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TO ASSESS THE CORRELATION BETWEEN PROSTATE SPECIFIC ANTIGEN DENSITY AND PROSTATE BIOPSY RESULTS OF PATIENTS WITH RAISED PROSTATIC SPECIFIC ANTIGEN LEVELS AT THE KENYATTA NATIONAL HOSPITAL
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TO ASSESS THE CORRELATION BETWEEN PROSTATE SPECIFIC ANTIGEN DENSITY AND PROSTATE BIOPSY RESULTS OF PATIENTS WITH RAISED PROSTATIC SPECIFIC ANTIGEN LEVELS AT THE KENYATTA NATIONAL HOSPITAL

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ABSTRACT

Background: **Prostate cancer remains the most common cancer among Kenyan men accounting for 17.3% of all cancers countrywide. Prostate Specific Antigen Density (PSAD) is a value used to diagnose prostate cancer. No ideal PSAD has been established due to the biological differences across populations.**

Objective: **To determine the utility of PSAD to predict prostate cancer in patients with PSA >4ng/ml.**

Methodology: **The study was a prospective cross-sectional study. 77 patients at Kenyatta National Hospital with PSA levels of >4ng/ml or suspicious digital rectal examination were enrolled. Thereafter, PSA levels were tested and PSAD calculated. Prostate biopsies were then taken by finger guided or trans-rectal ultrasound guided methods. The data collected was uploaded into the Statistical Package for Social Sciences (SPSS) software and analysed.**

Results: **The average age was 69.5years. The average PSA was 94.9 ng/ml with a median of 18 ng/ml. The average prostate volume was 89.8 cc. PSAD results showed that 64.9% had PSAD values of >=0.15 , while 35.1% had <0.15. Biopsy results showed 53.2% of the patients had prostate adenocarcinoma, 39% had benign prostatic hyperplasia alone while 6 (7.8%) had benign prostatic hyperplasia with prostatitis. A PSAD of 0.23 had a sensitivity of 82.9% with a specificity of 22.2%.**

Conclusion: **A PSAD of 0.23 can be used as a cut-off value to predict prostate cancer when evaluating patients with raised PSA in our population.**

Recommendation: **A PSA density of 0.23 should be adopted as the cut-off value for screening patients for Prostate cancer in our population.**

INTRODUCTION

Prostate cancer is the most common cancer among men in Kenya with an incidence of 17 per 100, 000 and accounts for 17.3% of all cancers in the country with most cases affecting males above 65year (1). Early detection of cancers, by use of reliable biomarkers, is ideal for the best chance of cure or decreased morbidity and mortality (2). Prostate Specific Antigen (PSA) has, over time, been used as a reliable biomarker for early diagnosis of prostate cancer. In the case of prostate cancer, several biomarkers have been discovered over the years to enhance the accuracy of diagnosis. Also known as Human Kallikrein 3, PSA is a 34kD, detected in prostatic fluid and serum, is a protein (serine protease), produced by the prostate gland.

The PSA is secreted as pre-pro-PSA, metabolized into pro-PSA and finally converted to PSA. The body secretes PSA into the seminal fluid, whose role is to liquefy the seminal coagulum. It exists in two forms: bound and unbound/free; the two forms constitute total PSA. The bound form is majorly bound to alpha-1 antichymotrypsin (ACT – a serine protease inhibitor) and has a half-life of 4-5 days. It is also bound to alpha-2 macroglobulin whose half-life is also 4-5 days. The PSA levels are raised in prostatic diseases including inflammatory, benign prostatic enlargement and in cases of prostate cancer. It is said to be organ specific but not cancer specific.

Normal PSA levels are generally 0-4ng/ml for men below 65yrs although slight variations between ethnic groups and age groups (3)(4). Additionally, the prostate size differs from race to race, translating to lower among some Asian races than Caucasians. (5) Patients with elevated PSA need further evaluation through biopsy of the prostate gland to rule out malignancy.

Prostate biopsies however are not without complications and risks. In a systematic review done by Loeb et al., some of the complications associated with prostate biopsy included haematuria (10–84%), rectal bleeding (1.3% and 45%), haemospermia (1.1–93%), infection, pain, erectile dysfunction, and occasionally, death (4). Locally, the most common complications of prostate biopsies were haematochezia at 31.9%, followed by UTI at 15.3%, haematuria at 12.5% and orchitis at 2.8% (6).

One of the less invasive modalities used to diagnose prostate cancer is PSAD. The PSAD is a derivative of PSA which helps distinguish between benign prostate disease and malignancy. To establish this, the prostate volume is assessed using trans-rectal ultrasound and the PSAD measured by dividing the PSA levels with Prostatic Volume. PSAD has been shown to be more sensitive in predicting prostate cancer than PSA alone (8). Although no consensus has been arrived for the cut off value for PSAD in predicting prostatic cancer, some researchers have set the cut-off point to 0.15 (9). This study therefore aimed at assessing the optimal cut-off point for PSAD levels that could predict the development of prostate cancer by comparing with the gold standard, histology.

Study Objectives

General Objective: The primary objective was to establish the correlation between prostate biopsy results with Prostate Specific Antigen density of patients with raised Prostate Specific Antigen at Kenyatta National Hospital.

Specific Objectives:

a) Assess the PSAD of patients with raised PSA at KNH.
b) Document prostate biopsy results of patients with raised PSA at KNH.
c) Correlate the PSAD and prostate biopsy results.
d) Determine the PSAD of 0.15 suitability as cut-off for Prostate cancer diagnosis for patients.

MATERIALS AND METHODS

This study adopted a cross sectional design where participants were enrolled from the patients attending the Urology Clinics, Interventional Radiology clinics, and the in-patient wards at Kenyatta National Hospital between May to June 2019. The KNH is a teaching hospital for the University of Nairobi, Faculty of Medicine and visiting students from other institutions. The hospital offers comprehensive speciality services including surgical and obstetrics and gynaecology departments.

The sample size of 74 participants was calculated using Krejcie's formula, considering a power of 80%, confidence interval of 95% and margin of error of 5%. Following ethical approval to conduct the study by the Kenyatta National Hospital – University of Nairobi Ethical Research Committee, sequential sampling of eligible patients was done. Eligible patients who consented to participate in the study were enrolled and subjected to an interviewer guided questionnaire.

Furthermore, the participants had their blood samples taken for assessing the PSA levels, had the prostate ultrasound done to assess the prostatic volume. A digital rectal examination as done on all participants and those with abnormal findings had a prostate biopsy done either digitally or using a 12 core transrectal prostatic biopsy, taken for histopathology. Patients with clinical symptoms or diagnosis of urinary tract infection (UTI), those who had previous prostate surgery, hormonal treatment, on alpha blockers or 5Alpha Reductase Inhibitors, radiation therapy were excluded from the study. Quality control was ensured using the Elecsys PreciControl Tumour marker 1 and 2 while PreciControl Tumor Marker was used for quality control of Elecsys immunoassays on Elecsys immunoassay systems.

The collected samples were taken to the KNH histology laboratory for processing and analysis by a trained consultant pathologists or senior house officer in pathology and the PSA levels assessed in the KNH biochemistry laboratory. All the laboratory results were counter checked and documented in the patients' questionnaires.

The collected data was cleaned and uploaded into the SPSS version 23 software for coding and analysis. Socio demographic characteristics of the study participants was analysed and presented as proportions. The values of the continuous variables such as PSA levels and age were analysed and presented as means +/- Standard deviation. Sensitivity and specificity, positive and negative predictive values of various PSADs was determined. Further analysis to establish the best cut off point for the PSAD test, taking prostate biopsy results as the standard diagnostic test was done using Receiver operating characteristic curves to estimate the sensitivity of different PSAD categories in predicting prostate cancer.

RESULTS

During the study period, 74 participants were evaluated and analysed. The mean age of the participants was 69.7 (SD=10.7) years, with majority of the patients belonging to the 65-74 age bracket (42.9%). For the IPSS score, 37 (48.1%) had a moderate score, 30 (39.0%) had severe, while 10 (13.0%) had mild score. The prostate exam had 47 (61.0%) with a firm prostate, 28 (36.4%) had a hard prostate, while 2 (2.6%) had a soft prostate.

Table 1

Patient and Clinical Characteristics of the Study Participants

	Frequency (n=77)	Percent (%)
Age		
45-54	7	9.1
55-64	14	18.2
65-74	33	42.9
75-84	18	23.4
85-94	5	6.5
IPSS Score		
Mild	10	13.0
Moderate	37	48.1
Severe	30	39.0
Prostate exam		
Soft	2	2.6
Firm	47	61.0
Hard	28	36.4

The overall mean PSA level was 94.9 (SD=415.14), while the median PSA level was 18 (IQR=44.9). The minimum value was 0.78 while the maximum was 3,514. For those with a positive biopsy result, the mean PSA value was 166.7 (SD=562.1), while those with negative biopsy result had a mean PSA value of 13.1 (SD=14.3). For the prostate volume the mean value was 89.8 (SD=75.5), while the median value was 73.0 (IQR=49.0). The minimum volume was 21.0 and maximum was 464.0. Fifty (64.9%) had PSAD values of 0.15 and above, while the 27 (35.1%) had below 0.15.

Table 2

Prostate Specific Antigen Density

	Frequency (n=77)	**Percent (%)**
Less than 0.15	27	35.1
0.15 and above	50	64.9

Out of the 77 patients who underwent prostatic biopsy, 41 (53.2%) had prostate adenocarcinoma, 30 (39.0%) had a benign prostatic hyperplasia, while 6 (7.8%) had a benign prostatic hyperplasia and prostatitis. A correlation There were significant differences between the ≥0.15 and <0.15 for the benign prostatic hyperplasia ($p<0.001$), which was also the case for the prostate adenocarcinoma ($p<0.001$), but no statistical difference was detected for those with benign prostatic hyperplasia and prostatitis ($p<1.000$).

Table 3

Prostate Biopsy Results

	Frequency (n=77)	Percent (%)
Benign Prostatic Hyperplasia	30	39.0
Prostate Adenocarcinoma	41	53.2
Benign Prostatic Hyperplasia and Prostatitis	6	7.8

The value for area under the curve (AUC) for PSAD is excellent (0.847), indicating that the cut off value of 0.233 is good for evaluation of patients at risk of prostate cancer. The value of the area under the curve (AUC) has achieved statistical

significance with p-value < 0.005, which means it has a favourable sensitivity and specificity characteristics.

DISCUSSION

Though widely used as a screening tool for prostate cancer, the PSA levels at 4 ng/ml has an approximate sensitivity of 67.5-80% and a specificity of values above 4ng/ml of 60-70%. Other derivatives of PSA such as free to total PSA ratios (f/t PSA), PSA velocity, PSA doubling times and PSA density have therefore been used to improve on the sensitivity and specificity.

In this study the mean age for the 77 participants was 69.7years (SD=10.7) with a majority, (approximately 50%) within the 65-74 years age bracket. This is in keeping with the average age of patients who develop prostate disease (both benign and malignant) (24). Thirty-seven of the participants (48.1%) had a moderate IPSS score, 30 (39.0%) had severe, while 10 (13.0%) had mild score.

On DRE, 47 (61.0%) had a firm prostate, 28 (36.4%) had a hard prostate, while 2 (2.6%) had a soft prostate. According to clinical practice a firm prostate on exam correlates with BPH while a hard prostate is common in prostate cancer patients. When compared with biopsy results, those who had firm prostate were found to be statistically significantly different in respect to the other groups (p=0.001), this was also the case for patients with hard prostates (p=0.001). The Soft examination finding, age and IPSS was not statistically significantly different.

The PSA levels for the patients in the study was ranging from a minimum value of 0.78 ng/ml while the maximum was 3,514 ng/ml. The overall mean PSA level was 94.9 ng/ml while the median PSA level was 18 ng/ml. This shows that our patients usually present with high PSA results warranting intervention.

Several studies have shown that very high levels of PSA (>50) has a greater than 90% predictive value in diagnosing Prostate cancer. Yang and colleagues concluded in their study that PSA > 100ng/ml had a 100% predictive value in diagnosing Prostate cancer (25)

For those with a positive biopsy result for prostate cancer, the mean PSA value was 166.7ng/ml. The mean PSA value for patients with benign disease was 13ng/ml. This is indicative of the fact that our population may have higher PSA values even in benign disease.

The Prostate volumes of patients enrolled in our study ranged from 21.0 cc to 464.0cc with a mean value of 89.8 cc while the median value was 73.0cc. This is indicative of larger prostates than the average population. The PSAD results show that 50 patients (64.9%) had PSAD values of 0.15 and above, while the 27 (35.1%) had below 0.15.

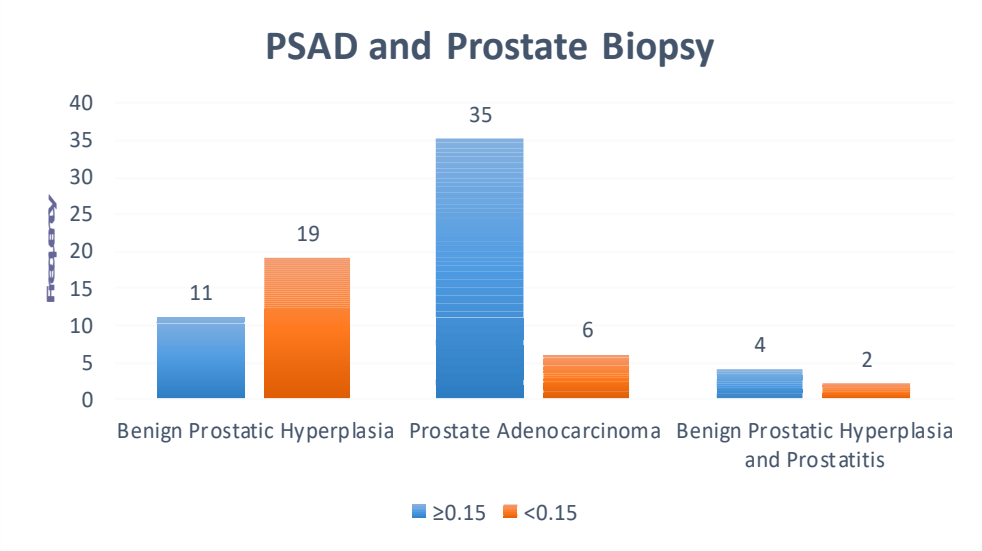


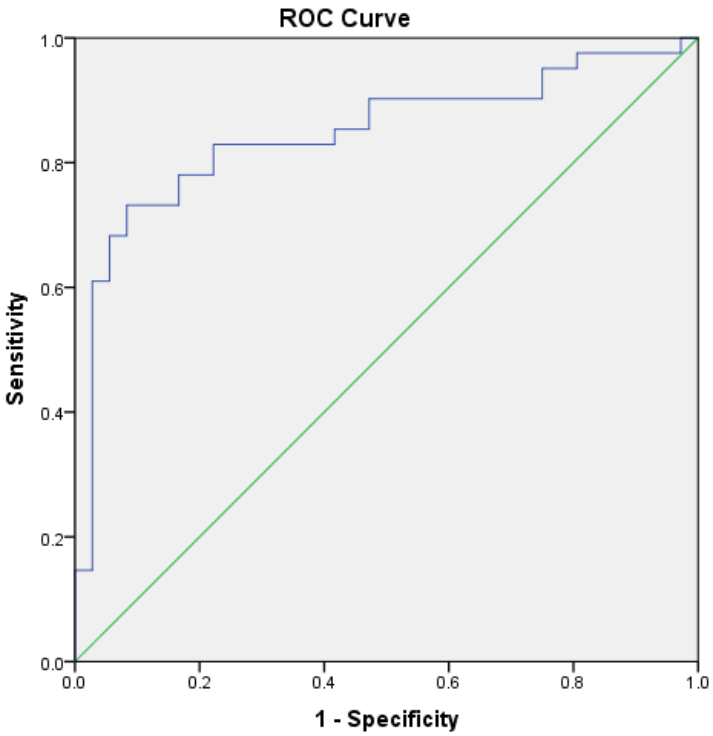
Figure 1: Comparison between PSAD and Histology Results

As for biopsy results out of the 77 patients, 41 (53.2%) of the patients had prostate adenocarcinoma, 30 (39.0%) had benign prostatic hyperplasia, 6 (7.8%) had benign prostatic hyperplasia and prostatitis. This indicates that the PSAD of 0.15 did not capture Prostate cancer in about 9 patients out of the 77. It was also noted that none of the patients were diagnosed with Prostatic Intraepithelial Neoplasia (PIN). This may indicate that PIN is a rare occurrence in our population.

Of the patients with prostate cancer, group 5 had the highest percentage of Gleason score t 35.6%. This shows that of the patients with adenocarcinoma of the prostate that present at the KNH, most patients have poorly differentiated, more aggressive tumours. The second most common group was Gleason group 2 (19.5%) followed by Groups 3 and 4(17.1% each) while the least common group is Gleason group 1(9.8%).

When comparing the PSAD and the biopsy results there were significant differences between the ≥0.15 and <0.15 for the benign prostatic hyperplasia ($p<0.001$), which was also the case for the prostate adenocarcinoma ($p<0.001$), but no statistical difference was detected for those with benign prostatic hyperplasia and prostatitis ($p<1.000$). This indicates a positive correlation between PSAD levels and prostate biopsy results. It was noted that more patients with adenocarcinoma had PSAD > than 0.15 while more patients with PSAD <0.15 had BPH.

For the PSAD cut-off the value with the highest specificity and sensitivity would be ideal. In our study the value with the highest sensitivity and specificity was found to be 0.23 with a sensitivity and specificity of 82.9% and 22.2% respectively. Thus, in our population a PSAD of >0.23 was more likely to be positive for prostate cancer.



Area Under the Curve					
Test Result Variable(s)	Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
PSAD value	.847	.047	.000	.755	.938

Figure 2: Receiver Operating Curve for PSAD and Histology Results

This value is close to but not the same as the cut-off recommended by Benson et al.(5) (19), in a study done the USA, where a cut-off of 0.15 was arrived at. The discrepancy may be attributed to the variation in size and PSA levels in the two populations.

CONCLUSION

The PSAD cut-off for our population is slightly higher than other populations. It was found to be at 0.23. The value for PSAD that we established as the cut-off to predict Prostate cancer can be used for screening.

RECOMMENDATIONS

A PSA density of 0.23 should be adopted as the cut-off value for screening patients for Prostate cancer in our setup. This would help to reduce the number of unnecessary biopsies.

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