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Comparison of Serum Microseminoprotein-Beta (MSMB) with Total Prostate Specific Antigen (TPSA) in the Diagnosis of Prostate Cancer in African Men

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Abstract:-

➢ ***Background***

The burden of prostate cancer is high globally and especially among men of African descent. Serum prostate specific antigen(PSA) has long been used for diagnosis,however,its low specificity and indiscriminate use has led to unnecessary biopsies,over-diagnosis and over treatment of apparently indolent tumours.This weakness of PSA as a biomarker for cancer prostate has necessitated the search and identification of an alternative to it.

➢ ***Aim***

To compare the sensitivity, specificity, positive predictive value, and negative predictive value of serum Microseminoprotein-beta(MSMB) with serum total prostate specific antigen (tPSA) in the diagnosis of prostate cancer in African men.

➢ ***Materials and Methods:***

This is a 12-month prospective study of patients aged 50 years and above with lower urinary tract symptoms (LUTS), PSA greater than 4ng/ml and/or abnormal digital rectal examination, leading to the suspicion of prostate cancer. Patients with a histological diagnosis of prostate cancer formed the study group while those with negative biopsy/benign prostatic hyperplasia on histology served as the control group.All had detailed history and focused examination with serum levels of Microseminoprotein-beta(MSMB) and total PSA (tPSA) determined using Enzyme-linked immunosorbent assay methods. Data were analyzed using SPSS version 20.0 for windows.

➢ ***Results***

The mean age of patients with prostate cancer and those with benign prostatic hyperplasia (BPH)/negative biopsy was 67.40 ± 9.08 and 65.43 ± 9.68 years, with an age range of 50-91 and 50-89 years, respectively. Compared to MSMB, tPSA had a higher sensitivity (82.5 vs 57.5%), specificity (77.5 vs 30.0%), PPV (78.6 vs 45.1), NPV (81.6 vs 41.4%) and diagnostic accuracy (80.6 vs 43.8%).

➢ ***Conclusion***

Serum total PSA had a higher validity than serum MSMB in diagnosing prostate cancer. Hence, tPSA remains a relevant serum tumour biomarker in diagnosing prostate cancer in our urological practice.

Keywords:- *Prostate Cancer, Microseminoprotein-Beta, Total Prostate-Specific Antigen, Sensitivity, Specificity, Diagnostic Accuracy.*

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I. INTRODUCTION

Prostate cancer ranks the second most common malignancy in men, and the fourth most common cancer in both males, and females worldwide and estimates show that about 1.1 million men were diagnosed with this cancer in 2012, thus accounting for 15% of the cancers in men and 70% of the diagnoses were made in developing nations.[1]

The incidence of prostate cancer varies worldwide, with the highest rates found in developed countries. This is primarily due to the widespread practice of routine prostate specific antigen screening tests and subsequent prostate biopsy in those with PSA elevation; however, the mortality from this disease is higher among people of African descent in those countries.[2] Contrary to reports from the literature on the global rankings by the World Health Organization (WHO), several studies indicate a higher incidence of prostate cancer in Nigerian men.[3]

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Early diagnosis of prostate cancer and appropriate intervention is associated with a low mortality rate. However, the aforementioned is contrary to what is obtained in developing countries like Nigeria.[4, 5]

Prostate biopsy and histology have remained the gold standard for diagnosing prostate cancer with associated invasiveness and resultant complications. Those mentioned above necessitated the use of biomarkers elaborated in the body in response to the presence of the disease, which plays a role in the early diagnosis of prostate cancer. The advantages of using blood or urine assayed biomarkers in the diagnosis of the Prostate include their accessible collection, minimal invasiveness, and absence of significant complications.[6]

Prostate-specific antigen is a serine protease, a member of the human kallikrein family, secreted into the seminal fluid as a product of both normal and cancerous prostate tissue whose physiologic function is the liquefaction of seminal ejaculate from its gel form.[7] Disruption of the prostate architecture that occurs in BPH, cancer, prostatitis, and prostatic manipulations following a massage, trauma, biopsy, or transurethral resection allows PSA to enter the circulation, thus causing its elevations in the disease as mentioned in the above conditions.[7] To increase the accuracy of PSA in the detection of prostate cancer, several isoforms of the molecules are utilized.[8, 9]

Despite the introduction of isoforms aimed at improving the performance of Prostate-Specific Antigen as a diagnostic tool in prostate cancer, it is still faced with many challenges. These challenges include missed diagnosis, inability to differentiate prostate cancer from benign prostatic hyperplasia, and aggressive from non-aggressive cancers, thus resulting in a poorly defined threshold for prostate biopsy.[10]

The need for a potential more disease-specific, non-invasive biomarker with an advantage over serum Prostate specific antigen necessitated the choice of Microseminoprotein-beta. Microseminoprotein-beta also referred to as prostate secretory protein, is one of the most highly secreted proteins from the prostate gland and whose expression is usually lost in prostate cancer. MSMB may be a putative biomarker for prostate cancer risk, diagnosis and prognosis.[11-13] Circulating levels of MSMB positively correlate with that of PSA both in BPH and prostate cancer[14] correlating with both free and total Prostate specific antigen levels.[11, 14] Strikingly, in contrast to PSA, the levels of MSMB measured in urine, serum, and prostate tissue are significantly lower in men with prostate cancer.[15, 16]

The objective of this study was to compare the value of a new serum biomarker, microseminoprotein-beta (MSMB), to total prostate-specific antigen (tPSA) in the diagnosis of prostate cancer in African men who underwent prostate biopsy.

II. MATERIALS AND METHODS

This prospective study was carried out between March 2019 and April 2020 at the Urology unit of [BLINDED FOR PEER REVIEW]. Approval for the study was received from the Health Research and Ethics Committee of the [BLINDED FOR PEER REVIEW] and the study was carried out according to the 1964 Helsinki declaration as amended in 2000.[17]

Consecutive patients aged 50 years and above with lower urinary symptoms (LUTS), elevated PSA, an abnormal digital rectal examination (DRE) finding, and an abnormal finding on TRUS/transabdominal scan or who had been diagnosed with Prostate cancer but were yet to start treatment were included in the study. The exclusion criteria included patients who had: a digital rectal examination in less than a week, a biopsy of the Prostate in less than three weeks, urethral instrumentation such as urethrocystoscopy or removal of stones from the urethra or urinary bladder in less than three weeks, BPH or prostate cancer subjects who had been commenced on medications such as 5α-reductase inhibitors and hormonal or radiation therapy, previous prostatectomy for benign prostatic hyperplasia or radical prostatectomy for prostate cancer and patients who refused consent to participate in the study.

All patients had a transrectal ultrasound (TRUS) guided biopsy of the Prostate using the Mindray Digi/prince®(DP-6600)-Germany 2007/2008 at a frequency of 6.5MHz and an 18 gauge,20cm long needle under local instillation of Xylocaine jelly. Twelve cores were taken from the prostate in all patients and samples were sent for histology in 10% formalin.

The biopsy samples were grossed, processed and embedded in wax. The tissues were cut into 5mm sections and stained with haematoxylin and Eosin (H&E). Slides were prepared and examined under the microscope by the consultant histopathologist for tissue diagnosis, and the Gleason grade of the malignant histology was determined.[18]

- *Serum Microseminoprotein-Beta (MSMB) assay procedure*

Under the aseptic condition, 4mls of the venous blood sample was collected from the upper extremity and put into plain venipuncture tubes without additives and anticoagulants. The serum required for Microseminoprotein-beta (MSMB) assay and total PSA was from this whole blood sample. The entire blood sample was kept in a serum separator tube and allowed to clot for two hours at room temperature before centrifugation for 15 minutes at 1000 revolutions per minute(rpm)—the serum was stored at -10ºC or lower as the analyses were done at a later date. The repeated freeze-thaw cycle was avoided. 0.1 ml of serum is required per determination.

➢ *Principle of the assay*

The assay for serum microseminoprotein-beta(MSMB) and total PSA(tPSA) was done using the enzyme-linked immunosorbent assay (ELISA) method based on the manufacturer's (PARS BIOCHEM-Nanjing, China, Catalogue NO.PRS-02685hu) and Monobind Inc- AccuBind ELISA Microwells Product Code:2125-300 instruction respectively.The ELISA kit assays the Human MSMB level in the serum sample, using purified Human MSMB antibody (provided by the manufacturers) to coat microtiter plate wells, making a solid-phase antibody, and then the MSMB is added to the wells. In combination with MSMB antibody alongside Horseradish peroxidase (HRP) labelled to become an antibody-antigen-enzyme-antibody complex. After washing this complex completely, 3,3',5,5'-Tetramethylbenzidine(TMB) chromogenic substrate solution is added resulting in a blue-coloured solution. Once the resultant solution is enzyme-catalyzed, the reaction is terminated by the addition of a sulphuric acid solution with the resultant colour change spectrophotometrically measured at a wavelength of 450nm. The concentration of MSMB in the samples was then determined by comparison of the optical densities of the samples to the standard curve.

➢ *Sample size estimation*

The sample size calculation for the comparative prospective cross-sectional study[19] is as follows:

$$n = \frac{\left[Z_{1-\alpha/2}\sqrt{P_0(1-P_0)} + Z_{\beta}\sqrt{P_1(1-P_1)}\right]^2}{(P_1 - P_0)^2}$$

- Z1-α/2 = percentage point of the normal distribution corresponding to the required (two-sided) significance level (α) of 0.05 = 1.96.
- Zβ = one sided percentage point of the normal distribution corresponding to 100% -the power, example if power = 80% (100% - power) = 20% (i.e. p value of 0.2) = 0.84
- P_0 = Null hypothesis proportion (i.e. no increase expected, which means that the proportion will remain as previously obtained i.e.sensitivity of prostate specific antigen from the previous study, 89.8%.[20, 21]=0.898
- P_1 = Alternative hypothesis proportion = 89.8% baseline + 10% increase = 99.8% = 0.998
- $P_1 - P_0$ = The difference (i.e. expected increase in the proportion of microseminoprotein -beta, new biomarker in the diagnosis of CaP) = 0.998– 0.898 = 0.1

$$n = \frac{\left[1.96 \times \sqrt{0.898(1-0.898)} + 0.84\sqrt{0.998(1-0.998)}\right]^2}{(0.998 - 0.898)^2}$$

$n = 32.67 \approx 33$ *patients or subjects.*

The sample size includes attrition of 20% {that is 6.30 approximately 7}. The minimum sample size for this research was forty(40). Out of the eighty patients(80) recruited, forty(40) patients returned with adenocarcinoma of the prostate on histology while the remaining forty(40) patients had a negative biopsy. All the patients had TRUS-guided biopsy of the prostate.

➢ *Data collection*

Relevant data were collected through a semi-structured proforma, which included clinical features and risk factors for prostate cancer, results of appropriate investigations, transrectal ultrasound (TRUSS) findings, and the results of histology, serum total PSA and MSMB assay.

➢ *Data analysis*

Data analysis was done using the Statistical Package for the Social Sciences (IBM SPSS) for Windows, Version 20.0. Armonk, NY: IBM Corp, 2011. Frequency distribution tables were drawn for categorical variables. Continuous variables such as age, serum total PSA, serum MSMB, prostate volume, mean, and standard deviation were calculated. The sensitivity, specificity, PPV, and NPV for serum microseminoprotein-beta (MSMB) and total Prostate Specific Antigen (tPSA) in the study were computed. The diagnostic power of PSA versus MSMB was assessed using positive and negative predictive values (PPVs, NPVs). The mean between the two groups was compared using an independent t-test. The relationship between the two groups (cancer prostate and negative histology) and levels of tumour markers (normal or elevated) were determined using Pearson's Chi-square tests or Fisher's exact test where appropriate. The receiver operating characteristic(ROC) curve was used to calculate the optimal cut-off value for MSMB with the highest sensitivity and specificity. The level of significance was set as $p < 0.05$ at a 95% confidence interval(95% CI).

The differences between serum MSMB and total prostate-specific antigen (tPSA) in the diagnosis of prostate cancer were determined using the Students' t-test. The significance level was set at $p < 0.05$ at a 95% confidence interval (95% CI).

III. RESULTS

A total number of eighty patients participated in the study, with forty each in the study group (patients with histological diagnosis of prostate cancer) and negative biopsy group. The peak age incidence in the CaP group was in the 8th decade (71-80 years). Similarly, patients' age range in the negative biopsy group was from 50 to 99 years, with a mean of 65.43 (± 9.68 years). There was a statistically significant difference in the age distribution of both groups($p<0.05$). The socio-demographic characteristics of the patients are shown in Table 1 below.

The patients presented with one or more obstructive, irritative, or a combination of lower urinary tract symptoms(LUTS) however among the patients in the CaP group, 30(75.0%) had LUTS and 10(25.0%) had no LUTS as compared to the negative biopsy group {34(85.0%) and 6(15.0%} respectively. ($p>0.005$).

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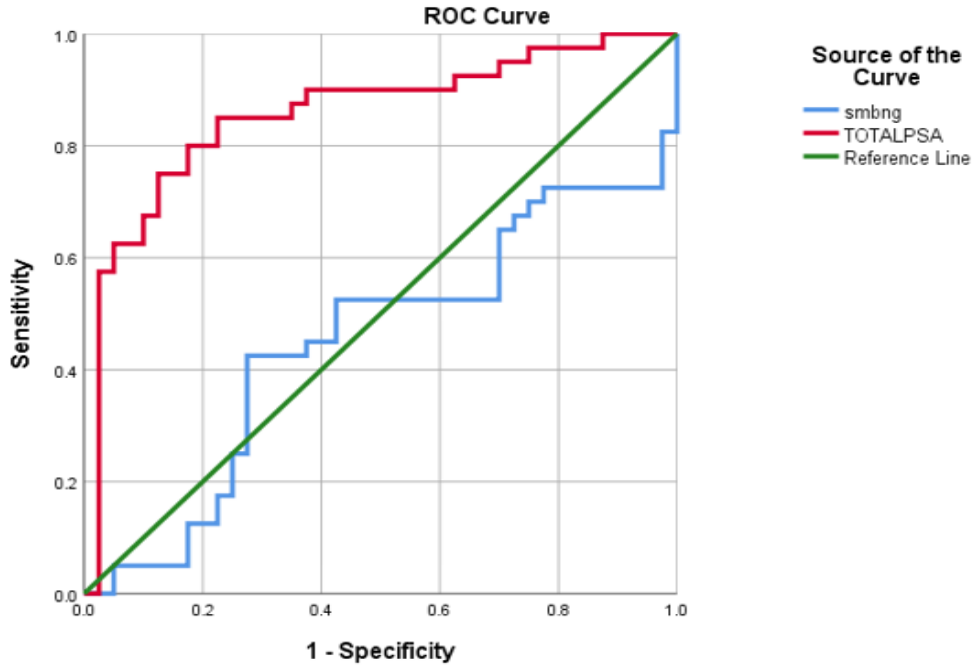
Table 1: Socio-demographic, clinical and histopathological characteristics of the study population

Variables	Prostate Cancer	Negative Biopsy	p-value
	Group n=40(%)	n=40(%)	
Mean± SD	69.38±8.08	65.43±9.68	**0.051**
Family History of Prostate Cancer			
Negative	4(10)	11(27.5)	0.898
Positive	2(5.0)	2(5.00	
Unaware	34(85.0)	27(67.5)	
Digital rectal examination Findings			
Benign	4(10.0)	22(53.8)	<0.001
Suspicious	36(90.0)	18(46.2)	
Serum biomarkers			
Total PSA(ng/mL)	82.93±35.02	28.85±30.92	<0.001*
MSMB (pg/ml)	20.72±21.99	21.96±31.91	0.839



AUC: MSMB =0.449 Total PSA= 0.859

Fig 1: Receiver Operating Characteristic (ROC) Curve of MSMB and PSA in the detection of prostate cancer.

Table 2: Comparison of the sensitivity, specificity, and predictive values of serum MSMB and total PSA.

Serum Biomarkers	Sensitivity	Specificity	PPV	NPV	DOR	DA	YI
PSA(4ng/mL).	100.0	7.5	51.9	100.0	1.5	54.0	0.08
MSMB(15pg/mL)	57.5	30.0	45.1	41.4	5.9	43.8	-0.13

CI: 95% confidence interval, **NPV**: Negative predictive values, **PPV**: Positive predictive values, **DOR**: Diagnostic odds Ratio, **DA**: Diagnostic accuracy. **YI**: Youden's index.

IV. DISCUSSION

This study compares a new serum tumour marker Microseminoprotein-beta (MSMB), to a known serum tumour marker, total Prostate-Specific antigen(tPSA), in diagnosing prostate cancer patients at a Nigerian tertiary hospital. In this study, the mean age and standard deviation of all the patients that were subjected to prostate biopsy on account of elevated PSA and abnormal digital rectal findings were 67.40 ± 9.08 years, corresponding to the age bracket of diseases of the Prostate as revealed in previous studies in our region.[22, 23] Though the mean age and standard deviation of negative biopsy (benign prostatic disease) and adenocarcinoma of the prostate patients were 65.43 ± 9.68 and 69.38 ± 8.08 years respectively being comparable to a similar study done in South-western Nigeria.[23, 24] There was no statistically significant difference between the mean age of the two groups studied (negative prostate biopsy and adenocarcinoma prostate group) (p=0.05). The detection of prostate cancer at a late age remains a typical presentation of prostate cancer in our environment and most African nations, most probably due to ignorance, poor access to urologic specialist care as well as the near absence of any form of screening protocol.[4, 5] The implication of the uniform presentation of both benign and malignant diseases of the Prostate in this study is that the age at presentation of prostate diseases in our environment may not be as a helpful tool in excluding prostate cancer in subjects with lower urinary symptoms coming to our practice.

Socio-demographic characterization of patients within the prostate cancer and negative biopsy groups, when compared, showed no statistically significant difference.

Patients presenting with suspicious findings were more likely to have a histopathological diagnosis of prostate cancer. Most of the patients in the CaP group had suspicious DRE findings ($p<0.001$), giving a cancer detection rate of 90% when compared to studies by Lee et al. in Seoul, South Korea and Cooner with a detection rate of 43.8% and 32.6% respectively. Thus the value in this study was higher than in previous studies. Although 46.2% of the patients in the negative biopsy group had suspicious findings on DRE, a previous study had explained similar occurrences with a significant proportion of patients with DRE findings suggestive of malignancy turning out to be negative for malignancy after histological evaluation.[25]

This suggests that DRE still plays a vital role in the diagnostic workup of patients with CaP. Digital rectal examination remains a handy tool for urologists, especially in most of Sub-Saharan Africa, where there are no organized screening programs or advanced diagnostic tools. Most patients present late to the hospital with progressive disease.

The mean serum concentration of MSMB in this study was lower in the Prostate cancer group than in the negative biopsy group otherwise no differences. The lower serum levels of MSMB noted in this study are likely due to a reduction in expression and the consequent lower serum level of MSMB in prostate cancer, as reported by other authors working among multi-ethnic, multi-racial populations.[15] A recent study involving 1,212 men with 49.2% having prostate cancer using the ELISA method revealed significantly lower values in the prostate cancer group than in the negative biopsy group.[26] The explanation behind lower MSMB levels among patients with prostate cancer remains unknown. However, its role as a tumour marker or risk factor for developing prostate cancer remains unclear.[26] The relationship between mRNA expression and dysplasia of the prostate cancer cells as observed in rat models may be responsible for observing that higher-grade cancers have lower MSMB levels.[26] MSMB transcription is downregulated in prostate cancer cells, while those prostate cancer cells that maintain MSMB expression tend to be well differentiated though aggressive.[26]

In this study, the difference in serum MSMB level between the prostate cancer group and negative biopsy groups was not statistically significant, suggesting the inability of serum MSMB to clearly distinguish patients with prostate cancer from those with benign lesions.

In this study, at a cut-off value of 4ng/mL and 32.02 ng/mL, respectively, for Serum total PSA in the prostate cancer group, the PPV and NPV were (52% and 100%) and (78.6% and 81.6%, respectively. Studies amongst Chinese men by Teoh et al. [27] showed a PPV and NPV of 28.6% and 89.0%, respectively, at a PSA cut-off value of 4.0ng/mL, which was lower than the results from our index study. However, the highest cut-off value from the same study for PSA was 7.0ng/mL with a PPV and NPV of 38.0% and 86.6%, respectively, showing no significant difference. A similar study by Heyns et al. from Cape Town revealed a PPV and NPV of 90% and 74% at a PSA cut-off value of ≥ 30ng/mL, which is slightly higher regarding the PPV compared to our study a lower NPV. This implies that in a selected cohort of patients, a very high level of serum total PSA may serve as a surrogate marker for the histological diagnosis of prostate cancer. This may further exclude the costs and morbidity that may be associated with prostate biopsy in such groups of patients bearing in mind the populace and the socioeconomic status of our patients.[28]

The sensitivity, specificity, PPV, NPV, and Area under the curve (AUC) for serum MSMB in the diagnosis of prostate cancer in our population was 58%, 30%, 45%,41%, and 0.449, respectively, at a cut-off value of 15pg/ml from the receiver operating characteristic (ROC) for MSMB in the study. Following a vigorous search, no similar study determined the above parameters concerning serum MSMB however, similar research by Flatley et al. [29] used urine MSMB against serum. In their study, the AUC of urine MSMB and total PSA were 0.700 and 0.650, respectively, yielding a sensitivity and specificity of

10% and 95-100%, respectively for urine MSMB, 28% and 100% for total PSA.

The effectiveness of serum MSMB and total PSA in the diagnosis of prostate cancer was determined using the ROC curve. Using AUC, the diagnostic accuracy for prostate cancer differed between the two serum markers. The AUC was 0.449 and 0.859, respectively. However, total PSA had a far better AUC than serum MSMB with better diagnostic accuracy for prostate cancer with a statistically significant difference ($p=0.430$ and $p<0.001$, respectively.

It is clear from the above findings that serum Microseminoprotein-beta has no superior performance to the popular and widely used serum total PSA.

V. LIMITATIONS OF THE STUDY

1. There were no group of patients as control who had lower urinary tract symptoms with no indications for biopsy or a group of asymptomatic age-matched individuals from the population.
2. Some of the patients included in the negative biopsy group may have prostate cancer despite negative TRUS biopsy.

VI. CONCLUSION

The serum total prostate-specific antigen is more accurate as a serum biomarker of cancer prostate than serum Microseminoprotein-beta. The poor sensitivity of serum Microseminoprotein-beta makes it an unsuitable tool for cancer prostate diagnosis.

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