Value of Prostate-Specific Antigen and Prostate-Specific Antigen Density in Detection of Prostate Cancer in an Iranian Population of Men

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Introduction: The objective of this study was to evaluate the value of serum prostate-specific antigen (PSA) and prostate-specific antigen density (PSAD) in the diagnosis of prostate cancer.

Materials and Methods: A total of 330 consecutive patients suspected of having prostate cancer due to either abnormal digital rectal examination or elevated serum PSA levels underwent transrectal ultrasonography-guided sextant biopsy of the prostate. The PSA and PSAD values were assessed based on the biopsy results.

Results: One hundred and twenty-one patients (36.7%) had prostate cancer. In this group, the mean PSA was 31.60 $\pm$ 30.85 ng/mL (range, 1.9 ng/mL to 166.0 ng/mL) and the mean PSAD was 0.83 $\pm$ 1.01 (range, 0.04 ng/mL/cm^3 to 6.38 ng/mL/cm^3). In those without prostate cancer the mean PSA and PSAD levels were 13.80 $\pm$ 18.72 ng/mL (range, 0.4 ng/mL to 130.0 ng/mL; $P < .001$) and 0.24 $\pm$ 0.32 (range of 0.01 ng/mL/cm^3 to 2.29 ng/mL/cm^3; $P < .001$). The receiver operating characteristic curve analysis revealed that the discriminating power of serum PSA for detecting prostate cancer, as estimated by the area under the curve, was 0.74 while that for PSAD was 0.81 ($P < .001$). For the PSA range of 3.5 ng/mL to 41 ng/mL (gray zone) the areas under the curve was 0.68 for PSA, while it was 0.78 for PSAD ($P < .001$).

Conclusion: The use of PSAD instead of PSA in the diagnosis of prostatic cancer improves the diagnostic accuracy.

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INTRODUCTION

Prostate cancer is one of the most common malignancies among men. Increasing mortality rates due to prostate cancer have been observed worldwide.[1,2] This disease usually progresses imperceptibly; for this reason, screening programs aiming at early detection have been developed.[3,4] Serum prostate-specific antigen (PSA) test is today among the best screening tools available in medicine, as it is recognized as the best marker for early detection of prostate cancer.[5,6] However the lack of specificity is an important limitation of PSA test.[7,8] Increased PSA concentrations are found not only in patients with prostate cancer, but also in patients with benign prostatic diseases.[1]

Several methods have been proposed to improve the specificity of PSA test, including measurement

of PSA density (PSAD), transitional zone PSA density, age-specific PSA, PSA velocity, free-total PSA ratio, and PSA isoforms.[8-13] In the early 1990s, Benston and colleagues introduced the PSAD to correct the PSA levels for prostate volumes, on the basis of the fact that prostate cancer releases more PSA per unit of volume in to the circulation than benign prostate hypertrophy (BPH).[14] Thus, it is suspected that the PSAD, as a quotient of total PSA and prostate volume, is higher in patients with prostate cancer than in patients with BPH.[1,14,15]

This study was designed to evaluate the diagnostic value of PSAD for the detection of prostate cancer. Our goal was to determine whether PSAD was a more accurate predictor of prostate cancer than PSA. Since there are no studies describing the accuracy of PSA and PSAD in the Iranian population, the aim of the present study was also to evaluate the utility of PSA and PSAD for discrimination between benign and malignant prostate disease in Iranian men.

MATERIALS AND METHODS

From August 2005 to April 2006, a total of 330 consecutive men were referred to ultrasonography department of Hasheminejad Hospital, as part of investigations to rule out prostate cancer due to either abnormal findings on digital rectal examination or elevated PSA levels. The objectives and methods of the study were explained to all of these men and written informed consent was obtained for participation in the study. The protocol for the research project was approved by the Ethics Committee of the Iran University of Medical Sciences, which conforms to the provisions of the Declaration of Helsinki (as revised in Edinburgh, 2000).

Prior to ultrasonography, blood was collected for serum PSA assay. The assay was performed using the enzyme immunoassay method (DRG instruments GmbH, Marburg, Germany). In all cases, transrectal ultrasonography was performed to monitor prostate echo texture and to calculate prostate volume using a Technus MP machine (Esaote, Genoa, Italy) with an endocavitary multifrequency 3- to 9-MHz transducer (model

EC123). Volume of prostate was calculated using the prolate ellipse formula and the three main diameters of the gland, in which the volume equals $0.52 \times (L \times W \times H)$, where L is the maximum length obtained from the longitudinal sonography, W is the maximum width obtained from the transaxial view and H is the maximum height obtained transaxially. The PSAD was calculated as PSA (ng/mL) divided by prostate volume (mL).

Transrectal biopsies of the prostate were taken by an experienced radiologist with a 18-gauge automatic Tru-Cut biopsy needle (TSK, Tokyo, Japan) under transrectal ultrasonography guidance. Our 12-core-based biopsy strategy was as follows: 2 specimens were obtained from the base of the prostate gland in each side and 2 from the apex of the gland in each side. The middle of the gland was divided into upper-mid and lower-mid sections in each side and 4 biopsies were performed from each section, 2 from more medial and 2 from more lateral areas. If any suspicious lesion was detected in the peripheral or central zone, additional biopsies of that area were also performed. In all of the patients with a negative pathology results for prostate cancer who had a PSA level higher than 10 ng/mL, systematic biopsy was repeated and the final results were considered in the study. Pathologic evaluation of the biopsy specimens were performed by one experienced pathologist.

Statistical Analyses

The statistical analyses of the collected data were performed by the SPSS software (Statistical Package for the Social Sciences, version 11.0, SPSS Inc, Chicago, Illinois, USA). The values of continuous variables were demonstrated as mean ± standard deviation. Comparisons of variables (age, prostate volume, PSA, and PSAD) between the patients with and without prostate cancer were done with the t test. For evaluation of the accuracy of PSA and PSAD in detection of cancer cases, we used the receiver-operating characteristics (ROC) curve analysis and the areas under the curve (AUC) for these two curves were compared. P values less than .05 were considered significant.

RESULTS

A total of 330 patients with a mean age of 67.6 ± 9.8 years (range, 43 to 90 years) were studied. The mean serum PSA level was 20.40 ± 25.33 ng/mL (range, 0.4 ng/mL to 166.0 ng/ml) and the mean PSAD was 0.46 ± 0.72 ng/mL/cm³ (range, 0.01 ng/mL/cm³ to 6.38 ng/mL/cm³). The mean volume of the prostate was 55.0 ± 28.4 mL (range, 12 mL to 220 mL). Prostate cancer was diagnosed in 121 patients (36.7%) and benign lesions comprising BPH with or without prostatitis, in 209 (63.3%). Among patients without prostate cancer, the most common pathology was chronic prostatitis (79 of 209; 37.8%). Patients with prostate cancer had a significantly smaller prostate, while they had higher PSA and PSAD levels compared to those without cancer. Data on age, prostate volume, PSA, and PSAD of patients with and without prostate cancer are shown in Table 1.

In the patients without prostate cancer, the maximum serum PSA level was 130 ng/mL, and the PSA was equal or more than 40 ng/mL in 12 patients (5.3%). Among 118 patients who had a prostate volume equal to or less than 40 mL, 61 (51.7%) had cancer, and among 212 patients who had a prostate volume greater than 40 mL, 60 (28.3%) had cancer; the sensitivity and specificity for diagnosis of cancer based on the prostate volume cutoff point of 40 mL were 50.4% and 72.7%, respectively.

The ROC curve analysis was performed to depict diagnostic accuracy of PSA and PSAD for diagnosis of prostate cancer (Figure 1). The discriminating power of serum PSA for detecting prostate cancer, as estimated by the AUC, was 0.74 (95% confidence interval [CI], 0.68 to 0.80; $P < .001$), while that was 0.81 (95% CI, 0.76 to 0.86; $P < .001$) for PSAD. Comparison between the ROC curves of PSA and PSAD for the detection of prostate cancer showed that the use
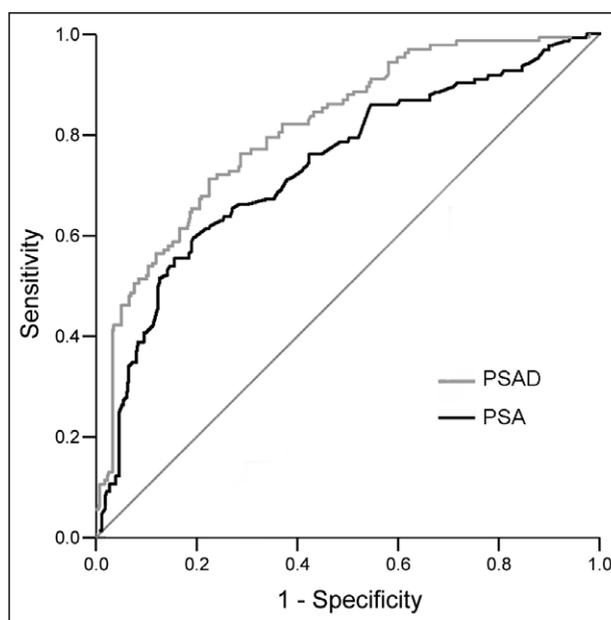

Figure 1. The receiver operating characteristics curve analyses for depicting the accuracy of prostate-specific antigen (PSA) and prostate-specific antigen density (PSAD) for diagnosis of prostate cancer.

of PSAD improves the AUC up to 7% ($P < .001$). According to these two ROC curves, the diagnostic indexes of the PSA and PSAD in different cutoff points are demonstrated in Table 2; in the similar sensitivities, the specificity of the PSAD is better than that of PSA. A cutoff point of 0.11 ng/mL/cm³ for PSAD had a 97.5% sensitivity and a 34% specificity for detecting prostate cancer.

Concerning the range of 4 ng/mL to 10 ng/mL for PSA level that is traditionally accepted as the gray zone, the PSA level of 4 ng/mL had a sensitivity of 93.4% and a specificity of 15.3% and the PSA level of 10 ng/mL has a sensitivity of 72% and a specificity of 59% for detection of prostate cancer. The ROC curve analysis was performed for patients with serum PSA levels of 4 ng/mL to 10 ng/mL (Figure 2). The discriminating power of serum PSA for

Table 1. Mean Age, Prostate Volume, and Prostate-Specific Antigen (PSA) Parameters in patients With and Without Prostate Cancer

Parameter	Participants		P
	With Prostate Cancer	Without Prostate Cancer	
Age, y	68.1 ± 10.7 (43 to 90)	67.3 ± 9.3 (45 to 90)	.47
Prostate volume, cm³	43.5 ± 17.8 (15 to 92)	61.7 ± 31.1 (12 to 220)	< .001
PSA, ng/mL	31.60 ± 30.85 (1.9 to 166)	13.80 ± 18.72 (0.4 to 130.0)	< .001
PSA Density, ng/mL/cm³	0.83 ± 1.01 (0.04 to 6.38)	0.24 ± 0.32 (0.01 to 2.29)	< .001

Table 2. Diagnostic Indexes of Prostate-Specific Antigen and Prostate-Specific Antigen Density for Differentiating Prostate Cancer*

Cutoff Points	Sensitivity	Specificity	PPV	NPV	PLR	NLR
PSA, ng/mL						
1.7	100	2.4	33.0	100	1.0	...
3.0	97.5	9.6	38.4	87.0	1.1	1.8
6.0	89.3	29.2	36.4	60.6	1.0	0.9
8.0	79.3	47.8	46.8	80.0	1.5	2.3
10.0	71.1	61.7	51.8	78.7	1.9	2.1
14.0	62.0	77.5	61.5	77.9	2.6	2.0
25.0	42.1	89.0	68.9	72.7	3.8	1.5
40.0	27.3	94.7	75.0	69.2	5.2	1.3
130.0	1.7	100	100	63.7	…	1.0
PSAD, ng/mL/cm^3						
0.04	100	2.4	37.2	100	1.0	…
0.11	97.5	34.0	46.1	96.0	1.5	13.7
0.14	89.3	45.9	48.9	88.1	1.7	4.3
0.21	79.3	65.1	56.8	84.5	2.3	3.1
0.27	71.1	76.6	63.7	82.1	3.0	2.6
0.33	63.6	81.3	66.4	79.4	3.4	2.2
0.60	43.0	94.7	82.5	74.2	8.2	1.7
1.00	28.9	96.7	83.3	70.1	8.6	1.4
2.30	5.7	100	100	64.7	…	1.0

*Values in columns 2 to 7 are percents. PPV indicates positive predictive value; NPV, negative predictive value; PLR, positive likelihood ratio; and NLR, negative likelihood ratio.

detecting prostate cancer in this range was 0.61 (95% CI, 0.48 to 0.73; P = .08), while that of PSAD was 0.76 (95% CI, 0.68 to 0.85; $P <$ .001). The difference between these two AUCs was significant (P = .03)

A PSA level of 3.5 ng/mL with a sensitivity of 95% and a specificity of 12% was considered as the lower cutoff point and a PSA level of 41 ng/mL with a specificity of 95% and a sensitivity of 26%, as the upper cutoff point of our gray zone.
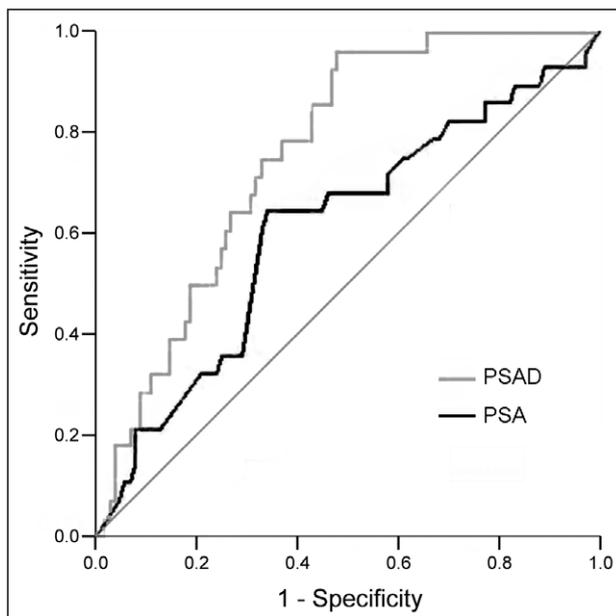

Figure 2. The receiver operating characteristics curve analyses for depicting the accuracy of prostate-specific antigen (PSA) and prostate-specific antigen density (PSAD) for diagnosis of prostate cancer in patients with a PSA level between 4 ng/mL and 10 ng/mL.
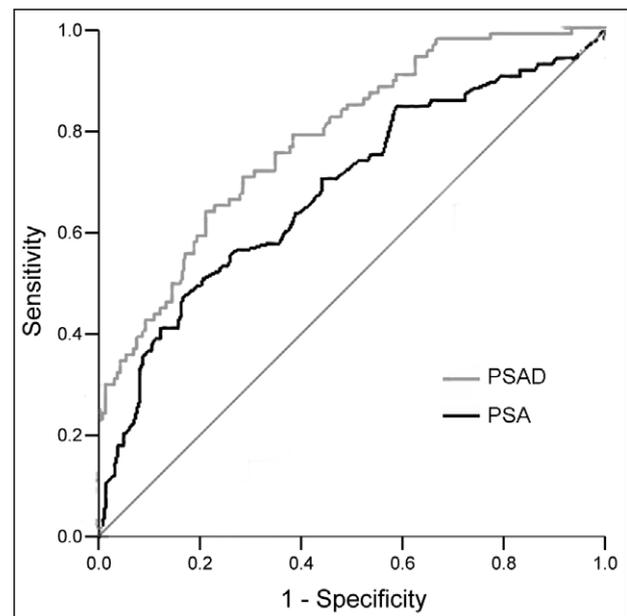

Figure 3. The receiver operating characteristics curve analyses for depicting the accuracy of prostate-specific antigen (PSA) and prostate-specific antigen density (PSAD) for diagnosis of prostate cancer in patients with a PSA level between 3.5 ng/mL and 41 ng/mL.

Table 3. Frequency of Prostate Cancer Cases Detected With Different Ranges of Prostate-Specific Antigen (PSA)*

PSA Range	Total Number	Prostate Cancer
<4	36	7 (19.4)
≥ 2 and < 4	29	6 (20.7)
≥ 4 and < 10	121	26 (21.5)
≥ 10	173	88 (50.9)
≥ 10 and < 20	78	23 (29.5)
≥ 20	95	65 (68.4)
≥ 2 and < 10	150	32 (21.3)
≥ 2 and < 20	228	55 (24.1)

*Values in parentheses are percents.

The ROC curve analysis for this range (Figure 3) showed that the discriminating power of serum PSA for detecting prostate cancer was 0.68 (95% CI, 0.61 to 0.75; $P < .001$), while that of the PSAD was 0.78 (95% CI, 0.72 to 0.84; $P < .001$). The difference between these two AUCs was significant ($P < .001$).

Different ranges of serum PSA that are mostly indicated in the literature were considered in the analyses. The frequency of cancer cases detected in different ranges of serum PSA is shown in Table 3. It shows that most of the cancers were detected with the PSA levels equal or greater than 20 ng/mL, and the least of the cancers were detected with the PSA levels less than 4 ng/mL.

DISCUSSION

In our study, statistical analyses showed that there was a significant difference in serum PSA and PSAD levels between the patients with and without prostate cancer. This finding is compatible with previous reports.[3,16] A serum PSA threshold of 4 ng/mL is usually an indication for prostate biopsy, and PSA levels between 4 ng/mL and 10 ng/mL, which is considered as gray zone, are shown to have a low sensitivity, but values above 10 ng/mL have a high sensitivity for prostate cancer. The sensitivity even reaches 100% if we consider values higher than 15 ng/mL.[11,17] In our study, the lower cutoff point of 4 ng/mL for PSA had a sensitivity of 93.4% and a specificity of 15.3%. We had 7 patients (2.1%) diagnosed with prostate cancer who had PSA levels below 4 ng/mL. This means that if we do not continue following up patients with PSA levels less than 4 ng/mL, we will miss some patients with prostate cancer. In addition, we

had 85 patients (25.7%) with PSA levels equal or greater than 10 ng/mL and 12 (5.3%) with PSA levels equal or greater than 40 ng/mL who did not have prostate cancer. The highest recorded level of PSA in patients with benign disease was 130 ng/mL.

The ROC curve analysis of the traditional gray zone showed that the AUC for PSA was 0.61 ($P = .08$). In this range, the PSAD had a larger AUC (0.76; $P < .001$). The ROC curve analysis of a gray zone of 3.5 ng/mL to 41 ng/mL showed that the AUC for PSA is 0.68 ($P < .001$) that is better than the gray zone of 4 ng/mL to 10 ng/mL. In this range also, the PSAD provided a better accuracy ($P < .001$) for diagnosis of prostate cancer. Considering the above results, the gray zone of 3.5 ng/mL to 41 ng/mL is better suited for our population than the gray zone of 4 ng/mL to 10 ng/mL. Our great dilemma remained in the serum PSA range of 3.5 ng/mL to 41 ng/mL, in which a large portion of our population (79.1%) had both benign and malignant lesions. The ROC curve analysis showed that also in this range, the use of PSAD improves the accuracy up to 10%, which is considerable in practice.

In a study on Arab men,[11] Sheikh and colleagues reported benign disease with the PSA levels up to 50 ng/mL. Our study and the others from Asian countries[18,19] show that BPH with prostatitis is a common cause of PSA elevation greater than 10 ng/mL that is in contrary to the reports from western countries,[17] where prostate cancer is the most common cause of PSA levels greater than 10 ng/mL. In order to eliminate the effect of other diseases such as BPH, Benston and colleagues introduced PSAD as a useful tool to increase specificity in the detection of prostate cancer,[14] and many studies have supported this indicator ever since; however, some did not confirm this advantage and reported that PSAD could not surpass PSA.[20,21] Table 2 shows that in our study, in all the given sensitivities, the specificity of PSAD is more than that of PSA. For instance, a PSAD threshold of 0.11 ng/mL/cm³ has a 97.5% sensitivity and a 34% specificity for detecting prostate cancer. The ROC curve analysis to depict diagnostic accuracy of PSA and PSAD in prostate

cancer showed that the AUC for PSAD is 7% larger than that of PSA, which means PSAD is more accurate than PSA in detecting prostate cancer.

In a study on 1809 patients,[1] Stephan and associates reported a significant difference in age between the patients with prostate cancer and the patients with BPH; however, we did not find any significant difference in age between the patients with and without prostate cancer, which is compatible with the study of Sheikh and coworkers.[11] We also found out that there was a significant difference in the volume of the prostate between the patients with and without prostate cancer; it means that the patients with prostate cancer have smaller prostates in comparison with patients without prostate cancer.[1]

CONCLUSION

We conclude that serum PSA per se does not have sufficient sensitivity and specificity to be useful in the routine evaluation of patients with prostate disease, and it is not accurate enough to include or exclude patients with prostate cancer. The use of PSAD, however, increases the accuracy and improves the sensitivity and specificity for detection of cancer.

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CONFLICT OF INTEREST

None declared.

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