74.9
Solid Hard	118	25.1
<b>Ultrasound Volume</b>		
< 30 ml	50	10.6
30-50 ml	224	47.7
51-80 ml	142	30.2
>80 ml	54	11.5
<b>PSA</b>		
< 4 ng/ml	124	26.4
4-10 ng/ml	135	28.7
10-20 ng/ml	102	21.7
>20 ng/ml	109	23.2
<b>PSAD</b>		
< 0,15 ng/ml <sup>2</sup>	220	46.8
$\geq 0,15$ ng/ml <sup>2</sup>	250	53.2
<b>Histopathology Results</b>		
BPH	415	88.3
CaP	55	11.7
<b>Surgery</b>		
TUR-P	454	96.6
Open prostatectomy	16	3.4
<b>DM Risk Factors</b>		
Yes	28	6
No	442	94
<b>Hypertension Risk Factors</b>		
Yes	153	32.6
No	317	67.4

values and PSAD density can be obtained through the ROC (*figs. 1* and *2*). Also, sensitivity is depicted on the Y ordinate with 1-specificity on the X-axis. PSA prognostic accuracy and PSAD with ROC (sensitivity, specificity, positive and negative predictive value, and Area Under Curve [AUC]) are presented in *table 3*.

Based on *table 3*, it is known that PSA cut-off value is 18.62, with 60.0% sensitivity, 79.52% specificity, 28% positive predictive value (PPV), 98.8% negative predictive value (NPV), and 0.724 AUC. Meanwhile, the PSAD cut-off value is 0.533,

**Table 2 - Patient characteristics based on anatomic pathology test results**

	Mean ± SD		p* value
	BPH (n=415)	CaP (n=55)	
Age	67.62 ± 9.20	69.31 ± 10.63	0.314
US	53.86 ± 25.72	51.04 ± 23.63	0.495
PSA	14.82 ± 20.1	48.10 ± 42.58	<0.001
PSAd	0.287 ± 0.40	1.19 ± 1.32	<0.001
	BPH (n=415)	CaP (n=55)	p** value
	n (%)	n (%)	
LUTS			
Yes	259 (62.4)	51 (92.7)	<0.001
No	156 (37.6)	4 (7.3)	
Hematuria			
Yes	32 (7.7)	18 (32.7)	<0.001
No	383 (92.3)	37 (67.3)	
Urinary Retention			
Yes	162 (39.0)	36 (65.5)	<0.001
No	253 (61.0)	19 (34.5)	
Consistency			
Solid Chewy	350 (84.3)	2 (3.6)	<0.001
Solid Hard	65 (15.7)	53 (96.4)	
Diabetes Mellitus type II			
Yes	26 (6.3)	2 (3.6)	0.760
No	389 (93.7)	53 (96.4)	
Hypertension			
Yes	140 (33.7)	13 (23.6)	0.168
No	275 (66.3)	42 (76.4)	

\* Mann-Whitney U Test \*\* Fisher's Exact test

with 54.55% sensitivity, 86.02% specificity, 34.1% PPV, 93.5% NPV, and 0.732 AUC.

## DISCUSSION

This study found more patients with BPH than those with cancer (CaP), with 88.3% and 11.7%, respectively. This finding is in accordance with research conducted by Siswandi et al. at Dr. H. Abdul Moeloek Hospital, which found more BPH (96.3%) than CaP (3.7%) (8). Likewise, in a study of 1177 patients with prostate enlargement, Capogrosso et al. found 94% had BPH, and the remaining 6% were CaP (5).

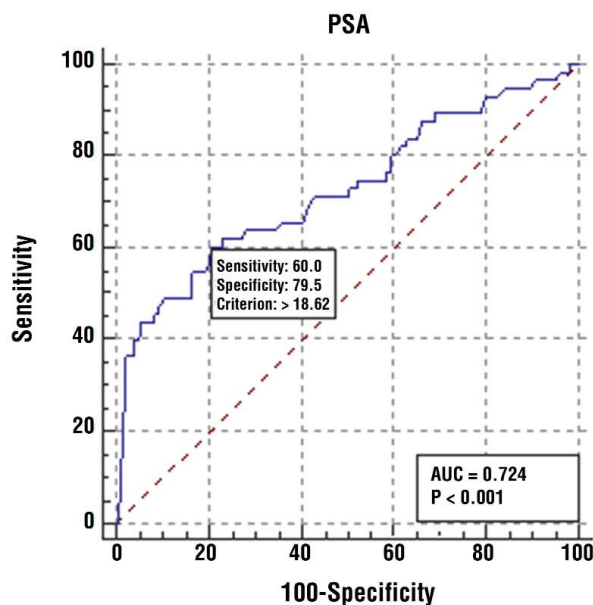


Figure 1 - ROC curves on PSA scores

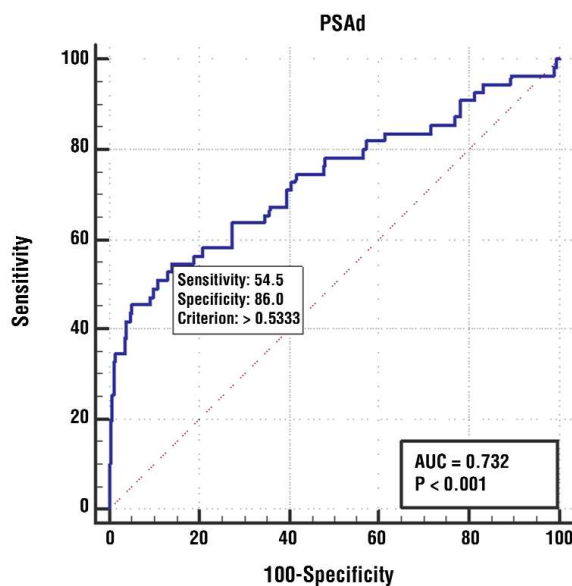


Figure 2 - ROC curves on PSAd scores

**Table 3 - Prognostic PSA and PSAD accuracy and Area Under Curve (AUC)**

	Sensitivity (%)	Specificity (%)	Positive Prediction Value (%)	Negative Prediction Value (%)	Area Under Cover	p* value
PSA						
>18.62	60.00	79.52	28.0	93.8	0.724	<0.001
PSAd						
>0.533	54.55	86.02	34.1	93.5	0.732	<0.001

\*ROC Test

The results indicate that patients with BPH and CaP were mostly found within the age range of 60-79 years (70.8%). Only 1.7% suffer from BPH and CaP under the age of 50. This finding is in accordance with the existing theory that about 50% of adult males aged 60-70 years have an enlarged prostate (both BPH and CaP), and the number increases to 90% in those over 70 (6,7). Furthermore, it was found that age was not a significant factor in distinguishing BPH and CaP patients. Also, research by Siswandi et al. found that patients with BPH and CaP were mostly between 60-69 years, with an average age of 61.52 (8).

In this study, 66% experienced lower urinary tract symptoms (LUTS), and when compared with histopathology results, 62.4% of BPH and 92.7% of CaP patients experienced LUTS, which predicts histopathology action towards both. These results are in accordance with the theory that those with prostate enlargement accompanied by LUTS are most likely to have cancer (9-11).

Of the patients, 10.6% had hematuria, and when compared with the results, only a small number of BPH (7.7%) patients experienced it. Meanwhile, 32.7% CaP patients had hematuria. Also, it was found that the symptoms can predict histopathology patients' outcome, which is in accordance with the theory that prostate cancer-related hematuria occurs due to tumors that cause bleeding into the prostatic urethra or invade the bladder. Furthermore, when the cancer develops, extracapsular neovascular anastomosis usually develops to the collateral vessels in the pelvis (11,12).

In the sample, 42.1% experienced urinary retention; this is supported by Rasul et al., who found that 34% of those with prostate enlargement had retention (7). Based on this theory, it can occur due to increased prostate size, which then causes urinary obstruction (13-14). According to the results, 39% of BPH and 65.5% of CaP patients experienced urinary retention. It was also found that its presence or absence predicts the outcome of prostate enlargement histopathology towards BPH or CaP.

Rectal toucher (RT) tests showed that the majority of BPH patients had prostate with a solid chewy consistency, whereas those with CaP had a solid hard consistency. This is in accordance with the theory that prostate cancer patients experience changes from solid to hard accompanied by median sulcus loss, difficulty in moving, and nodules appearance (15). Thus, these findings are similar to Aminsharifi et al (16).

BPH and CaP patients had the highest prostate volume (US results), ranging from 30-50 ml.

Furthermore, those with BPH had an average volume of 53.86 ml, while those with CaP had 51.04 ml. However, the volume cannot predict anatomical pathology results. Thus, the finding is quite different from Khalil et al., who found that patients with a small prostate volume (less than 35 ml) on average had CaP biopsy results, whereas those with large (more than 70 ml) had BPH results. This may be due to ethnicity, as well as sample differences (this study has a larger number of samples than that of Khalil et al) (17).

According to the literature, diabetes mellitus is a risk factor for both due to increased serum insulin, and fasting plasma glucose is thought to increase prostate size (6,18). However, this is quite different from this study, in which only 6% are diabetic.

Theoretically, hypertension may not play a direct role as a risk factor, but one theory suspects increasing the sympathetic activity in older men becomes a point of a pathophysiological relationship between prostate enlargement and hypertension. Therefore, it was found that 32.6% over 40 years had enlarged prostate and hypertension.

Several other risk factors, such as genetics, diet, alcohol, smoking, and lipid levels are thought to increase BPH and CaP incidence (6,18-21), but they were not examined in this study. Therefore, it was found that those with hypertension and diabetes comorbidities could not determine the results of anatomic pathology.

Furthermore, it was found that the average PSA of BPH patients was 14.82 ng/ml, while that of CaP patients was higher at 48.10 ng/ml and can also predict patients' histopathology outcomes. Similar findings were found by Putra et al (22), Hsuai et al (23), and Mochtar et al (24), who obtained higher PSA density in CaP compared to BPH patients.

Moreover, the cut-off point of effective PSA in distinguishing BPH and CaP patients was at 18.62 ng/ml (sensitivity 60%, specificity 79.52%, PPV 28%, NPV 93.8%, AUC 0.724). Research on Chinese men found that the optimal PSA cut-off point was at 4.5 ng/ml (sensitivity 94.4%, specificity 14.1%, PPV 29.5%, NPV 86.9%) (4), which is lower than this study's findings. In Indonesia, Mochtar et al. found an optimal cut-off point at 42.7 ng/ml (sensitivity 74%, specificity 73%, PPV 85.2%, NPV 57.5%, AUC 0.81) (24). Therefore, the point is higher than this study's optimal.

It was also found that the average PSAD of BPH was 0.28 ng/ml while that of CaP patients was higher at 1.19 ng/mL<sup>2</sup>. Thus, it can predict patients' histopathology outcomes.

The results indicate the cut-off point of PSAD

density is at 0.533 ng/mL<sup>2</sup> (sensitivity 54.55%, specificity 86.02%, PPV 34.1%, NPV 93.5%, AUC 0.732). This differs from Aminisharifi et al., who found that the optimal cut point was 0.08 ng/mL<sup>2</sup> (sensitivity 98%, specificity 16%, PPV 26%, NPV 96%) (16).

## CONCLUSION

This research found that the average PSA was 48.10 ng/ml with 18.62 ng/ml cut-off point, and for PSAD, the average was 1.19 ng/mL<sup>2</sup> with 0.53 ng/mL<sup>2</sup> cut-off point, which was higher than in Chinese, American, and other Indonesian studies due to high rates of urinary tract infections in patients treated in Makassar.

### *Conflict of interest*

All author declare that they have no conflict of interest.

### *Ethical approval*

All experimental procedures for the treatment of patients as the study samples were reviewed and approved by the local Ethics Committee, number: 1046/UN4.6.4.5.31/PP36/2019.

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