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Diagnostic Value of Prostate Specific Antigen and Its Density in Iranian Men with Prostate Cancer

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Abstract

Background: The specific threshold for prostate-specific antigen and density (PSA, PSAD) to delineate which patients are at the highest risk has been controversial. The purpose of this study was to evaluate the diagnostic value of PSA and PSAD in Iranian patients with prostate cancer.

Methods: Three hundred men with the serum PSA greater than 4.0 ng/ml, abnormal digital rectal examination and/or suspicious transrectal ultrasound underwent transrectal ultrasound-guided prostate biopsies. PSAD was calculated by dividing the serum PSA in ng/ml by the volume of the entire prostate in cm^3. Correlation with Gleason grade of the tumor was also made. The patients were divided into three groups according to their PSA values. The receiver operator characteristic (ROC) curve was produced from the raw data on all patients.

Results: One hundred and two patients showed a cancer rate of 34%. The mean PSA and PSAD of the cancer group were significantly higher than those of the non-cancer group with better performance of PSAD as confirmed by ROC curve. In patients with PSA levels between 4 and 10 ng/ml, mean PSAD values in positive and negative biopsy groups showed a significant difference while mean PSA values between these biopsy groups revealed no significant difference. The PSAD cutoff of more than 0.1 had higher sensitivity than 0.15 at the expense of increasing the number of unnecessary biopsies. Among those the patients with PSA levels above 10ng/ml, both mean PSA and PSAD values of positive and negative biopsy groups had significant differences. The sensitivity of PSAD cutoff of 0.1 was not significantly higher than 0.15 while PSAD of 0.15 showed a higher specificity. PSAD >0.15 missed cancer in 18 out of 102 patients, nearly half of those with clinically significant mid and high grade cancers.

Conclusion: Overall, PSAD is a better diagnostic tool for the detection of prostate cancer than PSA, especially in patients with PSA between 4 and 10ng/ml. PSAD cutoff of 0.15 is not inclusive enough in patients with PSA levels between 4 and 10ng/ml and we propose PSAD of 0.1 as a better threshold for prostate biopsy in men with PSA at this range to detect clinically important cancers. Also, we recommend transrectal ultrasound guided biopsy in any patient with PSAD greater than 0.15 and PSA more than 4 ng/ml.

Keywords: Prostate-specific antigen; Density; Prostate cancer

Introduction

The triad of digital rectal examination (DRE), serum prostate-specific antigen (PSA), and transrectal ultrasound-guided prostate biopsy is commonly used in the early detection of prostate cancer. The combination of DRE and serum PSA is the most useful first-line test for prostate cancer screening.[1] Prostate ultrasound has been accepted as the appropriate tool for prostate biopsy guidance to detect the presence of prostate cancer if the DRE is abnormal or if the PSA level is not normal.[2] Although PSA is secreted only by epithelial cells in the prostate, it is not specific for prostate cancer. A variety of other pathologic conditions cause elevation of PSA which include benign prostatic hyperplasia (BPH), prostatitis, prostate biopsy, and instrumentation, such as cystoscopy and

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transurethral prostatic resection. So using PSA test alone as an objective criterion may lead to an increased number of unnecessary biopsies. This is more of a concern when interpreting intermediate values of PSA levels between 4 and 10 ng/ml. To identify patients with prostate cancer who have intermediately elevated PSA levels, the concept of PSA density (PSAD) has been described.[3] PSAD is the PSA value divided by the prostate volume. This concept emerged from the information that benign prostatic hyperplasia produces 0.3 ng/ml of PSA per gram of prostate tissue and prostate cancer produces 10 folds of this amount.[4] Thus, men with intermediately elevated PSA levels associated with a small prostate may have prostate cancer while the same value of PSA in a man with a large prostate may indicate BPH. It has been suggested that a PSAD greater than 0.15 is associated with 25% incidence of cancer, and a PSAD less than 0.10 is associated with 5% incidence of cancer.[5]

However, the specific cutoff for PSA and PSAD to delineate patients at high risk who should undergo biopsy has been controversial, especially when the PSA and PSAD values are influenced by race and environment. Many investigations have been done to determine the usefulness of PSA and PSAD in detection of prostate cancer; however, few studies have been done to evaluate their performance in diagnosing prostate cancer in Iranian men. We performed a retrospective analysis of 300 men to determine the diagnostic value of PSA and PSAD in Iranian men with prostate cancer.

Material and Methods

This retrospective single institution study was conducted in Shahid Faghihi Hospital affiliated to Shiraz university of Medical Sciences in Shiraz, southern Iran from March 2005 to October 2006. Three hundred patients underwent transrectal ultrasound-guided prostate biopsies for abnormal digital rectal examination, suspicious transrectal ultrasound, elevated PSA, or any combination of these abnormalities. All the patients were referred to our center by their urologists and gave their formal consent for the study. PSA was determined by an immunoradiometric assay, using monoclonal antibodies (Kavoshyar, Tehran, Iran) which could measure PSA levels within 0.01ng/ml. The most recent determination of the serum PSA level in any patient was used for this study. The normal range was defined as PSA values less than 4ng/ml.

Preparation before the ultrasound examination and biopsy included a self-administered cleansing enema and a broad-spectrum prophylactic antibiotic. Men who were treated with 5-alpha reductase inhibitors and received hormonal therapy were excluded from this study. Transrectal ultrasound was performed by an expert radiologist who was unaware of the PSA results, using a GE logique 500 scanner with 6.0 to 8.0 MHZ, high- resolution, near- field, end-firing transducer. Each gland was examined in both axial and sagittal projections. The prostate volume was calculated as follows:

Volume equals (length × width × height) × 0.523, with length being measured in the longitudinal view, and width and height in the axial view.

PSAD was calculated by dividing PSA by the prostate volume. Biopsies were obtained using an 18-gauge biopsy needle in a spring-driven biopsy gun. All biopsies were performed under ultrasound guidance via the transrectal route on an outpatient basis.

All the patients were subjected to fourteen systemic biopsies (from medial and far lateral aspect of the base, mid and apical areas of the right and left peripheral zones plus one biopsy form each transitional zone on either sides). Additional transrectal ultrasound-guided biopsies were performed at the suspected regions, either hypoechoic or heterogeneous. The core specimens were fixed in separate formalin containers and labeled accordingly to denote the different sites. An expert pathologist examined all the slides. Each biopsy specimen was categorized histologically (normal tissue, hyperplastic changes, acute or chronic inflammation, prostatic intraepithelial neoplasia, or cancer) and a further classification into Gleason grade of the tumor was done as follows: Low-grade cancer=Gleason score 2 to 4, mid-grade cancer=Gleason score 5 to 7 and high-grade cancer=Gleason score 8 to 10.

Mann Whitney test was used to compare the means. Receiver operator characteristic (ROC) curves, comparing PSA and PSAD, were generated. $p<0.05$ was considered as statistically significant.

Results

102 out of 300 patients evaluated had final cancer diagnosis in biopsy, yielding a detection rate of 34 percent. The age range was 42 to 80 with a mean of 67.25 and standard deviation of 9.40. The patients were

divided into three groups based on different levels of their serum PSA: serum PSA <4 ng/ml, serum PSA between 4 and 10 ng/ml and serum PSA >10 ng/mL.

25 men had PSA levels of less than 4.0 ng/ml, of whom 3 (12%) had a positive biopsy for prostate cancer. The mean PSA and PSAD for the positive or negative biopsies were 3.07 (SD: 0.73) versus 2.45 (SD: 1.07) (*p*: 0.497) and 0.16 (SD: 0.077) versus 0.08 (SD: 0.04) (*p*: 0.01), respectively. A total of 159 patients had PSA levels of 4.0-10.0 ng/ml, of whom, 29 (18.2%) men had a positive biopsy for prostate cancer. The mean PSA and PSAD for the positive or negative biopsies were 7 (SD: 1.89) versus 6.6 (SD: 1.87) (*p*: 0.256) and 1.45 (SD: 6.83) versus 0.15 (SD: 0.1) (*p* value: 0.02), respectively. Of 116 men with PSA levels greater than 10.0 ng/ml, 70 (60.3%) men had positive biopsy results. The mean values for PSA and PSAD for men with positive and negative biopsies were 38.7 (SD: 42.28) versus 17.8 (SD: 9.27) (*p*: 0.0001) and 1.14 (SD: 1.65) versus 0.26 (SD: 0.16) (*p*: 0.0002), respectively. In general, the mean values for PSA and PSAD for patients in this study with positive or negative biopsies were 28.34 (SD: 37.87) versus 8.77 (SD: 7.01) ng/ml (*p*: 0.0001) and 1.20 (SD: 3.87) versus 0.16 (SD: 0.13), (*p*: 0.0007), respectively.

For each group, the mean values of PSA and PSAD in patients with positive and negative biopsy results were calculated and P values were measured. The overall results are summarized in Table 1. A ROC curve was produced from the raw data on all the patients, for both PSA and PSAD (Figure1). The areas under both curves were calculated, being 78.1 percent for serum PSA and 81.3 percent for PSAD, with a statistically significant difference between both areas (*p*: 0.0002).

The overall results are summarized in Table 1. ROC curves were produced from the raw data on patients in the second (Figure 2) and third (Figure 3) groups. The curves demonstrate the performance of different PSAD ratios in these two PSA ranges. Various sensitivities and specificities are noted for different PSAD cutoff points according to different PSA ranges. Tables 2 and 3 show the effects of changing PSAD cutoff points on the test's sensitivity and specificity for patients with different PSA ranges.

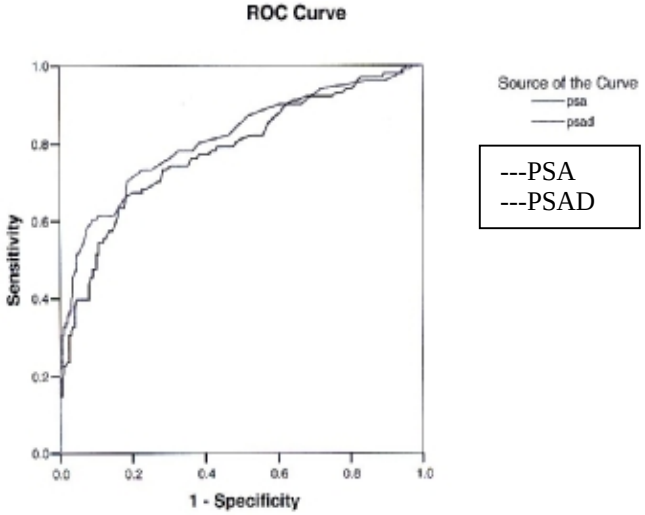

Fig 1: Comparing PAS and PSAD in detecting prostate cancer using ROC curve.

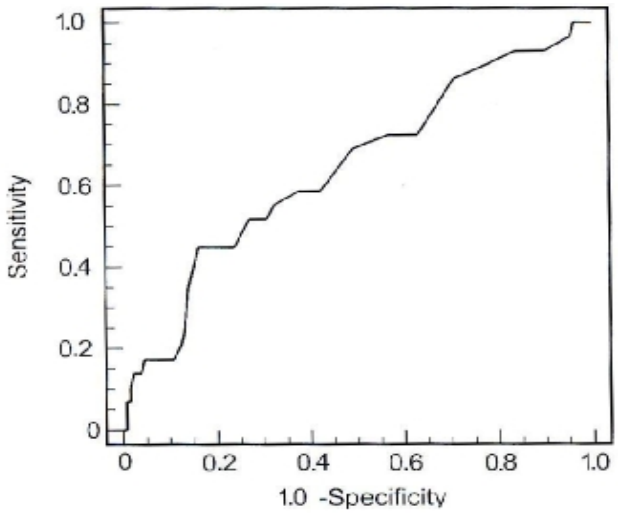

Fig 2: PSAD performance in patients with PSA levels between 4 and 10 ng/ml using ROC curve.

Table 1: Comparison of mean PSA and mean PSAD in patients with positive and negative prostate biopsies in 3 groups.

	PSA levels less than 4 ng/ml			PSA levels between 4 and 10 g/ml			PSA levels above 10ng/ml		
Biopsy	No. (%)	Mean PSA	Mean PSAD	No. (%)	Mean PSA	Mean PSAD	No. (%)	Mean PSA	Mean PSAD
Positive	3 (12)	3.07	0.16	29 (18.2)	7	1.45	70 (60.3)	38.7	1.14
Negative	22 (88)	2.45	0.08	130 (81.8)	6.6	0.15	46 (39.7)	17.8	0.26
Total	25	*p* : 0.492	*p*: 0.01	159	*p*: 0.256	*P*: 0.02	116	*p*: 0.0001	*p*: 0.0002

PSA: Prostate- specific antigen, PSAD: PSA density

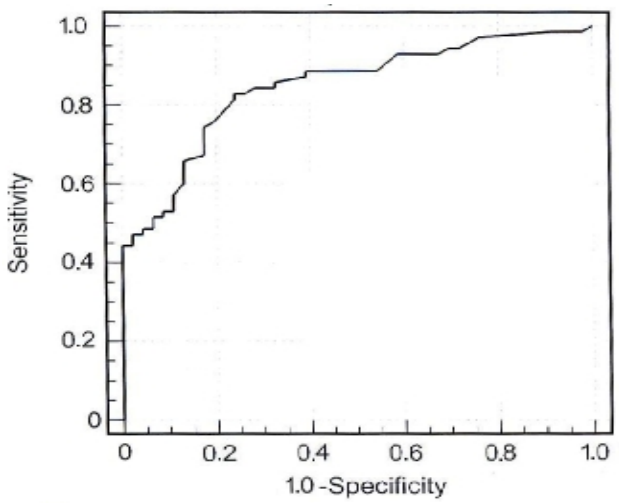

Fig 3: PSAD performance in patients with PSA levels above 10 ng/ml using ROC curve.

Regardless of the PSA or the PSAD values, 80% of the cancers diagnosed were in the mid-grade or high-grade range. Tables 4-6 compare PSA and PSAD levels in men with cancer and with Gleason grade correlation.

Discussion

Prostate cancer is a commonly diagnosed cancer in men, making this disease a significant public health

Table 4: Effect of changes in PSAD cutoff point in the number of patients with positive and saved unnecessary biopsies.

PSAD	Positive biopsies	Saved biopsies
0.21	76 (74.5%)	149 (75.3%)
0.15	84 (82.4%)	116 (58.6%)
0.1	97 (95.1%)	56 (28.3%)

PSAD: Prostate-specific antigen density

Table 5: Correlation between PSA levels and Gleason grade in men with cancer.

PSA	Men with cancer N0. (%)	Low grade	Mid-grade	High grade
<4	3/25 (12)	2	1	0
4-10	29/159 (18.2)	11	13	5
> 10	70/116 (60.3)	8	41	21
Total	102	21	55	26

PSA: Prostate- specific antigen

Table 6: Correlation between PSAD values and Gleason grade in men with cancer

PSAD	Men with cancer	Low grade	Mid grade	High grade
< 0.1	5/61	2	1	2
<0.15	18/134	8	6	4
< 0.21	25/175	10	10	5

PSAD: Prostate- specific antigen density

Table 2: Performance of different PSAD cutoff points in patients with serum PSA levels between 4 and 10 ng/ml.

Upper limit of PSAD cut-off point	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value	Negative predictive value
> 0.01	100.0 (87.9-100.0)	1.5 (0.2-5.5)	18.5	100.0
> 0.05	96.6 (82.2- 99.4)	4.6 (1.7-9.8)	18.6	85.7
> 0.1	72.4 (52.8-87.2)	36.9 (28.6-45.8)	20.04	85.7
> 0.15	55.2 (35.7-73.5)	67.7 (58.9-75.6)	27.6	87.1
> 0.21*	44.8 (26.5-64.3)	83.8 (76.4-89.7)	38.2	87.2
> 0.25	17.2 (5.9-35.8)	89.2 (82.6-94.0)	26.3	82.9

PSA: Prostate- specific antigen, PSAD: PSA density, CI: Confidence Interval

Table 3: Performance of different PSAD cutoff points in patients with serum PSA levels above 10 ng/ml.

Upper limit of PSAD cut-off point	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value	Negative predictive value
>= 0.06	100.0 (94.8-100.0)	0.0 (0.0- 7.8)	60.3	
> 0.1	98.6 (92.3-99.8)	8.7 (2.5-25.8)	62.2	80.0
> 0.15	94.3 (86.0-98.4)	30.4 (17.8-45.8)	67.3	77.8
> 0.21	88.6 (78.7-94.9)	50.0 (34.9-65.1)	72.9	74.2
> 0.25	84.3 (73.6-91.9)	67.4 (52.0-80.5)	79.7	73.8
> 0.30	82.9 (72.0-90.8)	76.1 (61.2-87.4)	84.1	74.5

PSA: Prostate- specific antigen, PSAD: PSA density, CI: Confidence Interval

issue. Serum prostate specific antigen is an important tool in screening and early detection of prostate cancer, and is considered one of the most important prognostic factors amongst patients with prostate cancer.[6] Racial differences in PSA levels have been found. Two studies performed to determine the reference values of serum PSA for Iranian men revealed that the PSA values in them were significantly lower than those for white and black Western men, and slightly lower than those for Japanese men.[7,8]

Attempts have been made to refine the use of PSA in detection strategies to decrease the number of unnecessary biopsies while minimizing the number of missed cancers. Since serum PSA levels can be increased by a number of processes besides prostate cancer, the concept of PSAD is described as a potentially better predictor of prostate cancer.[3] Although many studies have looked at the performance of PSA and PSAD in prostate cancer detection in afro-Caribbean and Caucasian populations,[9] few investigations have been done on Iranian population.

The patients in our study had a mean PSA level of 15.4 as compared with other studies[9] with a mean PSA level of 21.56 and 10.96 in Afro-Caribbeans and Caucasians, respectively. On the other hand, the mean PSAD for the studied group was 0.39 compared to 0.68 in Afro-Caribbean populations and 0.34 in Caucasians.[9] These possible differences may be accounted for by socioeconomic status, race, culture, health care access and differences in tumor biology; however, these issues need to be clarified in well-designed prospective studies.

159 men had PSA values between 4.0 and 10.0 ng/ml, of whom 29 (18.2%) had positive biopsies for prostate cancer. For this group as a whole, the mean PSA values of the positive and negative biopsy groups showed no significant difference. The mean PSAD was significantly different (*p*: 0.02) between the positive and negative biopsy groups. One hundred sixteen men had PSA values greater than 10 ng/ml. Both PSA and PSAD were effective in distinguishing men with positive or negative biopsies for prostate cancer in the entire group, being statistically significant.

By comparing the areas under the ROC curves which were produced from the raw data on all patients for both PSA and PSAD, it was found that PSAD was a better diagnostic tool for the detection of prostatic carcinoma. (*p*: 0.0002). Brawer *et al.* did not observe a benefit of PSAD over PSA in cancer detection.[10] This finding is contradictory to those of Benson *et al.*[5] In a current study by Gregorio *et al.*, it was also found that the combination of free PSA and PSAD could allow better discrimination between benign and malignant causes of increased PSA.[11]

Several series have compared PSAD cutoff values of 0.1 and 0.15 in prostate cancer detection. Bazinet *et al.* found that a ROC curve confirmed a PSAD of 0.15 as the best cutoff in patients with a negative DRE result, negative ultrasound result, and PSA levels between 4.1 and 10 ng/ml.[12] Catalona *et al.*, using similar group criteria (PSA 4.1-9.9 ng/ml, normal DRE and normal ultrasound result) found that half the tumors were missed by using a PSAD cutoff point of more than 0.15.[13]

Our analysis revealed that out of 102 patients 84 and 97 diagnosed with prostate cancer had PSAD greater than 0.15 and 0.1, respectively. We identified 18 out of 102 patients with cancer that would have been missed by using a PSAD cutoff of 0.15 in comparison to missing 5 patients with cancer in cutoff of 0.1.

In our series, the test results for prostate cancer detection in men with PSA levels between 4 and 10 ng/ml at PSAD cutoffs of 0.15 and 0.1 showed sensitivities of 55.2% vs. 72.4% and specificities of 67.7% vs. 36.9%, respectively. Calalona *et al.* observed sensitivities of 52% vs. 79% and specificities of 81% vs. 47% when comparing PSAD cutoffs of 0.15 and 0.1, respectively.[13] Using a PSAD cutoff of 0.15, Cookson *et al.* observed a sensitivity of 61% and a specificity of 22% in 44 patients with a normal DRE and PSA of 4 to 10 ng/ml.[14] However, this study and the previously mentioned ones failed to consider variations in ethnicity.[10]

Overall, at PSA values between 4 and 10 ng/ml, cutoff of 0.1 shows a better sensitivity than that of 0.15 at the expense of increasing the number of unnecessary biopsies and diminishing positive predictive value of the test. However, our data suggest that more than half of all men with cancer who have a PSAD less than 0.15 demonstrate mid to high grade cancers which are clinically significant.

In patients with serum PSA more than 10 ng/ml, applying PSAD of 0.15 will increase the specificity and positive predictive value of the test without significantly compromising the test sensitivity. In addition, it seems reasonable that all men with PSA greater than 4 ng/ml should have an ultrasound-guided biopsy if their PSAD is greater than 0.15.

This work is the first study which deals with diagnostic value of PSA and PSAD for detection of prostate cancer in Iran. Furthermore, few articles have analyzed and compared the accuracy of PSA and

PSAD in the range of PSA between 4-10ng/ml through the ROC curve,[11,15] as was performed in this work. Therefore, we believe PSAD of 0.15 is not an ideal cutoff point in patients with PSA between 4 and 10 ng/ml and that of 0.1 or greater and above should be used as an indicator for biopsy consideration in this PSA range.

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Conflict of interest: None declared.

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