Diagnostic Accuracy of Prostatic Specific Antigen Densityin Different Prostatic Disorders

Qamar Bashir, Zujaja Hina Haroon, Naveed Asif*, Azka Haroon, Muhammad Asif, Syed Raza Jaffar

Armed Forces Institute of Pathology/National University of Medical Sciences (NUMS), Rawalpindi Pakistan, *Combined Military Hospital Quetta/National University of Medical Sciences (NUMS), Pakistan

ABSTRACT

Objective: To determine the diagnostic accuracy of PSA density in Prostate Cancer, Benign Prostatic Hyperplasia (BPH) and Prostatitis, taking biopsy as the gold standard.

Study Design: Cross-sectional study.

Place and Duration of Study: Chemical Pathology and Endocrinology Department, Armed Forces Institute of Pathology (AFIP) in collaboration with Histopathology department, AFIP, Armed Forces Institute of Urology (AFIU) and Institute of Radiology (AFIRI) Rawalpindi Pakistan from Mar 2019 to Mar 2020.

Methodology: Prostate-specific antigen was analyzed on a fully automated random-access immunoassay-ADVIA® Centaur XP. Prostate volume was measured through transrectal imaging technique, and prostate density was obtained by dividing total Prostate-specific antigen by prostate volume. Specificity and sensitivity, along with the positive predictive and negative predictive value of both Prostate-specific antigen and Prostate-specific antigen density (PSAD), were calculated. In addition, the Receiver Operating Characteristic (ROC) curve was plotted for total Prostate-specific antigen and Prostate-specific antigen density PSA separately.

Results: Overall, 129 subjects were registered in the study. Out of these 129 individuals, 59 (45.7%) had prostate cancer, 52 (40.3 %) were benign prostatic hyperplasia (BPH), and 14% of subjects had other prostatic disorders. Total Prostate-specific antigen (PSA) had a sensitivity of 75.61% with a specificity of 76% while Prostate-specific antigen density showed 88% sensitivity and 86% specificity. The area under the curve (AUC) for total Prostate-specific antigen was 0.66, while that for total Prostate-specific antigen density (PSAD) was 0.87.

Conclusion: Prostate-specific antigen density is a better predictive and non-invasive diagnostic marker for different prostatic disorders than total Prostate-specific antigen. It has the potential to distinguish between prostate cancer and other prostatic disorders with high sensitivity and specificity.

Keywords: Benign prostatic hyperplasia (BPH), Prostate specific antigen density (PSAD), Prostatic biopsy, Prostate cancer, Total prostate specific antigen (PSA).

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INTRODUCTION

Prostate cancer is the most commonly diagnosed cancer and the principal reason behind cancer-related mortality among men around the globe. It is responsible for approximately 33% of all cancers seen in males. As per cancer statistics 2020, it is the second most common cause of cancer-related deaths in the United States.[1] Natural history of the disease is quite different, despite its high prevalence. Considering the number of deaths due to prostate cancer, major efforts have always been made to identify the disease in the early phase. For centuries different methodologies have been in trial in clinical practice for early diagnosis of the disease, including total PSA, free PSA, rectal examination (DRE), prostate ultrasound, and prostate biopsy.[2]

The serum PSA level is one of the biomarkers currently available in practice and is considered the potent marker for the diagnosis of prostate malignancy.[3] PSA is a single chain glycoprotein with 7% carbohydrate. Its structure consists of 237 amino acid residues. PSA is produced from acini and epithelial cells of the prostate; PSA is oozed into the lamina of the prostate duct. In the seminal fluid, PSA possesses chymotrypsin-like and trypsin-like activity, ultimately leading to liquefaction of the seminal coagulum.[4] Elevated levels are seen in different conditions like DRE, transrectal ultrasonography, prostatitis, prostatic hyperplasia and prostate cancer.[5,6]

Currently, PSA is a popular marker for the detection of prostate cancer. DRE with PSA can slightly increase its sensitivity for the timely diagnosis of prostate malignancy. Nevertheless, serum PSA is limited because of its comparative lack of specificity, particularly when its concentration rises moderately >4 ng/ml. Thus, with a marginal rise in PSA levels,

Correspondence: Dr Qamar Bashir, Combined Military Hospital, Lahore, Pakistan

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further assessment with biopsy is recommended to exclude prostate cancer. By using an upper limit of 4 ng/ml of PSA, one can effectively balance both the goal of decreasing the number of deaths and unnecessary procedures.[7]

Recently, several techniques have been introduced to augment PSA sensitivity and specificity. Among these tools' PSA density, PSA velocity and determination of molecular variants of PSA are highlighted.[8] Due to the increasing cases of prostatic hyperplasia and increased prostate size after 40 years, different calculated markers were suggested in combination with PSA. One of these techniques is PSA Density; the cut-off value used for PSAD is 0.15. However, many individuals with a PSA level of 4-10ng/mL were found to have prostate cancer.[9]

PSA and PSAD levels are greatly affected by ethnicity and environmental fac-tors. That is why the specific limit for biopsy patients with high values of PSA and PSAD has been contro-versial. In Western countries, the definitive cut-off value of PSA for prostate biopsies is not established yet: a PSA value of 0.15 ng/mL was observed to be abnormal, and prostate biopsies are recommended at this level. However, PSA values for local Pakistani communities need to be established.[10] In Asia, higher cut-off levels of PSA and PSAD are used because of the low prevalence of prostate cancer for advanced recognition of prostate cancer. Therefore, reducing unnecessary biopsies and increasing the cancer detec-tion rate are also important. The current study was conducted to determine the diagnostic accuracy of PSA density in prostatic disorders like prostate cancer, BPH and prostatitis, taking biopsy as the gold standard.

METHODOLOGY

It was a cross-sectional study conducted at the Chemical Pathology and Endocrinology Department, AFIP, in cooperation with the Department of Histopathology AFIP, AFIU and AFIRI Rawalpindi from March 2019 to March 2020. Prostate biopsy was done in AFIU and evaluated at AFIP, while prostate volume was measured by ultrasonography at AFIRI Rawalpindi.

Institutional Ethical Review Committee approval was taken for the study (ERC ID: READ-IRB/20/462). Patients were chosen through the convenience sampling technique after taking informed consent, and the sample size was calculated by the WHO sample size calculator. A total of 129 patients were enrolled for this study.

Inclusion Criteria: Subjects already diagnosed with prostatic disorders like BPH, prostate cancer and prostatitis were included in the study.

Exclusion Criteria: Patients with other co-morbidities like cancer of any other origin, metastatic disorders and those taking alpha-blockers were ruled out from the study.

In addition, detailed clinical history was obtained. A venous blood sample (5.0 ml) was collected from each patient in a yellow-topped gel tube. Serum was separated and stored frozen at -20^{0}C till analyzed for PSA. Total PSA was analyzed on competitive immunoassay (ADVIA Centaur® XP Random access Immunoassay System, Siemens Healthiness) using direct chemiluminescent technology and total PSA (LotNumber-36118304) reagent kit. Prostate volume was calculated through transrectal imaging technique and prostate density by dividing total PSA by the volume of the prostate. Internal quality control (IQC) did calibration and patient results validation.

Statistical Package for Social Sciences (SPSS) version 24.0 was used for the data analysis. Shapiro-Wilk test was used for analyzing the normality of data. All the subjects were divided into four age groups, i.e. 41-50, 51-60, 61-70 and >70 years. Quantitative variables were presented as median and inter-quartile range (IQR). Prostate biopsy was selected as the gold standard. Specificity, sensitivity, PPV, and NPV of total PSA and PSAD were calculated. The ROC curve was plotted between sensitivity and specificity for PSA and PSAD. The *p*-value of ≤0.05 was considered statistically significant

RESULTS

Overall, 129 subjects were registered in the study. Of these 129 individuals, 59 (45.7%) had prostate cancer, 52 (40.3 %) were of BPH, and 14% of subjects had other prostatic disorders (Figure-1).

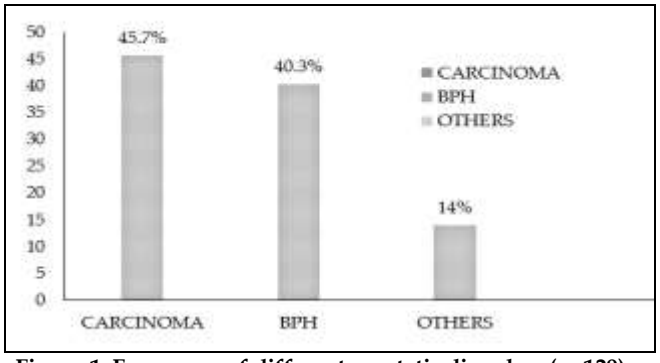

Figure-1: Frequency of different prostatic disorders (n=129)

Out of all the subjects presenting with prostatic disorders, most of them were of elderly age (>70 years) (Figure-2).

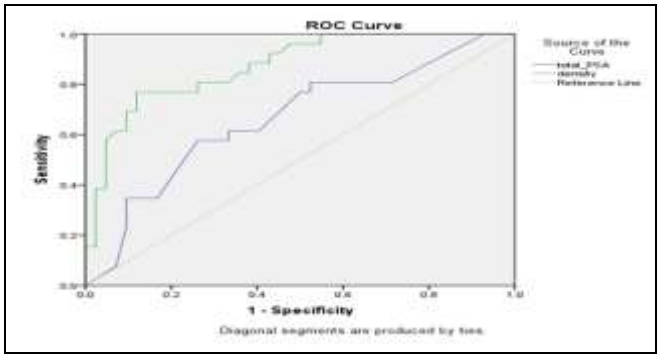

Figure-2: Receiver operating curve for prostate specific antigen density and prostate specific antigen (n=129)

The descriptive statistics of our study subjects for different age groups were shown in the Table-I. All the quantitative variables were computed as median and IQR. ROC curve was plotted between PSAD and total PSA (Figure-3). AUC for PSAD was 0.87 with a *p*-value of 0.001, while AUC for total PSA was 0.66 with a *p*-value of 0.024 (Table-II). It revealed that PSAD was more reliable and sensitive than total PSA for early diagnosis of different prostatic disorders.

Prostate biopsy was selected as the gold standard. Specificity, sensitivity, PPV, and NPV of total PSA and PSAD were calculated (Table-III).

This depicted that PSAD was more reliable and had better sensitivity, specificity, NPV, PPV and total accuracy (TA) than total PSA. In addition, a statisti-cally significant difference (*p*-0.001) has been found between PSAD and total PSA using the Kruskal Wallis test.

DISCUSSION

Screening for prostate cancer with PSA and PSAD has been proven controversial throughout literature, yielding inclusive results in terms of benefits. It has been shown that although it reduces the overall cancer-specific mortality, PSA screening might lead to unnecessary biopsies, ultimately leading to increased patient morbidity post-surgery and radiotherapy.[11,12] On the other hand, PSAD was viewed as a better alternative since it better reflects the amount of cancerous tissue within the prostatic gland. Our study proves that PSAD accomplished better results than

Table-I: Median and inter-quartile ranges of different parameters as per age groups (n=129)

Parameters	Subjects with 41-50 years Median (Inter Quartile Range)	Subjects with 51-60 years Median (Inter Quartile Range)	Subjects with 61-70 years Median (Inter Quartile Range)	Subjects with >70 years Median (Inter quartile Range)
Age (years)	45.5 (5.5)	60 (7.0)	66 (4.5)	76 (12)
Total prostate specific antigen (ng/L)	9.2 (11.7)	9.2 (47.1)	27 (111)	30 (186)
Prostate volume (ml)	61.5 (38.25)	69 (35)	80 (52.5)	93 (65)
Prostate Specific Antigen Density ng/ml	0.16 (0.20)	0.34 (1.14)	0.44 (1.63)	0.76 (3.57)

Table-II: Area under curve (AUC) of prostate specific antigen density and total prostate specific antigen of all study participants(n=129)

Parameters	AUC	*p*-value
Total prostate specific antigen density	0.87	0.001
Total prostate specific antigen	0.66	0.024

Table-III: Sensitivity, specificity, positive predictive and negative predictive values of prostate specific antigen and density in different prostatic disorders(n=129)

Diagnostic Parameter	Sensitivity= True Positive/(True Positive +False Negative)	Specificity= True Negative /(True Negative +False Positive)	Positive Predictive Value= True Positive/(True Positive+ False Positive)	Negative Predictive Value= True Negative/(True Negative +False Negative)	Diagnostic Accuracy=(True Positive +True Negative)/All Patients
Prostate Specific Antigen (PSA)	75.61 %	73.33 %	72.09 %	76.04 %	74.42 %
Prostate specific antigen density (PSAD)	88 %	86%	74.09%	77.0%	77%

PSA in assessing patients with prostate cancer. Efforts have been on the way to finding a definitive test for prostate cancer. Prostate biopsy was considered a reliable procedure for diagnosing prostate cancer in patients with raised serum total PSA and individuals with abnormal rectal examination results. Initially, a needle biopsy was recognized as an accurate method for providing a final diagnosis of doubtful prostate malignancy. However, a study by Levine *et al.*[13] in 1998 revealed that needle biopsy had a 30% false negative detection rate.

Our study revealed that PSAD had AUC0.87 with a *p*-value of 0.001 and a total PSA with AUC of 0.66 and a *p*-value of 0.024. The results of our study are comparable with a study conducted in China by Teoh *et al.*[14] in 2017. Overall, 2606 Chinese males were registered in the study. The result of this Chinese study revealed PSAD with AUC 0.77 ($p<0.001$).

In our study, the sensitivity of total PSA was 75.61% with a specificity of 76%, while PSAD had a sensitivity of 88% with 86% specificity. A study conducted by Na *et al.*[15] in 2013 on the Chinese population showed PSAD of 96% sensitivity at traditional cut-off, which may help avoid biopsies. A study by Wiwanitkit *et al.*[16] in 2004 in Thailand showed that overall sensitivity was 95.8% and specificity was 66.2% and could be used for screening purposes.

A study conduc-ted in the USA by Dominguez *et al.*[17] in 2020 stated that PSAD with 96.6% sensitivity, 87.5% specificity, and an AUC of 0.97. Another study was conducted by Sheikh *et al.*[18] in Kuwait in 2005 to find out the sensitivity and specificity of total PSA and PSAD at different cut-off values. At a cut-off value of 10ng/ml for PSA, both sensitivity and specificity were 80% and 42.2%, respectively.

The cut-off value for PSAD was 0.32; the sensitivity was 58%, with a speci-ficity of 76.6%. Similarly, a study conducted by Gohji *et al.*[19] in 1997 on the Japanese population revealed that for the diagnosis of prostate malignancy at a cut-off value of 0.18, PSAD sensitivity was 70%, and the specificity was 67%.

Thus, in the majority of the studies, PSAD has been proven better than total PSA in the diagnosis and prognosis of prostate disorders. This may help avoid invasive procedures which may cause extensive tissue damage.

CONCLUSION

Prostate specific antigen density is a better predictive and non-invasive diagnostic marker in different prostatic disorders than total PSA. It has the potential to distinguish between prostate malignancy and other benign prostate disorders with high sensitivity and specificity. Methodical use of PSAD as a benchmark could reduce the notable amount of unnecessary procedures.

Conflict of interest: None.

Author Contribution

QB: Direct contribution to conception, design, analysis Data interpretation, ZHH: Intellectual contribution to analysis ,literature review manuscript preparation & final approval, NA:, SRJ: Intellectual contribution to analysis ,data interpretation and final approval, AH: Manuscript preparation & data analysis, MA: Intellectual contribution to analysis, literature review.

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