Original Article

Defining Prostate-Specific Antigen (PSA) Threshold Level for Prediction of Advanced Prostate Cancer in a Subset of Karachi (Pakistan) Population

Zehra Abidi[1], Nuzhat Hassan[1], Faraz Ahmed Baig[2] and Inayatullah Khan[1]

ABSTRACT

Objective: The primary goal of this study is to determine the diagnostic potential of PSA levels in prostate cancer, the histopathological pattern of aggression in terms of the Gleason grading system, and bone metastasis in a subset of the Karachi population.

Study Design: Comparative cross-sectional study.

Place and Duration of Study: This study was conducted at the Ziauddin University, Karachi on 126 prostate biopsy specimens from a subset of the Karachi population from February 2023 to January 2024.

Methods: The samples were recruited after the histopathological confirmation and were composed of 68 prostate adenocarcinoma (PCA) and 58 benign prostatic hyperplasia (BPH) along with the clinic-pathological data. Quantitative analysis of PSA and Gleason scores was done. The area under the receiver operating characteristic curve (AuROC) was generated to determine the sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio, and diagnostic accuracy of PSA level was evaluated for diagnostic performance with positive biopsy. One-way ANOVA was applied among different grades of PCA.

Results: The PSA levels showed higher sensitivity (AuROC=0.999) for the diagnosis of PCA and good performance in determining tumoral grade and the possibility of distant metastasis. We found that PSA levels higher than 7.055 could be a threshold value for predicting PCA in suspected biopsy.

Conclusion: The data showed that PSA can predict PCA, Gleason grade, and bone metastasis. In addition to that, we were able to document a threshold point to suspect PCA during the early pathological course.

Key Words: PCA (prostate adenocarcinoma), BPH (benign prostatic hyperplasia), AUROC (area under receiver operating curve), PSA (prostate-specific antigen).

Citation of article: Abidi Z, Hassan N, Baig FA, Khan I, Defining Prostate-Specific Antigen (PSA) Threshold Level for Prediction of Advanced Prostate Cancer in a Subset of Karachi (Pakistan) Population. Med Forum 2024;35(9):26-31. doi:10.60110/medforum.350906.

INTRODUCTION

The second most common malignant tumor in older men is PCA[(1)]. Asia has seen an increase in PCA cases in recent decades[(2)]. Presently, Digital rectal examination (DRE) abnormalities and increased PSA levels are the basis for prostate cancer screening[(3)]. Although, when used together, PSA and DRE showed greater performance in the early onset of PCA, both investigations failed to achieve the definitive diagnostic value[(4)].

[1.] Department of Anatomy / Pathology, Ziauddin University, Karachi.

Correspondence: Dr. Zehra Abidi, Department of Anatomy, Ziauddin University, Karachi.
Contact No: 03312273704
Email: zehra.12526@zu.edu.pk, posshu@gmail.com

Received: March, 2024
Accepted: July, 2024
Printed: September, 2024

Higher sensitivity and low specificity of PSA are the biggest challenges in the clinical diagnosis of PCA[(5)]. As a consequence, higher false positive rates were reported, contributed by increased prostate volume commonly observed in benign conditions and factors such as infection[(6).] Despite that, elevated PSA levels still serve as a primary method of screening for PCA as novel biomarkers are currently unavailable[(7)].

The widely accepted cutoff for the serum PSA level is 4ng/ml which underlines 35 to 43% of cases diagnosed accurately[(8)]. Unfortunately, this cut-off value is more applicable to the Western population while no cutoff is available for the Pakistani population, which is genetically distinct. Additionally, elevated PSA levels may also reflect a greater likelihood of higher Gleason score and advanced disease[(9)]. We, therefore, studied the effectiveness of PSA levels for diagnosis and aggressiveness of PCA in routine clinical practice.

METHODS

This comparative cross-sectional study was performed at the multidisciplinary lab of Ziauddin University

Clifton campus, Karachi. The samples were retrieved from The Laboratory Sadder Karachi, Pakistan, after the ethical approval of the Ethics Review Committee of Ziauddin Hospital Karachi, Pakistan. (Reference code: 6360123ZAANA).

Data from 126 prostate biopsy specimens were collected by convenient sampling technique, which was recently diagnosed with PCA (n=68) and BPH (n=58). All patients were receiving primary care at different tertiary care hospitals in Pakistan. Any secondary pathology of the prostate by local invasion and poorly fixed tissues was excluded. The patient's demographic and pathological data were retrieved from biopsy reports following diagnosis, including specimen number, age, hospital, diagnosis, histopathological report, and history of bone metastasis. PSA levels were also collected.

Statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 24. Age, PSA levels, and Gleason score were represented by mean ±S.D. Gleason Grade and Bone metastasis were represented by frequency and percentage. ROC was plotted to assess the diagnostic performance of PSA levels. By using Youden's index method, the best cut-off value of PSA level was assessed to diagnose PCA.

By using this cut-off value of PSA, the sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy were also assessed. Gleason Grading and bone metastasis were also evaluated. One-way ANOVA was applied among PSA levels and different Gleason grade groups to compare the PSA levels among them. P-value ≤ 0.05 was considered statistically significant.

RESULTS

The clinical data of PCA (n=68) revealed that the mean age was 69.62±7.79 years while the average PSA level was 24.11±15.58 ng/ml. Similarly, BPH (n=58) showed the mean PSA and age of 4.12±1.71 ng /ml and 66.48±7.87 respectively. The other clinical variables showed an overwhelming majority of high-grade tumors (Gleason score >8) in the PCA group whereas the mean for the Gleason score was observed to be 7.32±0.8. Metastasis (bone) was reported in 15/68 cases of PCA (Table 1)

The plots for serum PSA showed higher levels in subjects of PCA with increased Gleason score and bone metastasis (Figures 1 and 2). These results were also in agreement with the area under the ROC reflecting an overall diagnostic predictability (0.99) for PCA, however, these values were (0.97) and (0.76) for Gleason score and bone metastasis respectively (Table 2). We found that the chances of diagnosing PCA were much higher than that of BPH when the PSA level was beyond the threshold point of 7.055 ng/ml. Overall, at this threshold point, the positive predictive value was 97.14% and the negative predictive value was 100%. Lastly, the recorded sensitivity and specificity of PSA for diagnosis of PCA were noted to be 100% and 96.5% respectively along with a diagnostic accuracy of 98.41% (Table 2).

PSA levels were compared among 5 different Gleason grades and statistically significant results were found at P-value < 0.001 by applying one-way ANOVA. Post hoc analysis among the multiple comparison of groups revealed statistically significant results for PSA levels as shown in (Table 3) grade 1 and grade 4 (P-value < 0.001), grade 1 and grade 5 (P-value < 0.001), grade 2 and grade 4 (P-value <0.001), grade 2 and grade 5 (P-value <0.001), grade 3 and grade 4 (P-value <0.001), grade 3 and grade 5 (P-value <0.001) and grade 4 and grade 5 (P-value <0.001).

Table No. 1: Descriptive Analysis:

VARIABLES	MEAN ± S.D / FREQUENCY (%)
AGE	68.17±7.95 years
PCA cases (n=68)	69.62 ± 7.79 years
BPH cases (n=58)	66.48 ± 7.87 years
PSA LEVELS	
Overall	14.91±15.22 ng/ml
PCA(n=68)	24.11 ± 15.5 ng/ml
BPH(n=58)	4.12 ± 1.71 ng/ml
Frequency of PCA Grades	
Grade 1(n=5)	7.4%
Grade 2 (n=18)	26.5%
Grade 3 (n=25)	36.8%
Grade 4 (n=1)	22.1%
Grade 5 (n=5)	7.4%
GLEASON SCORE(n=68)	7.32 ± 0.8
BONE METASTASIS(n=68)	
PRESENT	15(22.1%)
ABSENT	53(77.9%)

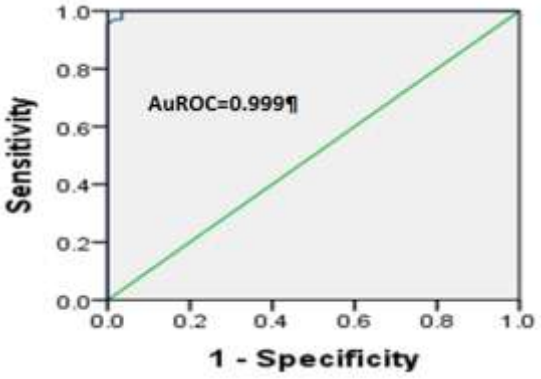

Figure No. 1: Receiver operating characteristic curve (ROC) of serum prostate-specific antigen in the prediction of tissue diagnosis.

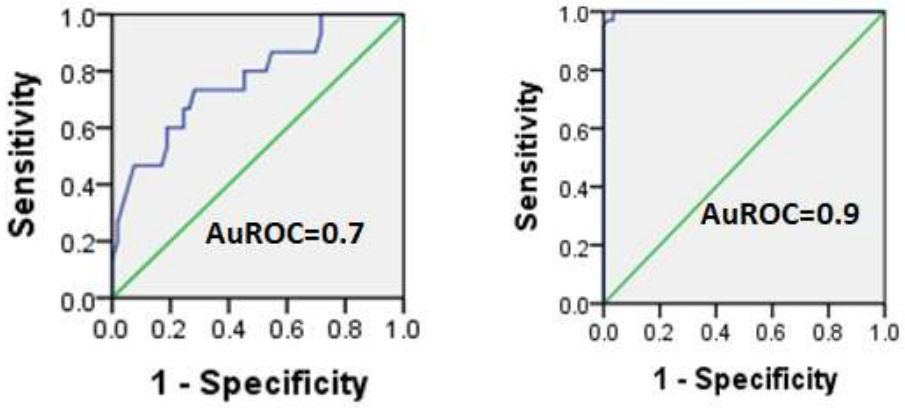

FIGURE 2: Receiver operating characteristic curve (ROC) of serum prostate-specific antigen in the prediction of aggressiveness (Gleason score>7) and bone metastasis respectively.

Table 2: Sensitivity, specificity, PPV, NPV and diagnostic accuracy of PSA levels.

PSA ng/ml Cut off point	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
7.055	100 % *(94.72)	96.55% *(88.09)	97.14% *(89.70)	100 % *(93.62)	98.41% *(94.38)

*Confidence interval

PSA, prostate-specific antigen; PPV, positive predictive value; NPV, negative predictive value;

Gleason grades	N	PSA levels (mean ±S. D)	P-value
Grade 1	5	9.53±1.93	
Grade 2	18	13.77±2.62	
Grade 3	25	20.09±6.92	
Grade 4	15	36.23±13.45	
Grade 5	5	59.70±11.59	
Total	68		
*ANOVA applied			
Multiple comparisons by post hoc analysis			
Gleason Grades		Mean Difference	P-Value
Grade 1	Grade 2	4.23	085
	Grade 3	10.55	0.08
	Grade 4	26.70	< 0.001**
	Grade 5	50.16	<0.001**
Grade 2	Grade 3	6.32	0.11
	Grade 4	22.46	<0.001**
	Grade 5	45.92	<0.001**
Grade 3	Grade 4	16.14	<0.001**
	Grade 5	39.60	<0.001**
Grade 4	Grade 5	23.46	<0.001**
*Tukey's test applied ** Significant result			

DISCUSSION

PSA and DRE are the initial steps taken by the clinician to diagnose prostate cancer. This is followed by prostate biopsy which is considered the gold standard of diagnosis.[3]. Guidelines for prostate cancer screening remain controversial. Two studies were conducted in the 1990s, in which a transrectal ultrasound-guided, systematic prostate biopsy was performed after PSA testing. Those were named the European Randomized Study of Screening for Prostate Cancer (ERPSC) and the randomized GÖTEBORG-1 experiment. PCA mortality was significantly reduced in both studies; however, there was also a greater risk of false

diagnosis[10]. Owing to the global controversy around PSA's diagnostic accuracy, several health professionals have developed unique guidelines for PSA-based PCA screening. Because of racial and cultural disparities in PCA causation, PSA may be less sensitive and specific to PCA across races. Therefore, assessing and ascertaining the diagnostic efficacy of PSA and its substitutes in all racial categories is critical[5]. We aimed to highlight the productivity of PSA levels in a subset of the Karachi population regarding PCA diagnosis, aggressiveness, and metastasis.

In our study, 126 patients of the prostate biopsy were included of which 68 were PCA with a percentage of 53.96% and 58 were BPH with a percentage of 46.03%. Since we have done convenient sampling to collect our sample size, they are not representative of the entire PCA and BPH case population in our country. However, a five-year study about prostatic lesions conducted in Lyari General Hospital, Karachi, Pakistan, which comprised 158 samples revealed a proportion of BPH and PCA 95.6% and 4.4% respectively. A meta-analysis in Pakistan showed an increasing prevalence of PCA between 2% to 8%[11].

In our study mean age and PSA in BPH cases were 66.48± 7.87 years and 4.12±1.71 ng/ml respectively. Similarly, the mean age and PSA in PCA cases were found to be 69.62±7.79 years and 24.11±15.58 ng/ml respectively. According to a study done at Dow University of Health Sciences, BPH patients were found to be typically between 60 and 70 years old, which is similar to our results[12]. Globally men over 65 are more likely to develop PCA, and over 80% of cases are detected after that age[13] Which is comparable to our results. However, in PCA patients mean PSA in the Asian population was found to be 14.8 ng/ml[14]. Higher values of 45.59 ng/ml were found in the Indonesian population in contrast to the international consensus[15] and also to our results. It is suggested that a large dataset for both groups with a uniform distribution should be assessed, and PSA levels adjusted according to racial variation.

In our study mean Gleason score was 7.32±0.8 and the most common Gleason grade with an intermediate risk category was grade 3. The score was comparable to a study based on the population of Bangladesh i.e. 7.28±1.7[16]. Another study showed high grades (grades 4 and 5) in the Chinese group and low grades (grade 2) in the U.S. cohort (17). In a collaborative report on PCA in Asia, there are more patients with the initial phase of PCA and positive Gleason Scores in most Asian parts with well-established economic and healthcare systems. Nonetheless, high-grade PCA remains the most common diagnosis for individuals in China (Gleason Score > 7)[2]. This might be the pattern of underdeveloped Asian countries with limited resources and budgets for the health care system resulting in late diagnosis. Early diagnosis is possible by upgrading the health care system.

In our study, PCA with bone metastasis had a lower frequency and percentage of about 22% which is contrary to a study in the Chinese population where a higher prevalence of 44% was found.[18]. An observational study in the Denmark population also showed reduced frequency of bone metastasis which was 9.2% with initial PCA diagnosis, later 5.7% of patients developed bone metastasis during 5-year follow-up.[19]. Even while the Danish population study produced results that were comparable to ours, the limited sample size in our study means that those results might not accurately reflect our population's estimation. Findings that diverge from those of the Chinese population could be the consequence of our community's underdiagnosis or delayed diagnosis brought on by the expensive cost of medical facilities and lack of awareness of symptoms. Updating cancer diagnostic programs, free resources, and a registration system could overcome the scenario.

In our study predictability of PSA in diagnosing PCA has shown very good performance as can be seen by the area under ROC (fig.1 and Table 2) at a threshold value of 7.055ng/ml. This threshold value showed 100% sensitivity, 96.55% specificity, 97.14% positive predictive value, and diagnostic accuracy of 98.41%. Our results are in contrast to a study conducted in Thailand revealing 66% sensitivity, 88% specificity, and 74% positive predictive value at the threshold value of 20ng/ml,[3]. Another study among the Korean population showed a 100% positive predictive value at a threshold value of PSA ≥50ng/ml. The idea that various ethnic groups had varying baseline PSA levels across all age groups is supported by another study conducted in multiethnic Asian settings[20]. Therefore, for individuals of different races and ethnicities, a given PSA value may have distinct clinical implications.

The AUROC analysis revealed that while the predictability of PSA levels with Gleason scores (aggressiveness) performed well, the performance with bone metastases was only fair (Fig.2). We didn't proceed further for the threshold value due to the small sample size. Our results of PSA performance for aggressiveness were similar to a Korean study.[21] And contrast with Jammu Kashmir population where PSA performance was good with bone metastasis[22].

In our study, there were statically significant variations in PSA levels seen among different grades of prostate cancer which are similar to the findings in the Asian population according to the United States Census Bureau[14]. This indicates that PSA levels were able to differentiate among different grades.

The strength of the study was that it generated data for the Pakistani population, although the sample size was small, we were able to generate a PSA threshold value of 7.055ng/ml for predictability of PCA. At this

threshold, the risk of developing PCA is more than the BPH. Limitations of the study were the small sample size and retrospective nature of the study.

We recommend carrying out similar studies in multiple centers in the country. The government should revise its policies of health care facilities for the population so that everyone has the opportunity to get related help. Data registries and surveys are encouraged by the authorities so that enough data can be generated as per our ethnicity and race.

CONCLUSION

According to the data, PSA can predict bone metastases, Gleason grade, and PCA. Furthermore, throughout the early pathological phase, we were able to identify a threshold point at which prostate cancer should be suspected.

Acknowledgements: I want to thank Ziauddin University for approving the research and Dr. Siraj-ud-Daulah for permission to collect samples from The Lab, Saddar. I also want to acknowledge Miss Fariha Anum for guiding me through the statistics of my article.

Author's Contribution:

Concept & Design of Study:	Zehra Abidi
Drafting:	Nuzhat Hassan, Faraz Ahmed Baig, Inayatullah Khan
Data Analysis:	Fariha Anum, Zehra Abidi
Revisiting Critically:	Nuzhat Hassan, Faraz Ahmed Baig, Inayatullah Khan
Final Approval of version:	By all above authors

Conflict of Interest: The study has no conflict of interest to declare by any author.

Source of Funding: None

Ethical Approval: No.6360123ZAANA dated 11 Jan 2023

REFERENCES

1. Berenguer CV, Pereira F, Camara JS, Pereira JAM. Underlying Features of Prostate Cancer-Statistics, Risk Factors, and Emerging Methods for Its Diagnosis. Curr Oncol 2023;30(2):2300-21.
2. Chen R, Ren S, Chinese Prostate Cancer C, Yiu MK, Fai NC, Cheng WS, et al. Prostate cancer in Asia: A collaborative report. Asian J Urol 2014; 1(1):15-29.
3. Lojanapiwat B, Anutrakulchai W, Chong-ruksut W, Udomphot C. Correlation and diagnostic performance of the prostate-specific antigen level with the diagnosis, aggressiveness, and bone metastasis of prostate cancer in clinical practice. Prostate Int 2014;2(3):133–139.
4. Okpua NC, Okekpa SI, Njaka S, Emeh AN. Clinical diagnosis of prostate cancer using digital rectal examination and prostate-specific antigen tests: a systematic review and meta-analysis of sensitivity and specificity. Afr J Urol 2021;27(1). https://doi.org/10.1186/s12301-021-00129-x.
5. Okwor CJ, Nnakenyi ID, Agbo EO, Nweke M. Sensitivity and specificity of prostate-specific antigen and its surrogates towards the detection of prostate cancer in sub-Saharan Africa: a systematic review with meta-analysis. Afri J Urol 2023;29(1). https://doi.org/10.1186/s12301-023-00372-4
6. Liu J, Dong B, Qu W, Wang J, Xu Y, Yu S, et al. Using clinical parameters to predict prostate cancer and reduce the unnecessary biopsy among patients with PSA in the gray zone. Scientific Reports 2020;10(1). https://doi.org/10.1038/s41598-020-62015-w
7. Kim JH, Hong SK. Clinical utility of current biomarkers for prostate cancer detection. Investig Clin Urol 2021;62(1):1-13.
8. Jin Y, Jung JH, Han WK, Hwang EC, Nho Y, Lee N, et al. Diagnostic accuracy of prostate-specific antigen below 4 ng/mL as a cutoff for diagnosing prostate cancer in a hospital setting: A systematic review and meta-analysis. Investig Clin Urol 2022;63(3):251-61.
9. Liu D, Kuai Y, Zhu R, Zhou C, Tao Y, Han W, et al. Prognosis of prostate cancer and bone metastasis pattern of patients: a SEER-based study and a local hospital based study from China. Scientific Reports 2020;10(1):9104.
10. Hugosson J, Mansson M, Wallstrom J, Axcrona U, Carlsson SV, Egevad L, et al. Prostate Cancer Screening with PSA and MRI Followed by Targeted Biopsy Only. N Engl J Med 2022; 387(23):2126-37.
11. Idrees R, Fatima S, Abdul-Ghafar J, Raheem A, Ahmad Z. Cancer prevalence in Pakistan: meta-analysis of various published studies to determine variation in cancer figures resulting from marked population heterogeneity in different parts of the country. World journal of surgical oncology. 2018;16(1):1-11.
12. Khan A, Sheikh SU, Ali R, Ahmed SB. Age and Prostatic Volume: The Prognosis for Benign Prostatic Hyperplasia. Pak J Med Dent 2023;12(2): 23-28. doi: 10.36283/PJMD12-2/005.
13. Ito K, Kimura T. Complex Epidemiology of Prostate Cancer in Asian Countries. Korean J Urological Oncol 2023;21(1):5-13.
14. Deuker M, Stolzenbach LF, Pecoraro A, Rosiello G, Luzzago S, Tian Z, et al. PSA, stage, grade and prostate cancer specific mortality in Asian American patients relative to Caucasians according to the United States Census Bureau race definitions. World J Urol 2021;39(3):787-96.

15. Shahab AA, Soebadi DM, Djatisoesanto W, Hardjowijoto S, Soetojo S, Hakim L. Prostate-specific antigen and prostate-specific antigen density cutoff points among Indonesian population suspected for prostate cancer. Prostate Int 2013;1(1):23-30.
16. J D, Ak P, N H, Kk D, S S, Ti K, et al. Correlation of Prostate Specific Antigen, Gleason Score and Bone Metastases in Bone Scan in Prostate Cancer Patient. SAS J Med 2021;7(3):85-9.
17. Zhang L, Liu X, Xia R, Chen F, Wang X, Bao J, et al. Comparison of the clinicopathologic features of prostate cancer in US and Chinese populations. Pathol Res Pract 2022;234:153933.
18. Zhuo L CY, Pan Y, et al. Prostate cancer with bone metastasis in Beijing: an observational study of prevalence, hospital visits and treatment costs using data from an administrative claims database. BMJ Open 2019;9(6):e028214.
19. Blanes-Vidal V, Tashk A, Cantuaria ML, Hansen RS, Poulsen CA, Poulsen MH, et al. Epidemiological description and trajectories of patients with prostate cancer in Denmark: an observational study of 7448 patients. BMC Res Notes 2023;16(1):341.
20. Lim J, Bhoo-Pathy N, Sothilingam S, Malek R, Sundram M, Hisham Bahadzor B, et al. Ethnicity is an independent determinant of age-specific PSA level: findings from a multiethnic Asian setting. PLoS One. 2014;9(8):e104917.
21. Song SH, Kim E, Jung YJ, Kim HM, Park MS, Kim JK, et al. Polygenic risk score for tumor aggressiveness and early-onset prostate cancer in Asians. Sci Rep 2023;13(1):798.
22. Manohar PR, Rather TA, Khan SH. Determination of the optimal cut-off value of serum prostate-specific antigen in the prediction of skeletal metastases on technetium-99m whole-body bone scan by receiver operating characteristic curve analysis. World J Nucl Med 2020;19(3):255-9.