CUT-OFF POINT OF PSA AND PSA DENSITY IN PROSTATE CANCER SUSPECTED PATIENTS

[1]Daniel TM Simanjuntak, [1]Ferry Safriadi.

[1]Department of Urology, Faculty of Medicine/Padjajaran University, Hasan Sadikin General Hospital, Bandung.

ABSTRACT

Objective: *In Hasan Sadikin General Hospital Bandung prostate biopsy is recommended for patients with prostate specific antigen (PSA) levels above 10 ng/mL or PSA density (PSAD) above 0.15 if PSA in between 4–10 ng/mL. However, there were other factors beside of prostate cancer (PCa) that could influence PSA value, such as racial differences and prostatitis. Thus, the optimal cut-off point for PSA is still debatable in national level. This research aimed to determine PSA and PSAD cut-off point for patient suspected of PCa in Hasan Sadikin Hospital Bandung.* ***Material & Methods:*** *A total of 502 patients underwent prostate biopsy for suspicion PCa from 2010–2014. The cut-off point of PSA and PSAD is generated from receiver operating characteristic (ROC) curve.* ***Results:*** *The cut-off point for PSA was 14.6 ng/mL (sensitivity 81.4%, specificity 29.8%). The cut-off point for PSAD was 0.23 (sensitivity 81.4%, specificity 34.8%). Positive predictive value (PPV) for this new cut-off point of PSA and PSAD were 41.1% and 37.6% respectively.* ***Conclusion:*** *PSA and PSAD cut-off point for patients in our center was 14.6 ng/mL and 0.23 respectively. This value is relatively higher compared to the Indonesian consensus. The difference might occur due to high rate of urinary tract infection in patients attending Hasan Sadikin General Hospital Bandung.*

Keywords: *Prostate specific antigen, prostate specific antigen density, prostate cancer.*

ABSTRAK

Tujuan: *Di RSUP Hasan Sadikin Bandung biopsi prostat direkomendasikan untuk pasien dengan kadar prostate specific antigen (PSA) diatas 10 ng/mL atau PSA density (PSAD) diatas 0.15 jika PSA diantara 4-10 ng/mL. Namun ada faktor lain selain karsinoma prostat (PCa) yang dapat mempengaruhi nilai PSA, seperti perbedaan suku dan prostatitis. Oleh karena itu, cut-off point optimal untuk PSA masih diperdebatkan di level nasional. Penelitian ini bertujuan untuk menentukan PSA dan PSAD cut-off point untuk pasien curiga kanker prostat di RSUP Hasan Sadikin Bandung.* ***Bahan & cara:*** *Sebanyak 502 pasien menjalani biopsi prostat untuk curiga kanker prostat dari tahun 2010-2014. Cut-off point PSA dan PSAD dihasilkan dari kurva receiver operating characteristics (ROC).* ***Hasil:*** *Cut-off point PSA adalah 14.6 ng/mL (sensitivitas 81.4%, spesifisitas 29.8%). Cut-off point untuk PSAD adalah 0.23 (sensitivitas 81.4%, spesifisitas 34.8%). Positive predictive value (PPV) untuk cut-off point baru PSA dan PSAD adalah 41.1% dan 37.6%.* ***Simpulan:*** *Cut-off point PSA dan PSAD untuk pasien di Departemen kami adalah 14.6 ng/mL dan 0.23. Nilai ini relatif lebih tinggi dibandingkan dengan konsensus Indonesia. Perbedaan mungkin muncul berkaitan dengan tingginya tingkat infeksi saluran kemih pada pasien di RSUP Hasan Sadikin Bandung.*

Kata kunci: *Prostate specific antigen, prostate specific antigen density, kanker prostat.*

Correspondence: Daniel TM Simanjuntak; c/o: Department of Urology, Faculty of Medicine/Padjadjaran University, Hasan Sadikin General Hospital Bandung. Jl. Pasteur No. 38 Bandung. Phone: +62 22 2039141. Email: danieldzire@yahoo.com.

INTRODUCTION

Prostate cancer (PCa) is one of the most common malignancies among men. In Europe, incidence of prostate cancer is above colorectal cancer and lung cancer and was in first place in United States for male cancer morbidity and in second place for cancer mortality, next to lung cancer, in 2009.[1] Increasing mortality rates due to prostate cancer have been observed worldwide. According to the American Cancer Society, there is a difference in incidence of prostate cancer between races. The incidence is highest in Afro-American race, followed by European and lowest incidence

found in Asian people.[2] Therefore, it can be concluded that there was a significant differences in incidence of prostate cancer in different region in the world.

One of the tools for prostate cancer detection is PSA (prostate specific antigen).[3] PSA measurement in patients with serum PSA level above 4.0 ng/mL has a significance in detecting prostate cancer and a cut-off point for undergo prostate biopsy.[4] It has sensitivity of about 20.5%, and the specificity of PSA measurements is approximately 93.6% at this cut-off. If patients with PSA levels below 10 ng/mL were submitted to prostate biopsy, 20.5% would be diagnosed with prostate cancer and 60–80% should undergo unnecessary biopsy without detecting prostate cancer. Therefore, the best PSA level cut-off for prostate biopsy was still on debate.[5]

Benign prostatic hyperplasia, urethral or prostatic trauma, and prostatitis, as well as prostate cancer, can all be associated with elevated serum PSA levels. Ejaculation and digital rectal examination shave been reported to increase PSA levels but studies have shown the effects to be variable or insignificant. These non-malignant conditions which were associated with elevation of a serum PSA would decrease the accuracy of a serum PSA. To improve low sensitivity of PSA, age-adjusted PSA, PSA density (PSAD), PSA velocity (PSAV), or percentage of free PSA (% Free-PSA) has been introduced and used. In Hasan Sadikin Hospital Bandung, the parameter for the patient to undergo prostate biopsy was, if the PSA level > 10 ng/ml or PSAD > 0.15 for PSA level 4-10 ng/ml.[5]

In 2004, Thompson et al report that 12.5% of prostate cancer found in PSA level below 4 ng/ml and 15.9% of them had a Gleason score above 6.[6] In Asia, where the incidence of prostate cancer is low, the cut-off point for PSA and PSAD is higher to undergo prostate biopsy. In Indonesia, Rahardjo et al (2000) reported that cut-off point for PSA was 8 ng/ml and PSAD 0.20 for prostate cancer detection.[7] They report that as much as 148 unnecessary biopsy (33%) can be avoided with this cut-off point. In Hasan Sadikin hospital, research for this cut-off point has been done by Sugandi et al in 2003, and resulted in PSA level 14 ng/ml for cut-off point. But until today there is no national standard for PSA level cut-off point.[8]

From Indonesian Society of Urologic Oncology (ISUO) data in 2011, there were 971 prostate cancer patients. Diagnostic procedure used in these cases were primarily biopsy, in 563 cases (57.9%). In Hasan Sadikin Hospital Bandung, there were 318 cases of prostate cancer in 2004-2010 period.[9] These patients were referred to Hasan Sadikin hospital as tertiary hospital, most often has been put on foley catheter or in long standing LUTS. These factors increase the possibility of prostatitis and elevate PSA level finding, and eventually led to biopsy procedure.[10] As we know, transrectal prostate biopsy procedure carry many serious complications, as bleeding, infection and sepsis.[11-13] A study in United States reported that there is a significant increase in hospitalization because of prostate biopsy complications.[14] Therefore, to determine a cut-off point for PSA and PSAD is very crucial to avoid unnecessary biopsy.

OBJECTIVE

To determine PSA and PSA density cut-off point for patient suspected of prostate cancer in Hasan Sadikin Hospital.

MATERIAL & METHOD

This was an analytic retrospective study in the Department of Urology, Padjadjaran University/Hasan Sadikin General Hospital Bandung, Indonesia, between January 2010 and December 2014. This study included 502 patients who were hospitalized in Hasan Sadikin and submitted to a transrectal ultrasonography (TRUS) guided prostate biopsy. TRUS-guided prostate biopsy was performed in at least 8 cores or more of tissue targeting the peripheral zone at the apex, mid gland, and base on each side of the prostate. Other data collection including age, nodule in rectal toucher, prostate volume, PSA level and histo-pathological finding. Patients who rejected PSA or biopsy examination were excluded from the study. The research attained ethical approval from the institutional review board of Hasan Sadikin Hospital, Bandung.

Whitney U test was used to compare between two groups. Receiver operator characteristic (ROC) curve was used to assess the availability as a differential diagnostic tool and the correlation. Simple linear regression was performed to analyze a correlation between histopathological finding and other factors such as age, PSA and PSAD level, prostate volume, and rectal toucher finding. Statistical significance was set at $p < 0.05$. All statistical analyses were performed with SPSS

software version 20.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

In 2010-2014 period there were 502 patients with prostate disease. Range of age was 48-94 years with mean of age was 66.93 years. Patients with prostate cancer age ranged from 48-94 years, with mean of age was 66.98 years. Patients with benign prostatic hyperplasia age ranged from 50-85 years, with mean of age was 66.59 years. Mean prostatic volume was 54.7 cc. From 502 patiens, 402 had benign prostatic hyperplasia and the other 100 had prostate cancer.

Table 1. Patient characteristics.

Variable	Range	
Mean Age (years)	48-94	66.93
Mean PSA (ng/mL)	0.146-3000	57.20
Mean PSAD	0.0014-150	2.52
Mean Prostate Volume	7.49-298	54.7
Histopathological finding		
BPH	50-85 (year)	402
Prostate cancer	48-94 (year)	100
Bladder stone		62
Positive urine culture		272
n = 502		

Total positive urine culture was 272 patients (54%). Positive urine culture in benign prostatic hyperplasia found in 230 patients (57%) and in 42 patients of prostate cancer (42%). There were 62 cases of bladder stone (21%) with prostate abnormality, 21 of them (4%) had PSA score above 10 with histopathological findings benign prostatic hyperplasia.

There were 110 patients (22%) with PSA level < 4 ng/ml, 135 patients (27%) with PSA level 4-10 ng/ml, and 259 patients (51%) with PSA level > 10 ng/ml. In PSA > 10 ng/ml patients, we found 88 patients (17%) with prostate cancer, PSA level 4-10 ng/ml 6 patients (1.2%) and in PSA level < 1 ng/ml was 1 patient (0.19%). Range of PSA level in prostate cancer patients were 2.3-3000 ng/ml, while in benign prostatic hyperplasia patients 0.146–48 ng/mL.

To get the PSA cut-off point, we used Receiver Operating Characteristics (ROC) curve, the area under the curve (AUC) below 0.820 showed optimal sensitivity and specificity to detect prostate cancer. From this calculation, we found that the cut-off point of PSA level to undergo prostate biopsy was 14.6 ng/ml with sensitivity 81.4% and specificity 29.8%. Positive predictive value (PPV) for this cut-off point was 41.1% and negative predictive value (NPV) was 93.7%.

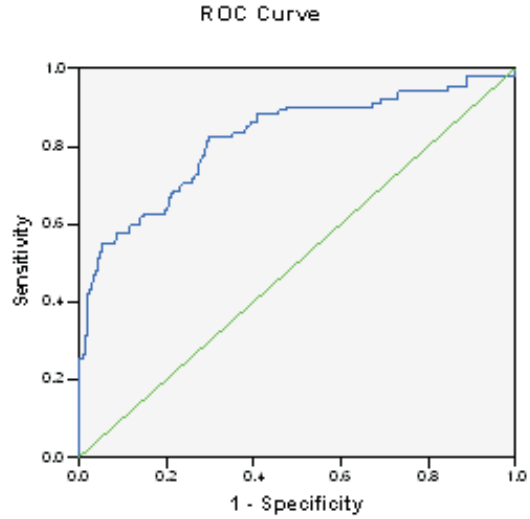

Figure 1. ROC PSA curve.

For PSAD cut-off point, the ROC curve showed that the AUC below 0.823, optimal sensitivity and specificity. From the AUC curve, the cut-off point for PSAD was 0.23 with sensitivity 81.4% and specificity 34.8%. Positive predictive value (PPV) for this cut-off point was37.6% and negative predictive value (NPV) was 93.2%.

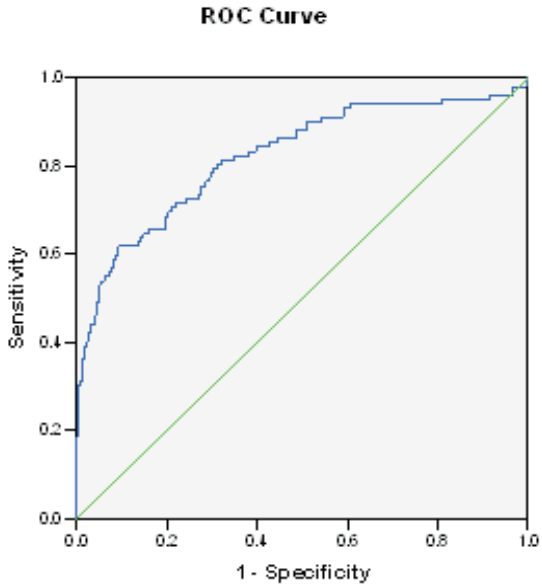

Figure 2. ROC PSAD curve.

Table 2. Cross-tabulation between PSA and histopathological finding.

Category	Histopathological finding		Total
	BPH	Prostate cancer	
PSA ≥ Cut-off	119	83	202
	58.9%	41.1%	100%
PSA < Cut-off	281	19	300
	93.7%	6.3%	100%
Total	400	102	502
	79.7%	20.3%	100%

Table 3. Cross-tabulation between PSAD and histopathological finding.

Category	Histopathological finding		Total
	BPH	Prostate cancer	
PSAD ≥ Cut-off	138	83	221
	62.4%	37.6%	100.0%
PSAD < Cut-off	262	19	281
	93.2%	6.8%	100.0%
Total	400	102	502
	79.7%	20.3%	100%

From cross-tabulation from the PSA and PSAD cut-off point we found data as shown in table 2 and table 3.

DISCUSSION

From the result of this study, it was found that PSA and PSAD cut-off in patients with prostate disease in Hasan Sadikin Hospital Bandung was higher than recommended cut-off to date. With PSA cut-off point 14.6 ng/ml and PSAD cut-off point 0.23, there were 202 cases that should undergo biopsy. With PSA cut-off point 10 ng/ml and PSAD cut-off point 0.15, there were 259 cases that underwent biopsy of the prostate. It means, that there were 57 patients (22%) that underwent unnecessary biopsy.

For PSA score 4-10 ng/ml, PSAD should be used to determine wether biopsy should be done or not. Recommended PSAD cut-off point to undergo biopsy was if the PSAD above 0.15. With > 0.15 cut-off point, 52 patients with PSA level 4-10 ng/ml underwent prostate biopsy. With > 0.23 cut-off point, only 12 patients should undergo prostate biopsy. It means that 40 patients (76%) could be avoided from unnecessary biopsy with new PSAD cut-off point.

Compared to previous study in Indonesia, there is a significant difference between result in Bandung and in Surabaya. Previous study in Jakarta (2000) resulted in cut-off point of 8 ng/ml and PSAD 0.20. A study in Surabaya conducted by Soebadi, et al in 2012 resulted in PSA cut-off point 6.95 ng/ml and PSAD cut-off point 0.7072.[15] This study result, compared to similar study in Bandung conducted by Sugandi, et al (2003) show us no much difference between the two studies. The difference of cut-off between these regions could be caused by the difference of ethnicity and incidence of UTI between the citizens of Bandung and Jakarta or Surabaya. This cut-off point, compared to internationally recommended cut-off point, was significantly higher. The American Urological Association (AUA) recommend PSA cut-off point 2.5 ng/ml.[16] AUA also recommend that the PSA score above also should be adapted with age, ethnicity, comorbidity, rectal toucher examination and previous biopsy history. The European Association of Urology (EAU) and Société Internationale d'Urologie (SIU) recommend that the cut-off point was 4 ng/ml to undergo biopsy. SIU recommends repeated PSA evaluation every 2 years for PSA above 3 ng/ml, every 2-4 years for PSA 1-

2.9 ng/ml and every 4-8 years for PSA 0-0.9 ng/ml.[17]

High PSA level can be caused by factors such as prostate infection, bladder stone, large prostate volume, advanced age and race. Among the factors that can affect the PSA level, infection can be significantly affect PSA level. In this study there were 272 patients (54%) with positive urine culture. Infection could lead to prostatitis and eventually increase the PSA level.[11,12,18]

This study had some limitations. First, the subject size was relatively small and the subject diversity was low due to the sourcing of the data from a single hospital. Thus, amulti-center study that includes patients with various characteristics will be required in the future. Second, referring to thestudy of Ellis et al, which showed that among patients who were not diagnosed with prostate cancer in the initial prostate biopsy, 20% were diagnosed with prostate cancer when subjected to a repeat prostate biopsy, there is a possibility that prostate cancer would be diagnosed in patients who were negative in the prostate needle biopsy that was conducted in this study if the prostate needle biopsy were repeated.

CONCLUSION

PSA and PSAD cut-off point for patients in our center was 14.6 ng/mL and 0.23 respectively. This value is relatively higher compared to the Indonesian consensus. The difference might occur due to high rate of urinary tract infection in patients attending Hasan Sadikin General Hospital Bandung.

REFERENCES

1. Boyle P, Ferlay J. Cancer incidence and mortality in Europe, 2004. Annals of oncology: Official Journal of the European Society for Medical Oncology. 2005; 16(3): 481-8.
2. American Cancer Society. Cancer facts and figures 2008. Atlanta: American Cancer Society; 2008.
3. Kim HW, Ko YH, Kang SH, Lee JG. Predictive factors for prostate cancer in biopsy of patients with prostate-specific antigen levels equal or to less than 4 ng/ml. Korean J Urol. 2011; 52: 166-71.
4. Reis LO, Zani EL, Alonso JC, Simoes FA, Rejowski RF, Ferreira U. Does the criterion for prostate biopsy indication impact its accuracy? A prospective population-based outpatient clinical setting study. Actas Urol ESP. 2011; 35: 10-14.
5. Catalona WJ, Smith DS, Ornstein DK. Prostate cancer detection in men with serum PSA concentrations of 2.6 to 4.0 ng/mL and benign prostate examination. Enhancement of specificity with free PSA measurements. JAMA. 1997; 277: 1452-5.
6. Thompson IM, Pauler DK, Goodman PJ. Prevalence of prostate cancer among men with a prostate-specific antigen level < 4.0 ng/mL. N. Engl. J. Med. 2004; 350: 2239-46.
7. Rahardjo D, Kamil S, Pakasi L. Rationale for using serum prostate-specific antigen (PSA) level and PSA density (PSAD) to detect prostatic malignancy in a country with low prostate cancer incidence. Gan to kagaku ryoho Cancer & chemotherapy. 2000; 27: 563-70.
8. Sugandi S, Putra M. PSA cut-off point for early prostate cancer detection in Hasan Sadikin Hospital Bandung. 2003; 6: 6-9.
9. Umbas R, Hardjowijoto S, Safriadi F, Mochtar C, Djatisoesanto W, Soedarso M, et al. Panduan penatalaksanaan kanker prostat 2011. IAUI. 2011; 1: 1-2.
10. Berger AP, Gozzi C, Steiner H, Frauscher F, Varkarakis J, Rogatsch H. Complication rate of transrectal ultrasound guided prostate biopsy: a comparison among 3 protocols with 6, 10 and 15 cores. The Journal of Urology. 2004; 171(4): 1478-81.
11. Tal R, Livne PM, Lask DM, Baniel J. Empirical management of urinary tract infections complicating transrectal ultrasound guided prostate biopsy. J Urol. 2003; 169: 1762.
12. Akduman B, Akduman D, Tokgöz H, Erol B, Türker T, Ayoğlu F. Long-term fluoroquinolone use before the prostate biopsy may increase the risk of sepsis caused by resistant microorganisms. Urology. 2011; 78(2): 250-5.
13. American Urological Association. Best Practice Policy Statement on Urologic Surgery Antimicrobial Prophylaxis; 2008. http://www.auanet.org/content/media/antimicroprop08.pdf. Accessed March 20, 2012.
14. Ghani KR, Dundas D, Patel U. Bleeding after transrectal ultrasonography-guided prostate biopsy: a study of 7-day morbidity after a six-, eight- and 12-core biopsy protocol. BJU Int. 2004; 94: 1014-20.
15. Soebadi DM, Shahab A, Djatisoesanto W, Hardjowijoto S, Soetojo S, Hakim L. Prostate-specific antigen and prostate-specific antigen density cutoff points among Indonesia population suspected for prostate cancer. Prostate Int. 2013; 1(1): 23-30.
16. Early detection of prostate cancer: AUA guideline. Linthicum (MD): American Urological Association Education and Research, Inc.; 2013. p.28
17. Schroder FH, Roobol MJ. PSA screening decisions-making aid. Rotterdam Netherlands. 2014; 2: 5.
18. Mottet N, Bastian PJ, Bellmunt J, van den Bergh RJ, Bolla M, van Casteren NJ, et al. Guidelines on prostate cancer. EAU. 2014; 6: 18.