ORIGINAL ARTICLE

PROSTATE CARCINOMA: ROLE OF PSA DENSITY IN DIAGNOSTIC ALGORITHM

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PJR July - September 2022; 32(3): 123-128

ABSTRACT

BACKGROUND: Prostate-specific antigendensity (PSAD) is an important, but under-utilized addition to clinical and laboratory diagnosis of prostate malignancy. It is calculated by dividing the level of prostate-specific antigen (PSA) in serum by the volume of prostate gland. **OBJECTIVES:** The aim of this study is to determine the sensitivity, specificity and accuracy of PSAD in outcome of prostate biopsies, and to compare PSAD values in patients of prostatic cancer with and without lymphovascular and perineural invasion at histopathology. **METHODS:** This study included data of seventy-seven patients who underwent transrectal ultrasound-guided (TRUS) biopsy of prostate gland at our centre. Volume of prostate was calculated sonographically using endorectal coil. PSAD was calculated by dividing serum PSA level by prostatic volume. **CONCLUSION:** Sensitivity of PSAD is high for diagnosis of prostate cancer with fair degree of accuracy and moderate specificity.

Keywords: Prostate-specific antigen density (PSAD), prostate, multiparametric MRI (mpMRI), lymphovascular invasion, perineural invasion

Introduction

Prostate cancer is the second most common cancer worldwide and the 6th leading cause of cancer deaths.[1] It has been reported as the third commonest cancer in Korean men in 2017.[2] According to the latest WHO data published in 2020, prostate cancer incidence in Pakistan is 2.6%.[3] Deaths due to carcinoma of prostate in Pakistan have reached 3559 in or 0.24% of total deaths. The age adjusted mortality is 5.9/100,000 and places Pakistan at number 159 in the world.[4]

More than 1000,000 prostate biopsies are carried out per year in the US alone, which may be associated with complications like hemorrhage, infections and psychological stress; increasing the individual s as well as healthcare system s burden.[5] Screening for prostate cancer using prostate-specific antigen (PSA) alone leads to unnecessary biopsying and may result in over/missed diagnosis.On the other hand, prostate-specific antigen density (PSAD) is a reliable tool in guiding the physician on deciding about biopsy. PSAD is calculated by dividing serum prostate-specific antigen (PSA) level by the prostatic volume (measured on ultrasound or MRI) and is expressed as ng/ml.[2] This simple calculation is helpful in deciding about performing biopsy in cases of indeterminate PSA levels (4 - 10 ng/ml), inconclusive digital rectal examination or in patients requiring repeat biopsy.[6] It is also used for active surveillance of prostate cancer, as a part of the Prostate Cancer Research International:

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Submitted 29 August 2022, Accepted 8 September 2022

Active Surveillance (PRIAS) criteria for prostate cancer surveillance.[7] PSAD is an important guide to the histopathologist to determine the aggressiveness of the cancer and staging. It is also a reliable tool for surgical planning.[8] Probability of lympho-vascular and peri-neural invasions is related to higher PSAD levels.[9]

The aim of this study is to determine the sensitivity, specificity and accuracy of PSAD in outcome of prostate biopsies, and secondly, to compare PSAD values in patients of prostatic cancer with and without lympho-vascular and perineural invasion at histopathology.

Materials and Method

Seventy-seven subjects were included in this retrospective single-centre study from July 2020 to February 2022. All patients who underwent trans-rectal ultrasound-guided biopsy at our diagnostic centre were included; biopsy samples received from outside facility were excluded. Cut-off value of PSAD for malignancy was taken as greater than or equal to 0.20ng/ml^2.[10] Histopathology was taken as the gold standard. Statistics were calculated using online sociostat and windows excel software. Approval from ethical review board was acquired.

Results

Age range of men included in this study was 50 to 91 years, mean being 70.12 + 8.51 years and median age 70 years. Prostatic acinar adenocarcinoma was present in 55 patients (Tab.1). These 55 subjects with histopathologically-proven prostate malignancy were further divided into two groups and their PSAD values were compared. Group 1 consisted of patients with perineural invasion (PNI) and or lymphovascular invasion (LVI); group 2 subjects had no PNR and or LVI (Tab.2).

Keeping histopathology as the gold standard, PSAD showed true positivity in 51 patients and true negativity in 12. Ten subjects were false positive and false negative were 4. Using conventional formulae, sensitivity, specificity, positive and negative predictive values and accuracy of PSAD were calculated (Tab.3).

Receiver operating curve (ROC) was plotted, comparing the biopsy outcome and PSAD levels. Area under curve was 0.77, which corresponds to a fair degree of accuracy (Fig.1).

We divided the patients with histopathologically proven malignancy into two groups: those with and without PNI and or LVI. Difference between the two groups was insignificant with p-value < 0.05 (Tab.4). Same results are graphically represented in (Fig.2).

	Positive for malignancy (n = 77)	Negative for malignancy (n = 77)
PSAD > / = 0.20 ng / ml^2	61 (79.22%)	16 (20.77%)
Histopathology	55 (71.42%)	22 (28.75%)

Table 1: Histopathological outcome of prostate biopsies. PSAD = prostate-specific antigen density

Invasion on histopathology	Group 1	Group 2
Perineural invasion (PNI)	40 / 55 (72.72%)	15 / 55 (27.27%)
Lymphovascular invasion (LVI)	15 / 55 (27.27%)	40 / 55 (72.72%)
PNI and LVI	40 / 55 (72.72%)	15 / 55 (27.27%)

Table 2: Comparison of prostate-specific antigen density (PSAD) values of two groups of patients with histo-pathologically proven prostate malignancy.

Statistics	Value	95% confidence interval (CI)
Sensitivity	92.73%	82.41% to 97.98%
Specificity	54.55%	32.21% to 75.61%
Positive predictive value	83.61%	76.23% to 89.02%
Negative predictive value	75.00%	52.02% to 89.25%
Accuracy	81.82%	71.38% to 89.69%

Table 3: Sensitivity, specificity, positive and negative predictive values and accuracy of prostate specific density (PSAD) in diagnosis of prostate malignancy

PSAD	Group 1 (with PNI and or LVI)	Group 2 (without PNI or LVI)
	n = 40	n = 15
Mean (±SD)	1.72 ± 3.14	1.08 (± 2.02)
Median	0.576	0.45

Table 4: Comparison of two groups of patients showing malignant outcome on biopsy. PSAD = prostate-specific antigen density, PNI = perineural invasion, LVI = lymphovascular invasion, SD = standard deviation

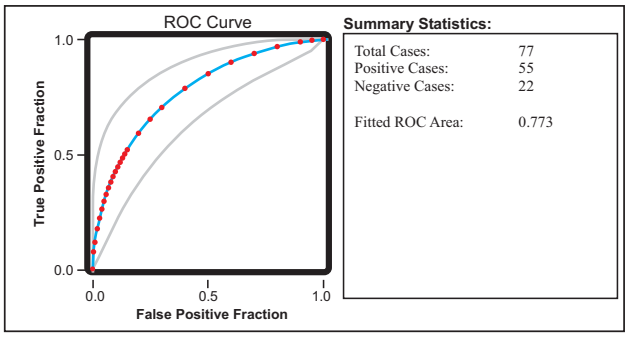
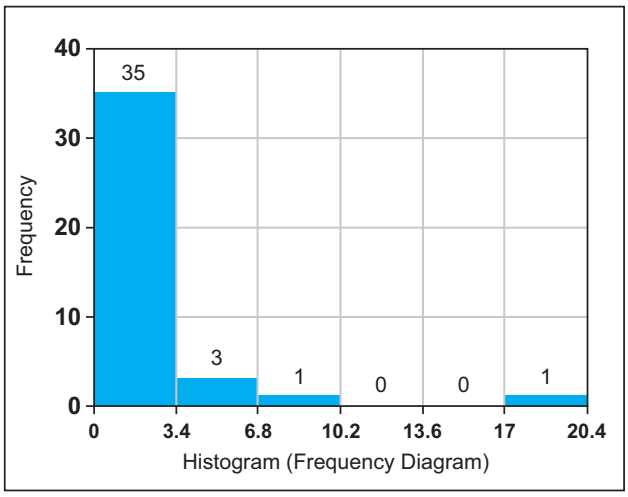
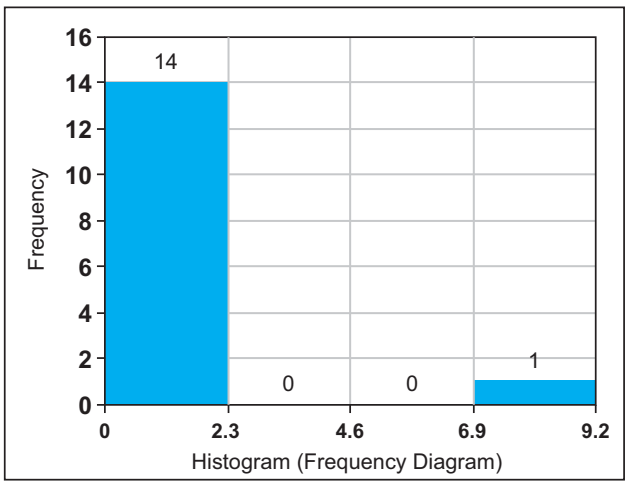


Figure 1: Receiver operating curve (ROC) of comparison between histopathological results and prostate-specific antigen density (PSAD)

a) PNI & LVI Positive (n = 40)



b) PNI & LVI Negative (n = 15)



PNI = perineural invasion, LVI = lymphovascular invasion

Figure 2: Frequency histograms using Mann-Whitney U-Test. The U-value is 261. The Z-Score is 0.72758. The p-value is 0.465. The result is not significant at $p < 0.05$.

Discussion

PSAD was introduced in 1992 by Benson et al, who described that this simple calculation (serum PSA level/prostate volume) is cost free, does not require intervention and is not time consuming, but significantly improved the PSA specificity in differentiating BPH from localized prostatic carcinoma. Soon after, Catalona et al incorporated PSAD as a reliable tool for biopsy indication.[11]

PSAD and details of core biopsy are a pre-requisite by the uro-oncological surgeons to assess the risk factors and to decide about lymph nodal dissection during radical prostatectomy. PSAD should be incorporated while assessing risk stratification in disease management. This was concluded after a 4-year study of 250 Japanese men who underwent robotic radical prostatic surgery. The results were published in 2017, stating that higher PSAD had independent association with advanced stage of malignancy. Prostate volume was calculated on pre-operative multiparametric MRI (mpMRI) of prostate; whereas we calculated its volume on transrectal ultrasound (TRUS) at the time of image-guided biopsy. Our results showed similar association of PSAD with malignant biopsy outcome.[12]

A three-year-long research in Germany comprising of 1040 participants analyzed if negative predictive value of mpMRI of prostate to detect significant malignancy could be improved using PSAD. By incorporating PSAD with mpMRI results, they concluded that 20% of unnecessary prostate biopsies could be safely avoided after ruling out significant malignancy.[13] Another recent published data of 263 men from two centres across the US from 2017 20 suggested that PSAD is decisive factor in selecting patients for biopsy in PI-RADS(prostate imaging, reporting and data system) category 3 lesions, hence reducing the biopsy-related morbidity.[14] However, MRI correlation was not part of our study project.

Low resistance along the nerves makes perineural dissemination easy. Perineural invasion (PNI) is the result of a complex multistep cellular and molecular mechanism and carries unfavourable prognosis in prostate malignancy.[15] Results of a 20-year long research were published in 2017; this study consisted of two cohorts: mean age of subjects in Swedish cohort was 73 years in comparison to the American

cohort with mean age of 66 years. Mean age of study population in our retrospective study is closer to the Swedish men i.e. 70.12 – 8.51 years. However, the duration and number of subjects of current study is much less than this long research project. They found out that patients with PNI on histopatholgy were at seven times greater risk of dying due to prostate cancer than those without PNI. PNI was present in 7% (43/615) biopsies in Swedish men and 44% (370/849) in American cohort.[16] Our results showed that PNI in malignant outcome was 72.72% (40/55); this percentage is closer to the results of a two-year long Iranian study of 354 men with proven prostatic malignancy, in which PNI was confirmed in 79.9% biopsy samples. Mean age of participants in their study was 68.62 – 8.81 years, whereas that of our study population was 70.12 – 8.51 years.[17] Another research from three cancer registries in the UK from 1990-2003 included 988 men with clinically localized disease; PNI was positive in 288 subjects (29.14%).[18] Malignant cells have a propensity to grow via blood vessels and lymphatic channels, known as lympho-vascular invasion (LVI), thus increasing metastases to lymph nodes and distant organs. This process involves extension of tumor cells into the endothelial-linedvascular and lymphatic channels, detected on histopathology. Since it carries adverse clinical and pathological prognosis, the College of American Pathologists recommended to include LVI in prostate routine histopathology reports since 1994. A meta-analysis of 20 studies consisting of 25,570 patients with prostate malignancy up to June 2018 concluded that LVI is associated with higher risk of biochemical recurrence, extra prostatic extension, higher Gleason-score, lymphnodal involvement, positive surgical margins and seminal vesical involvement.[19] In a retrospective data collection of 1634 cases of radical prostatectomy from 2005-2014, Kang et al showed that LVI was detected in 7.4%.[20] Similar results were shown by Jamil et al, who documented that 17,758 (8%) out of 232,704 patients had LVI on histopathology from 2010-15. Based on the histopathology reports, 27.27% (15/55) cases of prostatic adenocarcinoma in our study showed LVI; all these had evidence of PNI as well.

Limitation of our research is that it is a retrospective data review from a single centre; multicenter larger prospective studies are required to establish local cut-off criteria of PSAD in our population due to genetic and racial variation from other parts of the world. Regarding its strength, our study is the first to highlight the relationship of PSAD with histopathological results of prostate biopsies in Pakistan. No local published data was found comparing PSAD values in prostatic malignancy with and without LVI and PNI during literature search.

Conslusion

PSAD is a fairly accurate and a very sensitive tool for detecting prostatic malignancy; however, its specificity is only of moderate degree. It must be incorporated in radiological reports in order to guide the clinicians and histopathologists for management of prostate malignancy. Difference in raised PSAD values in patients having prostate carcinoma with and without LVI and PNI turned out to be statistically insignificant.

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