ORIGINAL ARTICLE

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Contribution of prostate-specific antigen density in the prediction of prostate cancer: Does prostate volume matter?

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ABSTRACT

Aims: We aimed to evaluate whether there is a specific subgroup of patients who benefit most from PSAD screening according to their prostate volume.

Methods: Transrectal ultrasound guided prostate biopsy performed patients were stratified in five groups according to their prostate size. PSAD values were compared between groups, and the diagnostic accuracy of PSAD was evaluated for different prostate volumes.

Results: Of 326 patients 98 (30.0%) had pCa. While total PSA and PSAD between pCa(+) and (-) patients were significantly higher in group 1,2 and 3, the differences was not significant in group 4 and 5. The highest AUC value was achieved for group 3 and the lowest for group 5. The optimal cutoff values were different between groups.

Conclusions: Demonstrating the greatest diagnostic accuracy of PSAD in prostates ≥60 and <80 cc makes an invaluable contribution to the current literature and would be a reference point for further studies.

Key words: *Prostate-spesific antigen, PSA density, prostate size, prostate cancer, screening.*

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Introduction

Prostate cancer (pCa) is one of the most common types of cancer in the western countries. After the emergence of Prostate Specific Antigen (PSA) as a marker of the disease nearly 20 years ago, a great effort came through in the early detection and treatment of pCa (1). However the use of PSA in pCa detection is limited due to low specificity of the marker and inability to differentiate indolent cancer from life-threatening disease (1,2). For this reason, a multitude of studies have been conducted to improve the performance of PSA as well as identifying additional biomarkers. As being one of them, many have advocated normalizing PSA by the volume of prostate gland, yielding a PSA density (PSAD) (3,4).

In this study, we retrospectively reviewed our database of prostate biopsies, and evaluated the contribution of PSAD in prostate cancer detection according to prostate size. Moreover, we sought out whether or not is there a specific subgroup of patients benefit mostly from PSAD measurements according to their prostate sizes.

Methods

Between January 2013 and March2017, a total of 394 patients underwent transrectal ultrasound guided (TRUS) prostate biopsy (bx) due to high serum total PSA levels or abnormal digital rectal examination (DRE). The patients with incomplete medical records were excluded from the study. The patients who had serum total PSA <4 ng/mL and ≥20 ng/mL were also excluded. Finally the medical records of 326 patients were retrospectively evaluated. All patients were provided written consent. TRUS prostate-bx was performed using an 18-G needle with a minimum 12-core firing. PSAD was calculated as total PSA divided by total prostate volume (5).

The patients were stratified in five groups according to their prostate size as follows; group 1: prostate<40 cc, group 2: prostate ≥40 and <60 cc, group 3: prostate ≥60 and <80 cc, group 4: prostate ≥80 and <120 cc, and finally group 5: prostate ≥120 cc. Patient age, prostate volume, total PSA, PSAD and TRUS-bx results were recorded for statistical analysis.

Statistical analyses were performed using the Statistical Package for Social Sciences software program (SPSS for Windows Ver 22.0). Mann-Whitney U test was used to compare variables between groups. Receiver operating characteristics curves (ROC) analyses were performed and area under curves calculated to evaluate the diagnostic accuracy of PSAD in pCa detection. Sensitivities, specificities, (+) and (-) likelihood ratios for optimal cutoff values were also defined for specific subgroups.

Results

Among 326 patients recruited to the study, 98 (30.0%) patients had pCa. Mean patient age, total PSA, PSAD and prostate volume for the entire groups were 64.5±8.3 cc, 8.1±3.6 ng/mL, 0.16±0.13 ng/ml/cc, and 66.3±39.2 cc, respectively (Table 1). Patient characteristics, PSA kinetics and statistical comparisons for pCa (+) and (-) patients according to prostate size were summarized in Table 2. While total PSA and PSAD between pCa(+) and (-) patients were significantly higher in group 1,2 and 3, the differences was not significant in group 4 and 5. The predictive value of PSAD was analyzed using ROC curves for each group (fig 1), and these invaluable results were confirmed. The areas under the curves with their 95% confidence intervals, best cutoff values, sensitivity and specificity values for these optimal cutoff levels, and likelihood ratios for each group was shown in table 3. The AUC results showed initially increasing and subsequently decreasing diagnostic value with increasing prostate volume. The highest AUC value was achi-

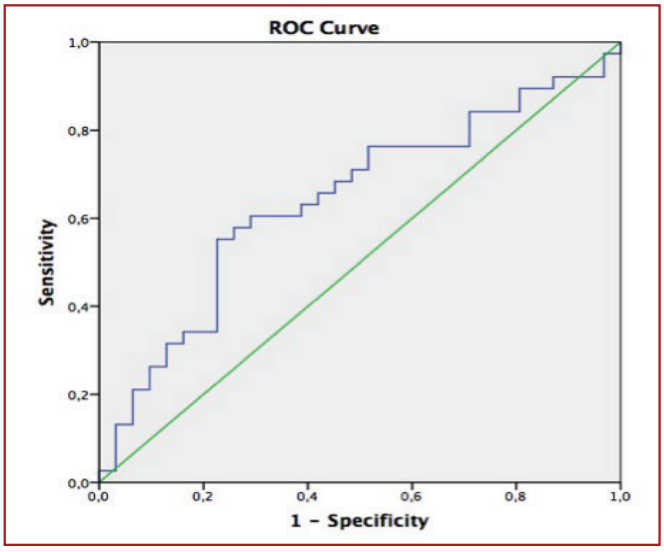


Figure 1. a. Receiver operating characteristic curve analysis of PSAD for prostate<40 cc, .

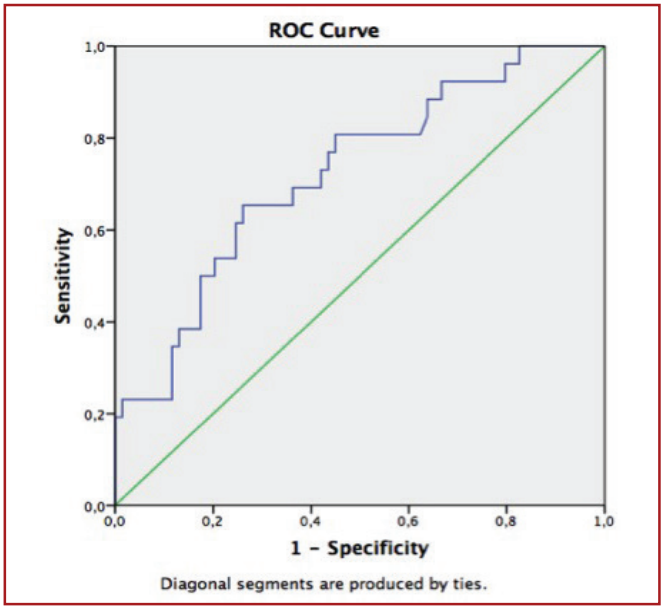


Figure 1. b. Prostate ≥40 and <60 cc,

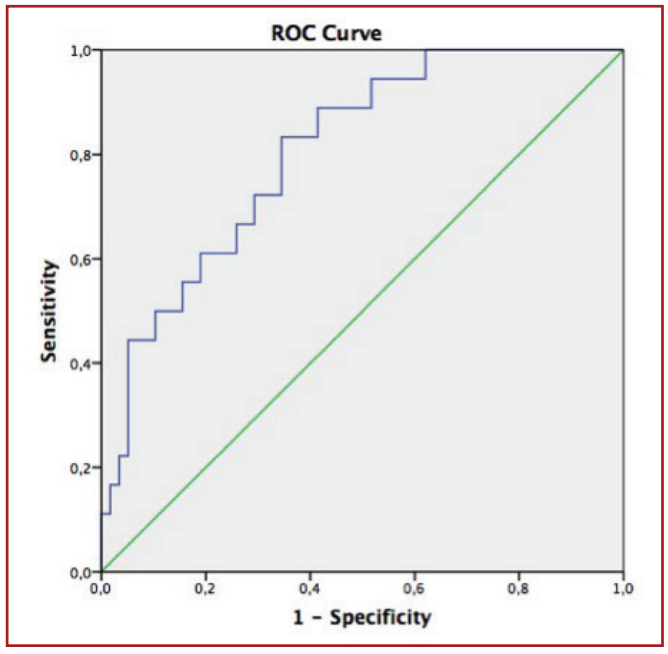


Figure 1. c. Prostate ≥60 and <80 cc,

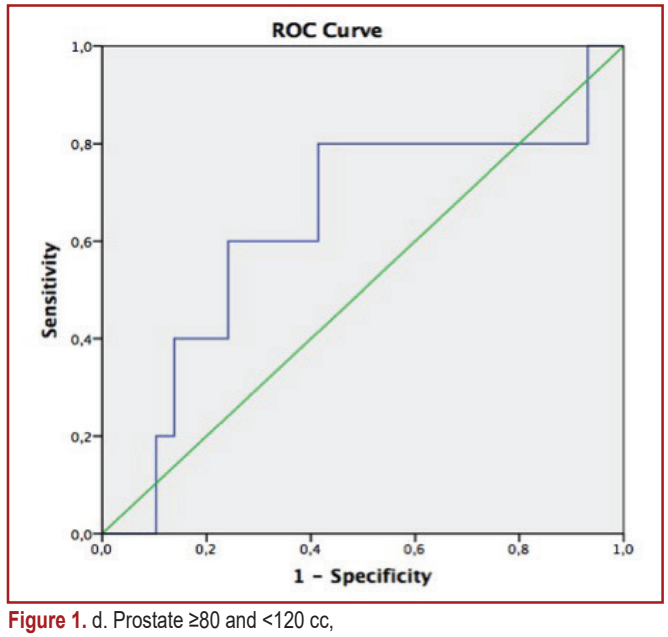


Figure 1. d. Prostate ≥80 and <120 cc,

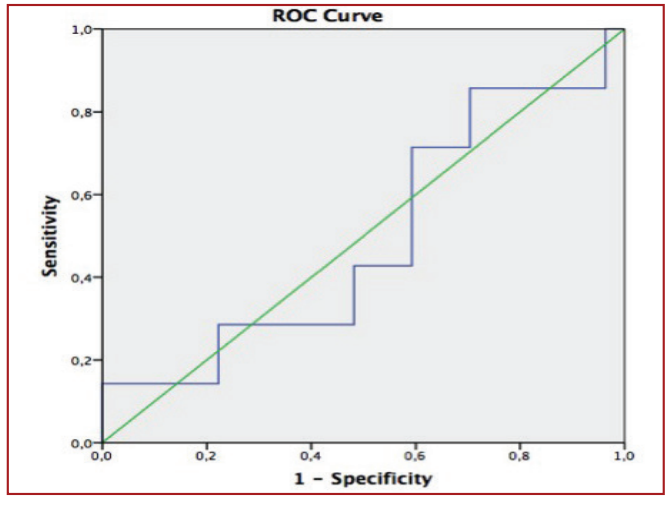


Figure 1. e. Prostate ≥120 cc.

Table 1. Patient charecteristics and PSA kinetics for the entire population according to prostate size

	Entire population (n:326)	Group 1: Prostate<40cc (n:74)	Group 2: Prostate ≥40 and <60 cc (n:101)	Group 3: Prostate ≥60 and <80 cc (n:80)	Group 4: Prostate ≥80 and <120 cc (n:36)	Group 5: Prostate ≥120cc (n:35)
Age (years)(Mean±SD)	64.5±8.3	63.3±10.2	63.3±7.4	64.8±8.4	68.2±6.6	65.6±6.5
PSA (ng/ml) (Mean±SD)	8.1±3.6	7.8±3.7	7.4±3.1	8.5±3.6	8.1±3.6	9.5±4.0
Free PSA (ng/ml) (Mean±SD)	1.6±1.0	1.1±0.6	1.5±1.3	1.8±0.7	1.8±0.7	2.3±1.1
PSAD (ng/ml/cc) (Mean±SD)	0.16±0.13	0.29±0.22	0.15±0.06	0.12±0.05	0.86±0.04	0.06±0.03
Prostate volüme (cc) (Mean±SD)	66.3±39.2	29.6±6.7	49.1±5.8	68.5±5.8	96.7±12.0	154.4±37.0

PSA: Prostate Spesific Antigene, , PSAD: PSA density.

Table 2. Patient charecteristics, PSA kinetics and statistical comparisons for pCa (+) and (–) patients according to prostate size.

	Group 1: Prostate<40cc (n:74)			Group 2: Prostate ≥40 and <60 cc (n:101)			Group 3: Prostate ≥60 and <80 cc (n:80)			Group 4: Prostate ≥80 and <120 cc (n:36)			Group 5: Prostate ≥120cc (n:35)		
	pCa+ (n:39)	pCa- (n:35)	p value	pCa+ (n:28)	pCa- (n:73)	p value	pCa+ (n:19)	pCa- (n:61)	p value	pCa+ (n:5)	pCa- (n:31)	p value	pCa+ (n:7)	pCa- (n:28)	p value
Age (years) (Mean±SD)	63.9±9.7	62.5±10.8	p≥0.05	66.9±8.1	62.0±6.7	p<0.05	70.5±9.7	62.9±7.1	p<0.05	73.0±9.4	67.4±5.9	p≥0.05	70.1±7.5	64.5±5.8	p≥0.05
PSA (ng/ml) (Mean±SD)	8.8±4.3	6.7±2.6	p<0.05	9.4±4.6	6.6±1.9	p<0.05	11.3±4.1	7.6±2.9	p<0.05	9.5±3.4	7.9±3.7	p≥0.05	10.1±4.0	9.3±4.0	p≥0.05
Free PSA (ng/ml) (Mean±SD)	1.1±0.6	1.0±0.6	p≥0.05	2.0±1.2	1.3±0.57	p≥0.05	2.0±0.8	1.7±0.7	p≥0.05	1.5±0.2	1.8±0.7	p≥0.05	2.4±1.0	2.3±1.1	p≥0.05
PSAD (ng/ml/cc) (Mean±SD)	0.33±0.24	0.25±0.18	p<0.05	0.19±0.96	0.13±0.04	p<0.05	0.17±0.06	0.11±0.04	p<0.05	0.10±0.03	0.08±0.04	p≥0.05	0.06±0.03	0.06±0.02	p≥0.05
Prostate volüme (cc) (Mean±SD)	29.6±7.3	29.6±6.2	p≥0.05	47.8±6.3	49.6±5.5	p≥0.05	66.2±5.3	69.2±5.8	p≥0.05	97.4±11.9	96.6±12.2	p≥0.05	168.0±55.3	150.8±31.2	p≥0.05

PSA: Prostate Spesific Antigene, , PSAD: PSA density. pCa: Prostate cancer.

Table 3. Areas under ROC curves, optimal cut-off levels and sensitivity and specificity values of PSAD.

	Area under the ROC Mean±SD (95% CI)	Optimal cutoff ng/mL/cc	Sensitivity	Specificity	(+) likelihood ratio	(-) likelihood ratio
Group 1: Prostate<40cc	0.64±0.06(0.51-0.77)	0.22	63%	62%	1.65	0.59
Group 2: Prostate ≥40 and <60 cc	0.72±0.05(0.60-0.83)	0.13	69%	64%	1.91	0.48
Group 3: Prostate ≥60 and <80 cc	0.80±0.05(0.69-0.91)	0.12	72%	71%	2.48	0.39
Group 4: Prostate ≥80 and <120 cc	0.63±0.14(0.34-0.92)	0.08	60%	60%	1.50	0.60
Group 5: Prostate ≥120cc	0.51±0.12(0.24-0.73)	0.05	71%	41%	1.20	0.70

eved for group 3 (prostate ≥60 and <80 cc) and the lowest for group 5 (prostate ≥120 cc). The optimal cutoff values with high sensitivity and specificity levels were 0.22, 0.13, 0.12, 0.08, and 0.05 ng/mL/cc for group 1,2,3,4, and 5 respectively (table 3). Group 3 (prostate ≥60 and <80 cc) reached the highest (+) and the lowest (-) likelihood ratios.

Discussion

PSA is the commonly used tool for pCa screening. While a cutoff value of 4.0 ng/mL is frequently used for increased cancer risk, this value often over-diagnose many men and leads morbidities associated with prostate biopsy (6). The main drawback of PSA testing is its lack of specificity. It is not a cancer specific marker, and several conditions like inflammation and benign prostatic hyperplasia (BPH) are known to increase its serum levels. The use of PSA density is based on the premise that BPH may contribute to PSA elevation even in the absence of pCa (7). From this point of view, Benson et al. described the concept of PSAD as a ratio of PSA concentration to prostate volume (8). They aimed to enhance the diagnostic accuracy of PSA and found significant differences in mean PSAD between men with pCa and BPH. While lower PSAD values are more suggestive for BPH, higher densities are associated with pCa (8,9). Subsequent several studies evaluated PSAD in additional clinical settings, and many demonstrated its diagnostic contribution to prostate cancer screening (3,4,10). However some did not confirm this advantage and reported no benefit for PSAD(11). We conducted this study from the point of view that larger prostates may contribute elevated PSA levels. We aimed to evaluate whether or not is there a specific subgroup of patients who benefit most from PSAD screening according to their prostate volume.

Our results demonstrated that PSAD and serum total PSA values were significantly higher in pCa(+) patients in group 1,2, and 3 (all prostates <80 cc). On the other hand, in group 4 total PSA and PSAD was higher in pCa(+) patients but the difference was not statistically significant. In group 5 PSAD was same but total PSA was slightly higher in pCa(+) patients. All data was suggestive for insufficient diagnostic accuracy of PSAD with increasing prostate size for prostates greater than 80 cc. The ROC analyses and AUC values showed that the diagnostic value of PSAD initially increased with increasing prostate volume and than decreased (after ≥80 cc). The most striking result of our study was demonstrating the maximum benefit of PSAD for patients whose prostates ≥60 and <80 cc (the AUC was 0.80±0.05(0.69-0.91, 95% CI)). The second most benefit group was the second group who had prostates ≥40 and <60 cc. Another invaluable result of our study was demonstrating the need of different cutoff values for different prostate sizes. The best sensitivity and specificity results were obtained with different cutoff values. While 0.12 ng/mL/cc cutoff value reached 72% sensitivity and 71%specificity for group 3, same cutoff value had 94% sensitivity but 7% specificity for group 1 and 40% sensitivity but 87% specificity for group4. Although these results were in contrast with most previous studies, which usually preferred PSAD cutoff levels near to 0.15 ng/mL7cc (3,12,13), some studies advocated using different total PSA values (14). In their study Stephan et al. reported that 0.05 ng/mL/cc cut0ff value should be used in the total PSA range 2-4 ng/mL and 0.1 ng/mL/cc in total PSA range 4-10 ng/mL (14). According to our results we concluded that different cutoff levels have paramount importance for different prostate size especially for larger prostates (prostates ≥80 cc).

The most important limitation is that prostate volumes were measured by different operators. Therefore inter-operator bias might interfere with our results. Additionally the study was conducted and performed retrospectively.

The greatest value of our study was in demonstrating the greatest diagnostic accuracy of PSAD in prostates ≥60 and <80 cc. This maximum benefit decreased with increasing prostate volume and reached nearly zero point for prostates greater than 120 cc. the second most important end point was the need for different cutoff values for different prostate volumes. Although prospective and larger studies including different PSA ranges warranted, our study makes an invaluable contribution to the current literature and would be a reference point for further studies.

Conflict of Interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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