https://doi.org/10.35845/kmuj.2022.21763

ORIGINAL ARTICLE

# CUT-OFF VALUES OF PROSTATE SPECIFIC ANTIGEN DENSITY - AN EFFECTIVE SCREENING MARKER BEFORE PROSTATE BIOPSY

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## ABSTRACT

**OBJECTIVE:** To determine cut-off values for prostate specific antigen density (PSAD) in diagnosing prostate carcinoma in symptomatic patients.

**METHODS:** This cross sectional, observational study conducted at Department of Chemical Pathology and Endocrinology, Armed Forces Institute of Pathology, Rawalpindi, Pakistan from June 2020 to May 2021. Symptomatic patients (309) having prostatic enlargement on ultrasound were selected through consecutive sampling. All the patients underwent prostate biopsy for histopathological diagnosis. Prostate specific antigen density was calculated and compared between different age groups and different diseases. ROC curve was constructed and area under the curve was calculated to find out cut-off values value for PSAD. Sensitivity, specificity and accuracy were calculated at the cut-off values.

**RESULTS**: Among 309 patients of median age was 68 years (IQR 43 75). There was a significant difference of PSAD in different age groups ($p<0.001$) and diseases like prostate carcinoma, benign prostatic hyperplasia and other prostatic disorders. PSAD had AUC of 0.878 at cut-off value of 0.135 ng/ml where sensitivity was 100%. A higher cut-off 0.20 ng/ml was suggested in younger age group as compared to the old age group where cut-off was found 0.135.

**CONCLUSION**: Using PSAD as part of evaluation profile for prostate lesion, number of unnecessary biopsies can be significantly decreased. PSAD cut-off to aid in decision of invasive prostate biopsy is suggested to be 0.135 ng/ml with close biochemical follow up afterwards.

**KEYWORDS**: Prostate (MeSH); Prostatic Hyperplasia (MeSH); Prostatic Neoplasms (MeSH), Prostate-Specific Antigen (MeSH); Cut-off (Non-MeSH); Prostate specific antigen density (Non-MeSH); Sensitivity and Specificity (MeSH)

**THIS ARTICLE MAY BE CITED AS:** Haroon ZH, Bashir Q, Haroon A, Khalid UB. Cut-off values of Prostate specific antigen density - an effective screening marker before prostate biopsy. Khyber Med Univ J 2022;14(1):16-20 https://doi.org/10.35845/kmuj.2022.21763.

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**Date Submitted:** June 30, 2021

**Date Revised:** January 21, 2022

**Date Accepted:** January 25, 2022

## INTRODUCTION

In men, disorders of prostate are fairly common especially in old age, ranging from prostatitis to benign prostatic hyperplasia (BPH) and invasive prostatic carcinoma. In recent past, these disorders are being reported in many young males below forty years of age. Carcinoma prostate or prostatic carcinoma has a high incidence among men i.e. about 33 % of total cancers in men. [1] This is one of the cancers which can be completely cured if detected early.[2]Clinically, pain lower abdomen, urinary retention, hematuria and constipation are the common symptoms of prostatic cancer. BPH also presents with almost similar signs and symptoms. It is very important to differentiate these two conditions early owing to the impact on treatment and prognosis. Digital rectal examination (DRE) and proctoscopy are very useful clinical tools in evaluation of prostate disorders. Radiological investigations are helpful in determining the size and extent of involvement. The patients are kept on periodic monitoring with serum prostate specific antigen (PSA) levels. Although it is the most commonly used biomarker for prostate disorders, but still it has failed to differentiate benign from malignant disease.[3,4] Prostatic biopsy remains the gold standard for diagnosis of prostatic carcinoma and Gleason score is used for grading of prostate cancers.[5] But this is inconvenient to the patients for screening purpose owing to its invasive nature and complications.[6,7] Hence, there is a need for a reliable, convenient, non-invasive diagnostic test with high sensitivity to screen these patients.

Keeping in view the high incidence of prostate cancer, many protocols for early diagnosis of prostate cancer have been in focus in different studies.[8,9] Prostate specific antigen density (PSAD), a PSA derived strategy adopted to improve sensitivity and specificity of PSA, is one of the effective noninvasive tools for diagnosis of prostatic carcinoma.[10] It has proved its role as outcome predictor before undergoing extended biopsies.[11,12] Studying the correlation of PSAD with different biochemical markers and Gleason Score has proved its promising role in diagnosis of prostatic carcinoma.[13] In order to minimize unnecessary biopsies, there is a need of defining a cut-off value of PSAD to proceed for biopsy in discriminating between benign and malignant disease. This study was conducted with an aim to determine cut-off value of PSAD to screen symptomatic patients for prostatic carcinoma. We propose a PSAD cut-off to reach decision of undergoing invasive prostate biopsy.

## METHODS

This cross-sectional study was conducted at Department of Chemical Pathology and Endocrinology, Armed Forces Institute of Pathology, Rawalpindi, Pakistan from June 2020 to May 2021. Symptomatic patients (n=309) were carefully selected through consecutive

sampling technique who were symptomatic and had prostatic mass on ultrasound. Written informed consent was taken before sampling or any further work-up. The patients having any other malignancy or thyroid disorders were excluded from the study. Samples were collected for serum PSA concentrations from antecubital vein in plain tubes and were analyzed within 4 hours on fully automated immunoassay analyzer ADVIA Centaur XP by Siemens. All the patients underwent prostatic ultrasound and ultrasound guided biopsy was taken by interventional radiologist. PSA density was calculated by dividing serum total PSA concentrations (ng/ml) with prostatic volume (ml). The biopsy specimens were processed and examined by histopathologist for diagnosis of prostatic carcinoma based on Gleason scoring system.[14]

For statistical analysis, data were entered on statistical package for social sciences (SPSS) version 21. After assessing normality of data by Kolmogorov-Smirnov test, quantitative variables were expressed as median and ranges. Mann-Whitney U test was used to find any significant difference between PSAD of two age groups. Kruskal Wallis test was employed for finding significance between PSAD in different diseases. Receiver operating characteristics (ROC) curve was plotted between PSAD and biopsy findings to calculate area under the curve (AUC) at different cut-offs. Sensitivity, specificity, predictive values and accuracy were calculated.

## RESULTS

Data from 309 men was collected with median age 68 years (IQR: 60 - 75). All of them presented with prostate mass and underwent biopsy.

Out of 309 patients 221 (71.5%) were ranging in age from 61 -90 years and 88 (28.5%) were in age group of 40 and 60 years (Table I).

After trans-rectal ultrasound, PSA density was calculated for all of these. Prostate cancer was confirmed on biopsy in total 139 (45%) cases (Table II).

Receiver operating characteristics (ROC) curve analysis done with PSA density showed area under the curve (AUC) of 0.878 taking prostate biopsy as gold standard (Figure 1).

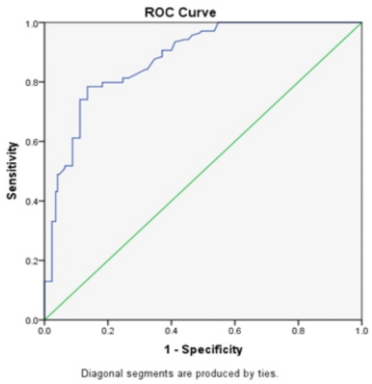


Figure 1: ROC curve analysis between PSAD and prostatic biopsy in study population (n=309)

For different PSA density cut-off levels, sensitivity and specificity were calculated. For screening purpose, highest sensitivity is desired which was 100% at cut-off 0.135 ng/ml. At this cut-off value (0.135 ng/ml), sensitivity specificity and total diagnostic accuracy of PSAD was 100%, 46.5% and 70.55% respectively (Table III).

**TABLE I: PROSTATE SPECIFIC ANTIGEN DENSITY (PSAD) IN YOUNG AND OLD AGE GROUPS OF STUDY POPULATION (N=309)**

| Age group | Frequency n (%) | PSAD (ng/ml) Median (IQR) | P value (Mann-Whitney U test) |
|---|---|---|---|
| Young (40-60 years) | 88 (28.5%) | 0.22 (0.09 – 1.07) | <0.001 |
| Old (>60 years) | 221 (71.5%) | 0.47 (0.16 – 1.76) | |

**TABLE II: FREQUENCY OF PROSTATIC DISORDERS AND PROSTATE SPECIFIC ANTIGEN DENSITY (PSAD) IN STUDY POPULATION (N=309)**

| Prostate disorders | Frequency n (%) | PSAD (ng/ml) Median (IQR) | P value (Kruskal-Wallis test) |
|---|---|---|---|
| Carcinoma prostate | 139 (45.0%) | 1.22 (0.55 - 2.60) | <0.001 |
| Benign Prostatic Hyperplasia | 118 (38.2%) | 0.19 (0.12 - 0.39) | |
| Others | 52 (16.8%) | 0.11 (0.06 - 0.23) | |

**TABLE III: CHARACTERISTICS OF PROSTATE SPECIFIC ANTIGEN DENSITY**

| Attribute | Value |
|---|---|
| Sensitivity | 100 % |
| Specificity | 46.5% |
| Positive predictive value | 0.55 |
| Negative predictive value | 0.60 |
| Positive likelihood ratio | 1.85 |
| Negative likelihood ratio | 0 |
| Total accuracy | 70.55% |

When ROC curve analysis was done separately for old age group i.e. 61-90 years, AUC remained almost the same (0.856) with same cut-off (0.135). But for younger age group increased to 0.917 with a higher cut-off i.e. 0.20 ng/ml.

Figure 2: ROC curve analysis between PSAD and prostate biopsy in old age (shown on left) and younger age (shown on right )This shows that higher cut-offs can be used in younger males less than 40 years for better specificity. But keeping in view the limited number of

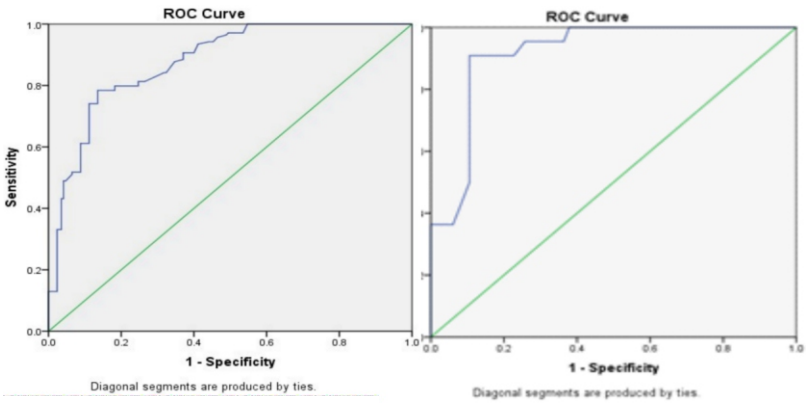


Figure 2: ROC curve analysis between PSAD and prostate biopsy in old age (shown on left) and younger age (shown on right)

data in this age group we recommend further studies with this age group in future for deciding cut-off.

## DISCUSSION

Development of tumour markers has revolutionized treatment and diagnostic protocols. For prostate CA, PSA has been used as diagnostic marker for many decades. But at present, we know that only PSA is not enough to decide the future of patients with suspicious prostate lesion. Many derived markers have been included in diagnostic and surveillance algorithms of PSA lesions. Among them, PSA density has attained much attention due to its decisive role in putting patients on close follow up instead of invasive investigations. Kosaka et al[15] have confirmed role of PSA density as predictor of Prostate CA in 50 years old men. Kundu et al[16] in their studied role of PSA density in determination of aggressiveness of PSA tumours. Keeping in view the above studies, the important role of PSA density in predicting future of patients with prostate lesions is evident. Currently we couldn't find any consensus on PSA density cut-off to be used for Pakistani population.

In our study we collected data from patients who underwent prostate biopsy to rule out prostate cancer. It included patients from 43 to 85 years of age with median age of 68 years. We analyzed PSA levels of same patients from blood and calculated their PSA density. Difference in PSA density was significant between patients with and without CA. With ROC curve analysis, we determined PSA density cut-off. A cut-off of 0.14 ng/ml with sensitivity of 100 and specificity of 46 % is recommended. This cut-off can be used as effective screening tool for deciding the non invasive follow up of patients. In comparison with Western studies, higher cut-offs have been proposed in Asian studies, probably due to comparatively lower incidence of prostate CA in Asia.[17-19] Lin et al,[20] proposed a cut-off of 0.33 ng/ml (sensitivity 60.3, specificity 82.7) in conjunction with PSA levels for patients falling in grey Zone. Similarly, Yanai et al,[21] proposed a cut-off value 0.20 ng/ml for PSAD in diagnosing prostatic carcinoma. Comparing with Yanai et al, this cut-off is comparatively low probably because our study population consists of patients with suspicious lesions instead of general population. Teoh et al. [22] suggested a cut-off of 0.12 n/ml wit 95 % sensitivity for Chinese population.

Age specific PSAD cut-offs are recommended throughout the world. As our study is focused on use of PSAD in screening assistance, same cut-off is recommended for both younger and old age groups to avoid missing any patient at risk of developing carcinoma. It is also recommended that these patients will be kept on close follow afterwards with clinical and biochemical picture.

## LIMITATIONS

Although it was a structured study with adequate sample size, multi-centric studies with extended sample size are needed to establish the age specific cut-offs to differentiate benign from malignant disease.

## CONCLUSION

Using PSAD as part of evaluation profile for prostate lesion, number of unnecessary biopsies can be significantly decreased. PSAD cut-off to aid in decision of Invasive Prostate Biopsy is suggested to be 0.135 ng/ml with close biochemical follow up afterwards.

## ACKNOWLEDGEMENT

Authors are grateful to Dr. Haroon Javaid and Dr. Saima Bashir, Department of Chemical Pathology and Endocrinology, Armed Forces Institute of Pathology, Rawalpindi, Pakistan for their help in manuscript writing.

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## AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

**ZHH:** Conception & study design, analysis and interpretation of data, critical review, approval of the final version to be published

**QB, AH, UBK:** Acquisition, analysis and interpretation of data, drafting the manuscript, approval of the final version to be published

*Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.*

**CONFLICT OF INTEREST**

Authors declared no conflict of interest

**GRANT SUPPORT AND FINANCIAL DISCLOSURE**

Authors declared no specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors

## DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request



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