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Original Article

Usefulness of prostate specific antigen density in detecting prostate carcinoma: a hospital-based study in patients with prostate biopsies

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ABSTRACT

Background: Prostate-specific antigen density has been suggested to enhance the diagnostic efficacy of serum prostate-specific antigen alone in detecting prostate cancer, thereby reducing unnecessary biopsies and associated morbidities. This study aimed to assess the diagnostic performance of prostate-specific antigen density in detecting prostate cancer.

Materials and Methods: A retrospective analysis of histologically proven benign and malignant prostate diseases, submitted in the histopathology department was performed from April 2019 to March 2020. The diagnostic performance of prostate-specific antigen density was assessed and its optimum cut-off value was determined using the receiver operating characteristic curves. The diagnostic efficacy of prostate-specific antigen density was also compared with prostate-specific antigen in detecting prostate cancer.

Results: The AUC to predict prostate cancer was 0.89 (95% CI 0.79-0.98. p <0.001) for prostate-specific antigen density. The diagnostic performance of prostate-specific antigen density at cut-off 0.18 ng/ml/cc was better than prostate-specific antigen alone (AUC, 0.838 vs 0.662). Sensitivity was 80% for both prostate-specific antigen density at cut-off 0.18 ng/ml/cc and prostate-specific antigen. But, prostate-specific antigen density had a higher specificity of 87.7 % than prostate-specific antigen (52.3%)and thus it could better distinguish benign diseases from prostate cancer. It would have reduced unnecessary biopsy by 35%.

Conclusion: The diagnostic efficacy of prostate-specific antigen density was good and it was found to be a better predictor of prostate cancer at the cut-off value of 0.18ng/ml/cc when compared to prostate-specific antigen alone.

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INTRODUCTION

Prostate cancer is the 5th leading cause of cancer-related death in men.[1] In Nepal, it has been reported to be the third most common cancer in men and its incidence has an increasing trend with a percentage of 47.62 from 1990 to 2017.[2] Serum prostate-specific antigen (PSA) is a widely used tumor marker in screening patients for prostate cancer (PCa) risk.[3,4] The test, however, lacks both the sensitivity and specificity to accurately detect the presence of prostate cancer (PCa)[3,5] PSA can be elevated in various benign conditions such as benign prostatic hypertrophy, prostatitis, etc. apart from prostate carcinoma, and thus can cause significant overtreatment and associated morbidity from

unnecessary biopsies.[6]

This has led to the development of various PSA indices in prostate screening to overcome the limitations of PSA alone, such as free/total PSA ratio, PSA density (PSAD), PSA velocity, prostate cancer antigen 3, prostatic health index (PHI), 4K score test, etc.[7,8] Among these different PSA-related parameters, PSAD is a simple and inexpensive tool in the detection of prostate cancer. Various studies[7,9,10] suggest that PSAD which is the ratio between the PSA value and the prostate volume might increase the specificity of the PSA test avoiding unnecessary biopsy. In Nepal, there are sparse studies that have been published related to the diagnostic role of PSAD in prostate cancer. This study aimed to study the utility of PSAD in detecting prostate carcinoma in comparison to serum PSA alone.

MATERIALS AND METHODS

This is a hospital-based retrospective study. All the prostatic tissues submitted for histopathological examination in the histopathology department of Shree Birendra Hospital, Chhauni, during the period of one year from April 2019 to March 2020 were included for the study purpose. Prostatic tissues with histopathology reports indicating inadequate for evaluation or crushed tissues especially for, transrectal ultrasound-guided needle biopsies were excluded. Clinical data regarding age, digital rectal examination (DRE) findings which were performed prior to biopsy, radiological finding i.e., prostate volume determined by transabdominal ultrasound (TAUS) guided method and prebiopsy serum PSA values were retrieved from record files. Prebiopsy serum PSA values of patients were determined using the CLIA immunoassay method. Histopathological findings were retrieved from the histopathology database. Histopathology slides (hematoxylin and eosin-stained) were retrieved and reviewed for final histological diagnosis.

Benign lesions were diagnosed based on Rosai and Ackerman's Surgical Pathology, 11th edition[11] and NIH guidelines(1999).[3] Diagnostic criteria and grading system for prostate cancer were adapted from WHO the classification of tumours of the urinary system and male genital organs (2016).[12]

Serum PSA value 0-4 ng/ml was considered normal.[7,8,13,14] PSAD was determined, by dividing PSA value by prostate volume. Prostate volume measurement with transrectal ultrasonography is considered superior to the transabdominal ultrasound (TAUS) method. However, Kobayashi et al[15]have suggested the use of TAUS guided measurement of prostate volume if the TRUS method is not feasible, since PSAD determined using TAUS showed a significant difference from PSA. Ethical approval was obtained from Institutional Review Committee, NAIHS.

Statistical analysis was done using Statistical Package for Social Science (SPSS) version 22. The receiver operator characteristics (ROC) curve was used to assess the diagnostic performance of PSAD, and to determine its cut-off value. Statistical significance was considered at p-value < 0.05. The optimum cut-off for PSAD was determined by selecting the highest area under the curve (AUC) provided by ROC analysis with the highest sensitivity and specificity. ROC curve analysis was also applied to compare the diagnostic efficacy of PSA and PSAD in detecting prostate cancer.

RESULTS

Of the total 80 prostate biopsies, which constituted 3.2% of total biopsies during one year study period (80 cases/ 2500 specimens received in the histopathology department), 65

Table 1: Patients' characteristics and the comparison of their mean values

Patient characteristics		No. of cases (%)	Benign (%)	Malignant (%)	p-value
Total no. of cases (%)		80 (100%)	65 (81.25)	15 (18.75)	-
Age (years)	Mean ±SD	-	69.3±7.5	70.9±6.2	0.437
	Range	52-87	52-87	62-86	
	Median	-	69	71	
DRE* finding	DRE positive	21 (26.2)	8 (12.3)	13 (86.7)	<0.001
	DRE negative	59 (73.8)	57 (87.7)	8 (12.3)	
Serum PSA† (ng/ml)	Mean ± SD	-	6.65±7.2	24.06±23.21	<0.001
	Range	-	0.13-0.42	4-100	
	Median	-	4	22	
Prostate volume (cc)	Mean ± SD	-	59.85±15.06	50.39±15.64	0.03
	Range	-	32-113.5	24.3-78	
	Median	-	58	55	
PSAD‡ (ng/ml/cc)	Mean ± SD		0.10±0.1	0.47±0.3	<0.001
	Range		0.003-0.53	0.06-1.2	
	Median		0.06	0.44	

**Digital rectal examination, †Prostate specific antigen, ‡Prostate specific antigen density*

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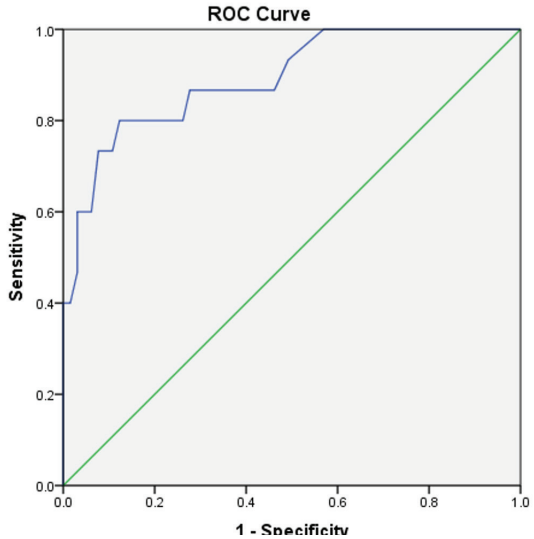

Figure 1: Receiver operator characteristic (ROC) curve demonstrating the diagnostic performance of PSAD (Area under the curve: 0.89; 95% CI 0.79-0.98, p<0.001)

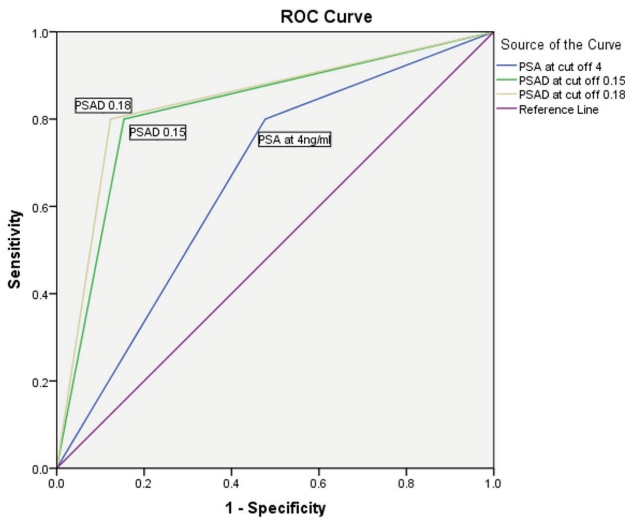

Figure 2: Comparison of diagnostic performance of PSA and PSAD at 0.18 ng/ml/cc and 0.15 ng/ml/cc

Table 2: Prostate cancer histology among the study population (n=80)

Histologic diagnoses	Gleason score	No. of cases (%)
Acinar adenocarcinoma grade group 2	3+4=7	9 (60)
Acinar adenocarcinoma grade group 3	4+3=7	1 (6.6)
Acinar adenocarcinoma grade group 4	4+4=8	1 (6.6)
Acinar adenocarcinoma grade group 5	4+5=9* (1) and 5+4=9† (2)	**3 (20)**
Metastatic adenocarcinoma	-	**1 (6.6)**
Total		**15 (100)**

**Gleason score: 4+5=9, one case; †Gleason score: 5+4=9, two cases*

Table 3: Distribution of PSA value in ranges in benign and malignant prostatic lesions

Serum PSA in range (ng/ml)	Benign lesions n (%)	Malignant lesions n (%)	Total cases N (%)
0-4	34 (52.3)	3 (20)	37 (46.2)
4.1-10	**18 (27.7)**	**0 (0)**	**18 (22.5)**
10.1-20	**10 (15.4)**	**4 (26.7)**	**14 (17.5)**
20.1-30	**2 (3.1)**	**6 (40)**	**8 (10)**
>30	**1 (1.5)**	**2 (13.3)**	**3 (3.8)**
Total	**65 (100)**	**15 (100)**	**80 (100)**

cases (81.25%) were diagnosed as benign and 15 cases (18.75%) were malignant lesions. Benign diseases were most commonly seen presenting in the age range of 60-69 years while prostate cancer (PCa) patients were frequently diagnosed during the 6th to 7th decade of age. Among 80 prostatic biopsies, prostatic tissue obtained via transurethral resection of the prostate (TURP) comprised of 65 samples followed by TRUS guided needle core biopsies accounting for 13 tissue specimens and 2 tissues via retropubic simple prostatectomy methods.

Table 1 presents the patient characteristics and their comparison between benign and malignant prostatic diseases. The patients presenting with prostatic disease ranged from 52 years to 87 years. Histologic type of benign diseases included predominantly benign prostatic hyperplasia (BPH) (64/65 cases) and remaining one was diagnosed as chronic inflammatory lesion. Of 64 cases of BPH, 12 cases were associated with acute inflammation NIH type I (3 cases), chronic inflammation NIH type IV (8 cases)and granulomatous inflammation (1 case). All of the prostate cancer except one (a known case of metastatic rectal adenocarcinoma) were primary acinar adenocarcinoma (14/15 cases). Of 14 cases of acinar adenocarcinoma 9 (60%) were classified as grade group 2 (Table 2).

Table 3. demonstrates the distribution of different serum PSA ranges in benign and malignant prostatic lesions. Benign lesions had serum PSA value mostly in the range of 0-4 ng/ml (n=34, 52.3%) followed by 4.1-10 ng/ml range (n=18, 27.6%). Elevation of PSA >20ng/ml was seen in 3 benign lesions, wherein two cases were BPH without inflammation and one was a chronic inflammatory lesion. Malignant lesions had mostly higher range of PSA value i.e., 20.1-30 ng/ml (n=6, 40%); though three cases had normal PSA value in the range of 0-4 ng/ml and none had intermediate-range PSA value (iPSA) or 4.1-10ng/ml. Metastatic adenocarcinoma also had elevated PSA in the range of 10.1-20 ng/ml.

Figure 1. presents the receiver operator characteristic curve (ROC) for PSAD. The area under the curve (AUC) to predict prostate cancer was 0.89 (95% CI 0.79-0.98. p <0.001) for PSAD.The PSAD cutoff point obtained from ROC curve for diagnosing prostate carcinoma was 0.18ng/ml/cc. At this cutoff, PSAD had a sensitivity of 80% and specificity of 87.7% for detecting prostate carcinoma. PSAD at cut-

off 0.15 ng/ml/cc had a sensitivity of 80%, a specificity of 84.6%.

The comparison of diagnostic efficacy of PSAD at 0.18 and 0.15 and PSA is depicted in figure 2. and Table 4. PSAD at cut off 0.18 ng/ml/cc had maximum AUC (0.838 vs 0.823 vs 0.662) with highest specificity (87.7% vs 84.6% vs 52.3%), highest positive predictive value (60% vs 54.5% vs 28.6%) and lowest false positivity rate (12.3% vs 15.4% vs 47.6%). There was no improvement in sensitivity, which is equal for PSA (80%), and PSAD at 0.18 (80%) and 0.15 (80%). With the reduction in false positivity rate, PSAD could identify a considerable number of benign diseases and would have reduced unnecessary biopsy by 35% (23/65 benign cases) at PSAD cut off 0.18 ng/m/cc when compared to PSA alone.

Of 80 cases, 21 cases (49%) were clinically suspicious for malignancy according to DRE findings, of which 13 cases were proven malignancy by histology with sensitivity and specificity of 86.7% and 87.7% respectively. Among 18 cases of histologic proven benign prostatic diseases in the iPSA range, 17 cases could be detected as benign and one was misinterpreted as malignant by PSAD at both cut-offs 0.18 and 0.15. Whereas DRE could detect only 14 cases as benign among patients with the iPSA range,[4] were misdiagnosed as malignant.

DISCUSSION

Serum PSA is a widely used biomarker for screening prostate cancer. However, it is organ-specific and not prostate cancer-specific, thus having a suboptimal specificity. Various studies have demonstrated that PSAD is useful in discriminating benign from malignant prostate tissue especially when PSA is >4ng/ml, and is informative on decision making for prostate biopsy which helps to reduce morbidity associated with a prostate biopsy.[10,16-20]

The frequency of histologically proven prostate cancer was 18.7% with a predominance of primary acinar adenocarcinoma in concordance with several studies conducted in Asian, African and Western countries and ranged from 14% to 23% including Nepal.[14,21- 24] In most of the studies[21,24-26], the patients presented with PCa in the 7th decade, while we found 6th to 7th decade as the most common age group for cancer presentation. The mean age was not significantly different between benign and PCa patients in our study which was consistent with studies conducted by Kochanska et al.[27] and Lujan et al.[28]. Acinar adenocarcinoma grade group 2 was frequently encountered (60%) and was consistent with a study[29] conducted in a cohort of 992 patients. In contrast, Teoh et al[30] found the highest cases of advanced PCa (41%) with Gleason score [8-10] or grade group 5.

In the present study, prostate carcinoma had raised serum PSA values most commonly encountered in the range of 20.1-30ng/ml (40%, 6/15)in concordance with Mainali et al[26] (33%). Khant et al.[31] and Putra et al.[32] have also reported the highest PCa detection rate in the patients with PSA >20ng/ml. We found benign diseases mostly having low PSA value ≤ 4ng/ml (52.3%, 34/37)inconsistent with similar studies[26,33].All of the prostatic diseases with serum PSA in the range of 4.1-10 ng/ml (iPSA range) had BPH accounting for 22.5% (18/80). Pudasaini et al.[21] and Mainali et al.26alsoobserved 39% and 19.6% of prostatic diseases in the iPSA range, of which 90% and 91% of them, respectively, had benign histology. The fact that PSA is synthesized by prostatic epithelial cells and, any conditions with an increased number of epithelial cells, and pathologic lesions, that will aid in the leakage of PSA, such as inflammation-causing duct disruption and ductal obstruction, as frequently observed in BPH, ultimately would result in elevated serum PSA.[6,34] Therefore, elevated serum PSA may be observed in BPH with or without inflammation beside PCa.

Benson et al[14] stated that PSA alone is not a good predictor of PCa at cut-off 4ng/ml as it fails to distinguish BPH and prostatitis from PCa when PSA is in the intermediate range of 4.1 to 10ng/ml. They developed the concept of PSAD, which is based on the postulation that epithelial cells of normal and benign prostatic diseases would produce PSA which will require a given amount of stromal support (reflected by prostate volume); whereas in PCa, both cellular proliferation and infiltration also affect cell number (PSA)but only minimally affect gland volume.[6] Bretton et al.[19] also have quoted that PSA produced in BPH is 0.3ng/ml per gram of prostate tissue while cancerous tissue produces 10 times that amount. Therefore, small-sized prostate with a minimally elevated PSA level might have prostate cancer and the same value with a large prostate may indicate BPH. So far, several studies have demonstrated the use of PSAD is a good predictor to differentiate BPH and other benign prostatic diseases from PCa.[9,19,29,35,36]

Teoh et al.30 investigated 2606 Chinese patients, and ROC analysis demonstrated an AUC of 0.82 (p<0.001) for PSAD. Similarly, Putra et al32and Sasaki et al37 both found an AUC of 0.84 (p <0.001) for PSAD and concluded it to be a powerful predictor of PCa. Our study also demonstrated that PSAD performance on cancer detection was good which showed an AUC of 0.89 (p <0.001). However, some investigators have criticized the diagnostic role of PSAD as

Table 4: Diagnostic performance of PSA and PSAD at cut off values 0.15 and 0.18 ng/ml/cc

Cut off values	AUC	Sensitivity (%)	Specificity (%)	FP* (%)	FN† (%)	PPV‡ (%)	NPV§ (%)
PSA- 4 ng/ml	0.662	80	52.3	47.6	20	28.6	92.1
PSAD- 0.15 ng/ml/cc	0.823	80	84.6	15.4	20	54.5	94.8
PSAD- 0.18 ng/ml/cc	0.838	80	87.7	12.3	20	60	95

**False positive, †False negative, ‡Positive predictive value, §Negative predictive value*

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a screening tool in determining prostate cancer.[28,34]

There is no consensus yet, upon determining the cut-off value of PSAD in distinguishing benign and malignant prostatic diseases. Benson et al.[14] recommended 0.15ng/ml/ml as a cut-off point to distinguish between benign and malignant prostatic disease in the intermediate PSA range (iPSA) which could avoid 80-85% benign conditions undergoing biopsy. Some investigators have also reported very low PSAD cut-off values for the early cancer detection, such as 0.01, 0.04, 0.05 and 0.07.[17,18,20,38]

According to the literature review of studies conducted among the Asian population, recommendations for PSAD cut-off varied. Teoh et al.30have recommended cut-off of 0.12 ng/ml/ml in Chinese men as a significant predictor of PCa detection since near 95% sensitivity and NPV 92.7% was achieved with OR 6.22 (95 CI 4.2-9.22, p <0.001). However, specificity was only 26.6%. Nath et al.35from Northeast India reported 0.13 PSAD cut off as a predictor for cancer detection in a study conducted in 106 men with a PSA range of 4 to 9.99 ng/ml which gave the highest sensitivity of 90%. Chaudhary et al.39 from India, whereas, demonstrated that a maximum number of prostate cancer patients had the PSAD value >0.15 with a sensitivity of 87.50%, a specificity of 92.59%. We found 0.18 ng/ml/cc as a better predictor of cancer detection which could have helped in sparing 35% of biopsy. It is comparable to a study37conducted in a cohort of 316 Japanese patients, wherein an optimum PSAD of 0.18 was chosen which provided the highest sensitivity (92%) and specificity (54%) at serum PSA level of 4.1 to 10 ng/ml. At this PSAD cut-off, they showed that 51% of biopsy could have been spared and, missing only 9% of PCa.

The variation in optimum PSAD value might be attributed to geographical, racial factors, and physiological differences. Sasaki et al37 state that BPH in the Asian population tends to have predominantly glandular proliferation (related to PSA) and less stromal proliferation (related to prostate volume) and thus affecting PSAD resulting in a higher optimum cut-off value. Study design may also affect the result, as most of the studies for PSAD cut-offs were evaluated in the intermediate PSA range (iPSA), however, we only evaluated in patients with all PSA ranges. In some studies[30,35], the determination of cut-off value was based on the highest sensitivity (≥90%) despite low specificity which could be one of the reasons for divergent PSAD cut-off observed contrary to the present study.

In the current study, the comparison of mean PSA values at cut off value of 4ng/ml between benign and PCa, was significantly different (6.6 vs 24 ng/ml, p <0.001) in consistent with Yusim et al.29Sensitivity for PSA was 80%, but specificity was low (52.3%) with a very high false-positive rate (47.6%) in concordance with studies conducted by Pudasaini et al.21and Mainali et al.[26] in Nepal. The comparison of PSAD and PSA analyzed by ROC demonstrated higher AUC for PSAD at both 0.18and 0.15 than PSA, with remarkable improvement in specificity, PPV, and FP rate, though, there was no increment in sensitivity (Table 4). Benson et al.[6] agree that PSAD improves specificity while maintaining sensitivity, the goal of which, is to detect prostate cancer by immediate biopsy while not exposing the entire benign population to a biopsy that could be misinterpreted as malignant by PSA alone.

In this study, we calculated PSAD value using prostate volume, which was measured via transabdominal ultrasound rather than the TRUS method, which is considered a standard method. This might have affected the overall result when compared to other studies which used TRUS-guided prostate volume estimation. Most of the studies14,19,29,35,37 related to the diagnostic efficacy of PSAD have concluded its use, particularly in the range of intermediate or gray zone for the early detection of cancer so as to decide on biopsy for further management. However, the sample size was also small in our study, therefore, a significant number of cases in the subset of the intermediate zone was not obtained thereby, limiting our study to prove the statistical significance of PSAD in the patients with iPSA range.

CONCLUSIONS

the diagnostic performance was better for PSAD in detecting prostate cancer with remarkable improvement in specificity when compared to PSA. PSAD at cut-off 0.18 ng/ml/cc could be considered a good predictor of prostate cancer and be a useful tool in distinguishing benign from PCa, therefore avoiding a substantial number of unnecessary biopsies. In the future, community-based evaluation of PSAD on a larger scale would be helpful to establish its use as a screening tool in the detection of clinically significant prostate cancer in our population and might assist in decision making of prostate biopsy for cancer detection whenever there is the clinical dilemma in the patients with intermediate PSA range.

Conflict of interest: None

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