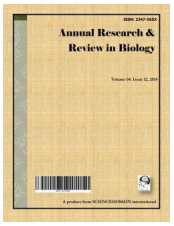

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Prognostic use of Prostate Specific Antigen, Some Renal Indices and Uric Acid in the Diagnosis of Prostate Cancer and Renal Impairment at Urology Clinic Federal Medical Centre Lokoja, Nigeria

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Authors' contributions

This work was carried out in collaboration between all authors. Author IPE designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors NRU and CCO managed the analyses of the study. Author NKN managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Improved diagnosis of prostate cancer has led to increasing life expectancy in adult men. The use of PSA as the current practice for screening and treatment has become a key prognostic factor in the management of PCa. This study was designed to evaluate the prognostic use of serum PSA, creatinine, urea, protein and uric acid in PCa subjects with or without renal impairment.
Study Design: The study was a prospective study conducted between March and September 2016 at federal Medical Centre Lokoja, Kogi State, Nigeria.
Methods: One hundred and ten adult men aged 51 - 70 years were conveniently recruited for the study. Diagnosis was based on biopsy, PSA, Cr/U and UA results obtained, and grouped as (A) PCa subjects with RI (35), (B) PCa subjects without RI (35) and 40 apparently healthy men (Controls) which is regarded as group (C). Blood samples were collected and analyzed for PSA and renal indices using ELISA and colorimetric methods respectively.
Results: The result showed that serum tPSA, fPSA, cPSA, %fPSA, creatinine, urea and uric acid were significantly higher while total protein was significantly lower in PCa subjects with RI compared with controls (*P<.05*). Similar results were obtained in PCa without RI compared with controls except for urea (*P=.001* respectively). However, tPSA, fPSA, cPSA were significantly lower while creatinine, urea and uric acid were significantly higher in Pca with RI compared with the corresponding values in PCa without RI (*P<.05*). The correlation between cPSA, creatinine and urea showed association between PCa and RI. ROC showed that tPSA and cPSA had significantly higher diagnostic performance than fPSA and % fPSA in the prediction of PCa associated with RI while Creatinine, urea and uric acid had significantly higher diagnostic accuracy in the prediction of RI associated with PCa within the age range of 50-61 than 61-70 years.
Conclusions: Increased serum uric acid level observed in RI subjects suggests decreased excretion of uric acid by the kidney. ROC analysis shows significant evidence that tPSA and cPSA have higher predictive value for PCa with or without RI while creatinine, urea and uric acid have higher predictive efficacy for RI in PCa subjects. Adult men from 50 years are recommended for early screening for PDs to minimize progression to RI.

Keywords: Prostate cancer; diagnostic performance; PSA; uric acid; renal Impairment.

ABBREVIATIONS

PSA : Prostate specific antigen
tPSA : total prostate specific antigen
cPSA : complexed prostate specific antigen
fPSA : free prostate specific antigen
%fPSA : Per cent free prostate specific antigen
RI : Renal Impairment
SUA : Serum Uric Acid
PSAD : Prostate specific antigen density
PSAV : Prostate specific antigen velocity
CKD : Chronic kidney failure
BPH : Benign prostatic hyperplasia
ROC : Receivers operating characteristics
AUC : Area under curve
FMC : Federal Medical centre
PD : Prostate Disorder
ELISA : Enzyme linked Immunosorbent Assay
UA : Uric acid
PSA-ACT : Purified human PSA-ACT Complex antigen
Cr/U : Creatinine/Urea

1. INTRODUCTION

Evidence has shown that the rising incidence of death from prostate cancer has been brought to a minimum due to recent improvement in screening, diagnosis, guide to treatment decision and therapy [1]. Prostate cancer is the most common malignancy among elderly men and is the second leading malignancy of black African ancestry as well as Western world [2,3]. In Nigeria, reports have shown that the incidence of PCa may be underestimated. Ogunbiyi et al. [4] reported 11% of all male cancers while studies in Kano [5], Zaria [6], and Maiduguri [7] showed CaP as 16.5%, 9.2%, and 6.15% of male cancers respectively. Recently, a study in Calabar University Teaching Hospital Nigeria, observed that prostate cancer comprises a large proportion (31.3%) of all male cancers histologically diagnosed with a peak incidence between the ages of 61 – 70 years [8]. The hospital based incidences have also been shown to be on the increase [9,10].

Report has shown that some PCa patients were asymptomatic and therefore, needed no treatment and might eventually be killed by diseases other than PCa [11,12]. Some genetic and life style factors may play some role in the development of PCa. The risk factor for developing prostate cancer in men is related to his age, genetics, race and lifestyle. The primary risk factor is age and it is uncommon in men less than 45, but becomes more common with advancing age with average time of diagnosis at 70.

Prostate specific antigen (PSA) has been a useful parameter for screening and monitoring of prostate cancer though, it is controversial [13]. No significant disparity was seen in the distribution of PSA between a rural Nigeria population and unscreened US population [14]. Some studies in Nigeria have reported high PCa values above the normal cut off level [14-16]. According to Federal Drug Agency (FDA), 4ng/ml was chosen as a decision level for detection of prostate cancer in men aged 50 years and above [17-19]. Prostate specific antigen however, exists in the serum mostly as PSA-ACT complex [20]. Reports have established that direct measurement of PSA-ACT complex does not only eliminate the technical errors associated with PSA assay but largely enhances discrimination of BPH from prostate cancer [21, 22]. About 86% of the total PSA that predominate the prostate cancer patients serum is complexed with ACT. Total PSA is a combination of fPSA and cPSA and its concentration is higher in blood when there is PCa [23]. It has been shown that fPSA as a percentage of tPSA is lower in men with prostate cancer when compared with men with benign prostatic hyperplasia, %fPSA therefore, can be used to differentiate PCa from BPH [20,24]. However, the level of free PSA is usually low in Pca [25]. Some researchers found a median of 18% free PSA in carcinoma and 28% free PSA in BPH [23,26]. Christensson et al. [20] also confirmed that the complexed total ratio was significantly increased in patients with prostate cancer than in BPH. Measurement of the fPSA and the calculation of % fPSA have been used to discriminate between the prostate cancer and BPH. This helps to minimize the frequent and unnecessary biopsies often done on patients with BPH. Several PSA derivatives, including fPSA, % fPSA), PSA density (PSAD), and PSA velocity (PSAV) have made a major improvement in patient selection for prostate biopsy. Determination of the presence or aggressiveness of prostate cancer before prostate biopsy is still limited [27]. However, up to 45% of men with organ-confined prostate cancer have a PSA <4 ng/ml [28]. Therefore, if proper diagnosis of these potentially curable men should be established, then methods of increasing the sensitivity of the test are very necessary.

Renal disease is caused by several factors and it becomes difficult to separate the association of BPH and PCa from all other causes of renal disorders [29]. It is estimated that 27 million people have renal impairment in United States [30]. In Nigeria, the prevalence of BPH and PCa among renal impairment subjects is 25%. This can be brought to a minimum by proper diagnosis and treatment to enable the kidney to regain some independent function. Statistics has shown that Pca is the second most prevalent solid malignancy in transplantation and the second leading cause of cancer death among men [31]. Furthermore, PCa associated diseases such as end stage renal disease (ESRD) has been reported [32,33]. In order to prevent renal impairment from progressing to end stage renal disease, early screening, diagnosis and management of Pca is necessary.

Plasma creatinine ≥ 133 umol/l (1.5mg/ dl) defined renal impairment [34]. A study has shown that higher serum creatinine levels that are still within normal ranges are associated with a significantly increased risk of prostate cancer [35,36]. Increased serum urea and/or creatinine levels could be an early hint towards prostate cancer and blood urea greater than 8.3 mmol/l has been associated with renal impairment [37, 36].

The uric acid in prostate disorders (BPH & PCa) and renal impairment has been reported to be high due to poor excretion [38]. A good number of younger men have been diagnosed with PCa. Modern treatment for PCa includes procedures like robot-assisted laparoscopic radical prostatectomy and cryotherapy. These treatment modalities have the advantage of reducing complication and increasing the quality of life of affected patients [39]. The complications of prostate disorders therefore, needs to be recognized, monitored and managed properly to decrease the gaping dearth of diagnosis, adverse effects and loss of patients' quality of life from prostate disorders particularly PCa. The present study therefore seeks to evaluate the diagnostic performance of serum PSA, Creatinine, urea, protein and uric acid in prostate cancer subjects.

2. MATERIALS AND METHODS

2.1 Subjects

Federal Medical Centre (FMC) Lokoja, a 400 bed tertiary health centre, serves peoples of Kogi State, in Nigeria and also receives patients from the neighbouring states like Kwara State, Benue State and Ekiti State in Nigeria. Federal Medical Centre was established by the Federal Government in June 1999 and took off year 2000 as second generation Federal Medical Centre. The population served is mainly the Igala, Ebira and Okun (Yoruba).

A total of One hundred and ten (110) adult male subjects aged (51–70) years were recruited for the study using convenient sampling technique. Seventy (70) participants from urology clinic of Federal Medical Centre, Lokoja, Nigeria, who had undergone Transrectal ultrasonography (TRUS), Digital Rectal examination (DRE), and/or histologically confirmed and diagnosed, were recruited. The participants werefurther grouped based on the results of PSA, biopsy, urea, creatinine and uric acid levels obtained from urology clinic at Federal Medical Centre, Lokoja as (A): Prostate cancer subjects with renal impairment (n=35). (B): Prostate cancer subjects without renal impairment (n=35).The remaining forty (40) participants were apparently healthy volunteers grouped as (C) and were recruited among the hospital staff and served as controls.

Seven millilitres of venous blood were collected from each subject for the biochemical investigations. The blood was allowed to clot, separated and the serum stored at − 20°C till analysis of the biochemical parameters (PSA, urea, creatinine, protein and uric acid) at Clinical Chemistry Laboratory at Federal Medical Centre Lokoja, Kogi State, Nigeria.

2.2 Laboratory Techniques

Determination of Prostate Specific Antigen (PSA, Free PSA Assay) in human serum using enzyme immunoassay method (EIA) AcuBind USA as described by [40] with microplate reader for ELISA model: BIORAD 5100 Australia, while complexed prostate specific Antigen (cPSA) was calculated mathematically by the formula cPSA = Total PSA – (fPSA).

Determination of serum creatinine was done by colorimetric method [41] while serum urea was measured by the colorimetric method [42].

Determination of serum uric Acid was measured by the colorimetric method [43].

Also serum total protein was measured by the colorimetric method [38]. The device used for was CHEM-5 AUTO auto-analyzer model: J13683 USA with reagents from AGAPPE Diagnostics LTD Switzerland.

2.3 Inclusion Criteria

Participants having prostate cancer with or without renal impairment were included in the study. Apparently healthy subjects were included in the study as controls.

2.4 Exclusion Criteria

Participants having BPH with or without RI were excluded from the study. Prostate cancer subjects with or without RI who refused to give their consent, control subjects with ailment related to BPH, Pca and RI such as subject with Hypertension, lung disease, tracheal disease, mumps were excluded from the study as control.

2.5 Statistical Analysis

The data obtained from the study were analysed using SPSS version 21.0 statistical Package. The result was expressed as mean± SEM, statistical difference between groups was done using analysis of variance (ANOVA), Pearson's Correlation and Receivers Operating Characteristics [44]. The differences were considered significant when $P<0.05$.

3. RESULTS

3.1 Levels of PSA (tPSA, fPSA, cPSA, %fPSA) in PCa with RI, PCA without RI and Control Subjects

The values of tPSA, fPSA, cPSA, % fPSA, in Pca and RI were significantly higher compared with control subjects. In PCa without RI, the values were also significantly higher compared with the corresponding values in control subjects (*P<.05*). However, the values of tPSA, fPSA, cPSA in Pca with RI were significantly lower while Urea, creatinine and Uric acid levels were significantly higher in PCa subjects with RI compared with the counterpart without renal impairment (*P<.05*) (See Table 1).

Table 1. Mean (+SEM) PSA (tPSA, fPSA, cPSA)(ng/ml), % fPSA in PCa with RI, PCa without RI and control subjects

Group	Age(years)	tPSA	fPSA	cPSA	%fPSA
PCa with RI (A) (n=35)	67.3 ± 0.86	25.64 ±0.26	1.53 ± 0.10	24.00 ±0.24	7.16 ± 0.63
PCa without RI (B) (n=35)	60.3 ±0.83	49.22 ± 0.04	4.56 ± 0.32	44.66 ±0.95	9.88 ±0.72
Control subjects (C) (=40)	52.0±0.62	2.27±0.15	0.05±0.00	2.20±0.15	2.74±0.27
F-value	41.08	65.28	110.77	67.74	280.13
Pvalue	0.001*	0.001*	0.001*	0.001*	0.001*
A V B	0.001*	0.001*	0.001*	0.001*	0.057
A V C	0.001*	0.001*	0.035*	0.001*	0.002*
B V C	0.001*	0.001*	0.001*	0.001*	0.001*

**values differ significantly from controls (p<0.05), n= sample size, SEM = standard error of mean.. Reference ranges for tPSA:0-4-0ng/ml, fPSA:0.5-1.5ng/ml,cPSA:1.5-3.5ng/ml, %fPSA less than 23% define PCa*

3.2 Levels of Urea, Creatinine and Uric Acid in PCa with RI, PCA without RI and Control Subjects

The values of Urea, creatinine, Protein and Uric Acid in PCa and RI were significantly higher compared with control subjects. In PCa without RI, the values of urea and uric acid were also significantly higher compared with the corresponding values in control subjects (*P<.05*). However, the values of tPSA, fPSA, cPSA in PCa with RI were significantly lower while Urea, creatinine and Uric acid levels were significantly higher in PCa subjects with RI compared with the counterpart without renal impairment (*P<.05*) (See Table 2).

3.3 Distribution of PSA, Urea, Creatinine and Uric Acid in Pca with RI, PCA without RI and Control Subjects According to Age

The mean values of tPSA, fPSA, cPSA, %fPSA, urea, creatinine and uric acid according to the age ranges (51-60 and 61-70 years) are shown in Table 2.

The mean values of tPSA, cPSA, Urea were significantly higher in ages 51-60 years compared with the corresponding value in ages 61-70 years in PCA subjects with RI (*P<.05*) while creatinine and uric acid levels were significantly lower in ages 51-60 years compared with ages 61-70 years in same subjects (*P<.05*). However, In Pca without RI Subjects, the mean values in 51-60 years were not significantly different compared with ages 61-70 years (*P>.05* respectively) (See Table 3).

3.4 Pearson's Correlation Studies in Pca with RI, PCA Without and Control Subjects

In PCA with renal impairment, There was a significant positive correlation between tPSA & cPSA, fPSA & %fPSA, %fPSA & protein, cPSA & creatinine, creatinine & urea (*P=.01*). There was a negative correlation between tPSA & %fPSA, cPSA & % fPSA, cPSA & creatinine, (*P=.01*).

Table 2. Mean (+SEM) Urea (mmol/l), total protein, creatinine (µmol/l) and uric acid (mg/dl) in PCa with RI, PCa without RI and control subjects

Group	Age(years)	Urea	Creatinine	Total protein	Uric acid
PCa with RI (A) (n=35)	67.3 ± 0.86	29.83 ± 0.77	998.77±0.00	61.28 ± 0.53	9.46 ± 0.21
PCa without RI (B) (n=35)	60.3±0.83	6.89 ±0.78	138.66 ±0.56	61.22 ± 0.66	7.20 ± 0.56
Control subjects (C) (=40)	52.0±0.62	4.80±0.20	83.57±0.42	72.07±0.80	5.23±0.14
F-value	41.08	130.31	108.04	51.11	101.20
Pvalue	0.001*	0.001*	0.001*	0.001*	0.001*
A V B	0.001*	0.001*	0.001*	0.960	0.001*
A V C	0.001*	0.001*	0.001*	0.001*	0.001*
B V C	0.001*	0.144	0.342	0.001*	0.001*

**values differ significantly from controls (p<0.05), n= sample size, SEM = standard error of mean. Reference ranges for tPSA:0-4-0ng/ml, fPSA:0.5-1.5ng/ml,cPSA:1.5-3.5ng/ml, %fPSA less than 23% define PCa*

Table 3. Distribution of PSA (tPSA, fPSA, cPSA)(ng/ml), %fPSA, Urea (mmol/l), Creatinine (umol/l) and Uric acid (mg/dl) PCa with or without RI and control according to age

	Group PCa with RI		P-value	PCa without RI		P-value	control subjects		P-value
Age range	**51-60 (n=18)**	**61-70 (n=17)**		**51-60 (n=18)**	**61-70 (n=17)**		**51-60 (n=20)**	**61-70 (n=20)**	
Tpsa	30.61 ± 0.10	20.39 ±0.58	0.022	49.77±0.42	48.64 ±0.23	0.856	2.41±0.23	2.10±0.19	0.378
fPSA	1.42 ± 0.15	1.65 ±0.15	0.307	4.63±0.53	4.48±0.37	0.824	0.07±0.01	0.04±0.00	0.118
Cpsa	28.97 ±0.12	18.24±0.75	0.020	45.14±0.33	44.15±0.00	0.871	2.30±0.24	2.09±0.19	0.511
%Fpsa	4.64±0.11	8.10±0.68	0.251	9.88±0.44	8.50±0.28	0.233	2.90±0.71	1.90±0.31	0.100
Urea	34.76 ±0.48	24.60±0.87	0.003	6.16±0.51	7.67±0.52	0.345	5.02±0.37	4.58±0.18	0.296
Cr	722.32±0.34	761.12±0.15	0.001	106.39±0.09	172.82±0.58	0.198	86.60±0.22	80.55±0.33	0.397
UA	94.6±0.32	9.52±0.46	0.003	7.00±0.92	7.31±0.35	0.233	4.03±1.30	4.70±1.20	0.231

Values differ significantly from controls (P<0.01),* ***n* *= sample size,* ***SEM*** *= standard error of mean. Reference ranges for tPSA:0-4-0ng/ml, fPSA:0.5-1.5ng/ml,cPSA:1.5-3.5ng/ml, %fPSA less than 23% define PCa*

Table 4. Pearson's correlation studies of PCa subjects with or without RI

	Group PCa with RI (n=35)		PCa without RI (n=35)	
Parameter	**R**	**P**	**R**	**P**
tPSA vs cPSA	0.998	0.000*	0.995	0.000*
tPSA vs % fPSA	-0.649	0.000*	-0.357	0.037*
fPSA vs% fPSA	0.501	0.002*	0.739	0.000*
cPSA vs % fPSA	-0.672	0.000*	-0.210	0.226
fPSA vs Creatinine	-0.138	0.430	0.739	0.000*
cPSA vs creatinine	0.670	0.003*	-0.449	0.007*
%fPSA vs protein	0.309	0.110	-0.423	0.011*
Creatinine vs Urea	0.598	0.000*	0.957	0.000*
Urea vs Uric acid	0.291	0.090	0.752	0.000*
Creatinine vs Uric acid	0.243	0.160	0.662	0.000*

** denotes significance level*

In PCA without renal impairment, there was significant positive correlation between tPSA & fPSA, tPSA & cPSA, fPSA & %fPSA, fPSA & Creatinine, creatinine & Urea, creatinine & UA, Urea & UA (*P=.01*). There were negative or inverse correlation between tPSA & %fPSA, cPSA & Creatinine, %fPSA & protein, (*P=.01*) (See Table 4).

3.5 ROC'S/AUC'S

ROCs are receivers operating characteristics, AUCs are area under the curve used to determine the diagnostic performance and association of different variables used in the assessment of PCa and RI.

3.5.1 ROC of PSA (tPSA, cPSA, fPSA and %fPSA) Cr/U, protein and UA in PCa with RI, PCa and controls

The result showed the diagnostic performance of tPSA, fPSA, cPSA, %fPSA, Creatinine Urea, Protein and Uric Acid for PCa with RI subjects. The results were tPSA (AUC.903), fPSA (AUC.551), cPSA (AUC.949) %fPSA (AUC.468), Creatinine (AUC.911), Urea (AUC.958), Protein (AUC.223) and Uric acid (AUC.890). tPSA and cPSA had significantly higher diagnostic accuracy than fPSA and %fPSA in the prediction of PCa associated with RI. Creatinine, urea and uric acid had significantly higher diagnostic accuracy than protein in the prediction of RI associated with PD (PCa) (See Fig. 1).

3.5.2 Diagnostic performance of tPSA, fPSA, cPSA, %fPSA, Creatinine, Urea Protein and uric acid in PCa without RI subjects

The results were tPSA (AUC.942), fPSA (AUC.679) cPSA (AUC. 0.947) % fPSA (AUC.433), Creatinine (AUC.314), Urea (AUC.329), Protein (AUC.0.236) and Uric Acid (AUC.521). tPSA and cPSA had a significantly higher diagnostic accuracy than fPSA and %fPSA in the prediction of PCa. Uric Acid had significantly higher diagnostic accuracy than protein in the prediction of PCa without RI (See Fig. 2).

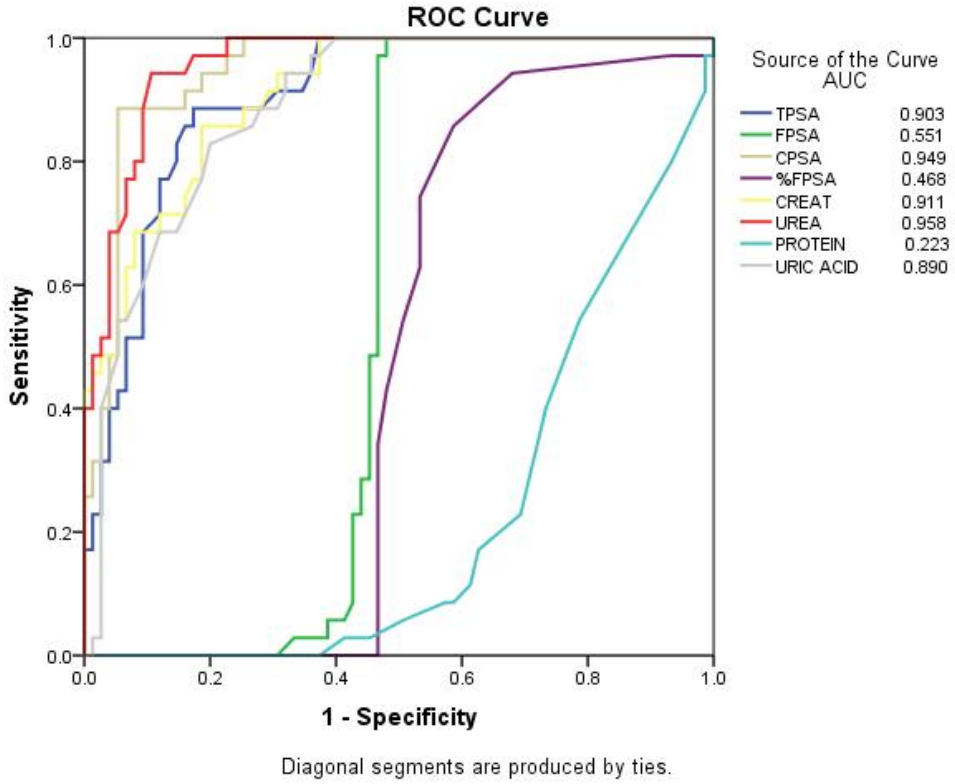

Fig. 1. ROC of tPSA, cPSA, fPSA, %fPSA, creatinine urea, protein and uric acid in PCa with renal impairment

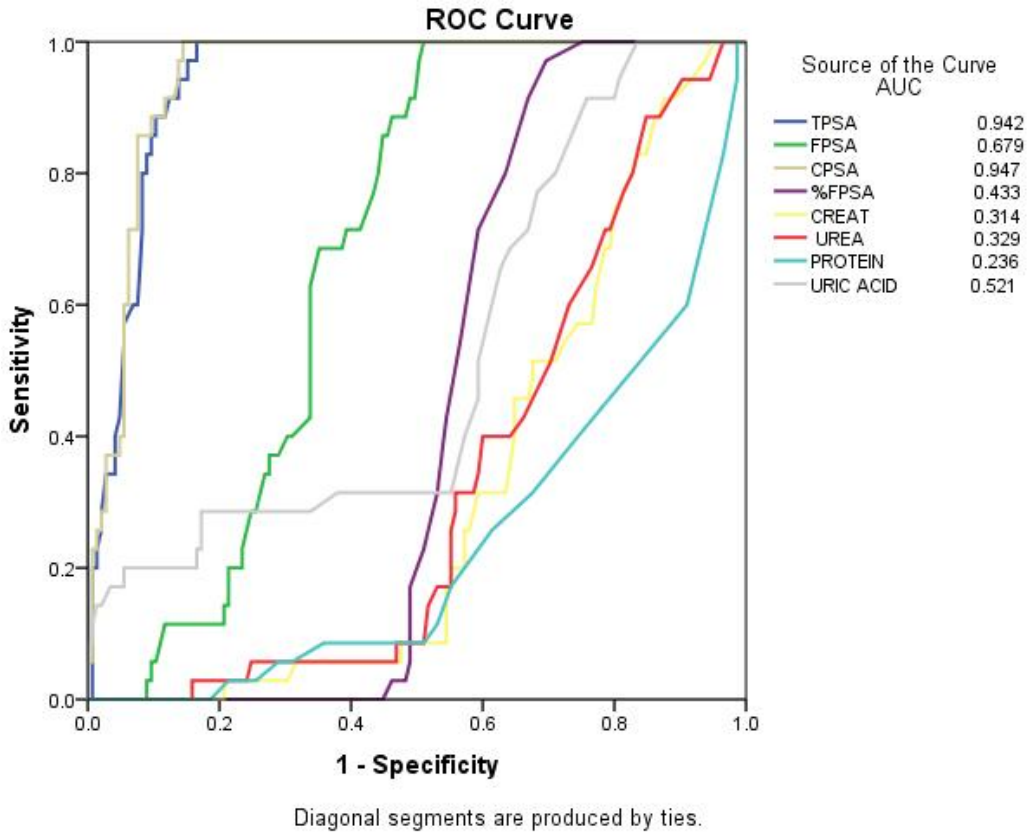

Fig. 2. ROC of tPSA, cPSA, fPSA, %fPSA, creatinine urea, protein and uric acid in PCa without renal impairment

3.5.3 ROC of tPSA, fPSA, cPSA, %fPSA, creatinine, urea protein and uric acid in control group

The results were tPSA (AUC.000), fPSA (AUC.000), cPSA (AUC.0.004) %fPSA (AUC.062), Creatinine (AUC.000), urea (AUC.001) Protein (AUC. 0.924) and uric acid (AUC.049). %fPSA showed higher predictive value than tPSA and fPSA. Protein had statistically higher prediction value in control than urea and creatinine and uric acid (See Fig. 3).

4. DISCUSSION

The present study observed that serum levels of tPSA, fPSA, CPSA, %fPSA, creatinine, urea and uric acid were significantly higher in Prostate cancer subjects with or without renal impairment compared with control subjects. Conventionally, it has been indicated that the sum of fPSA and cPSA roughly corresponds to total PSA (tPSA) [23] and increased release of tPSA in the blood is caused by prostate cancer while % fPSA helps in discrimination of prostate cancer from BPH [20]. In men with moderately elevated tPSA, %fPSA has been reported to improve the diagnostic potential of PSA in early detection of prostate cancer [24]. However, in men with tPSA values greater than the cutoff value of 4.0 ng/mL, complexed PSA (cPSA) was shown to improve specificity in the detection of prostate cancer over that of total PSA (tPSA) [45]. A cut-off value of 4 µg/L tPSA was used to categorize patients with prostate cancer [46]. Although our study did not categorize the degree of and aggressiveness of prostate cancer, it showed multiple increases in the values of PSA in PCa subjects with or without renal impairment. This suggests that these men may have advanced to high grade prostate disease much higher than previously known, indicating that men still present late with aggressive PCa vis-avis renal impairment. The present study is in conformity with the work done by Akinremi et al. [13]. Previous researchers have shown that blacks may have a higher PSA value than the generally accepted value for Caucasians possibly, as result of increased

prostatic volume or chronic prostatic inflammation [16,10]. The prevalence of prostate cancer as reported by different researchers across Nigeria is between 2% and 11% [4, 47–50]. According to World Health Organization, Nigeria was ranked first out of the nine African countries with highest incidence of this disease and third among countries with significant death from prostate cancers after the United States and India [29], hence, the need for greater awareness and more improved measures to increase early detection.

The significantly higher fPSA and %fPSA in PCa men with RI compared with control in the present study is also in conformity with the study reported by Bruun and colleagues, even though our study did not determine the degree of renal impairment. The authors observed significant increases in serum fPSA and %fPSA in men with chronic kidney disease and impaired renal function compared to their control counterparts [51]. It has been established that renal dysfunction may alter the relative proportions of the two PSA forms by reducing the elimination of fPSA and increasing %fPSA [52 - 54]. However, Bruun et al. [55] in their earlier study have indicated the need for a better marker for detection and monitoring of men with prostate cancer, since increased %fPSA has been reported in men with terminal renal insufficiency and severe renal dysfunction. This helps to eliminate misdiagnosis of men with benign disease as having renal dysfunction.

The present study observed significantly higher tPSA in PCa subjects with or without RI compared with controls. This is contrary to the report by Bruun et al. [51]. However, our study used apparently healthy adult men without any form of cancer as control while the authors used patients with benign prostate hyperplasia for their controls.

The insignificant difference in the value of %fPSA between PCa subjects with RI and PCa without

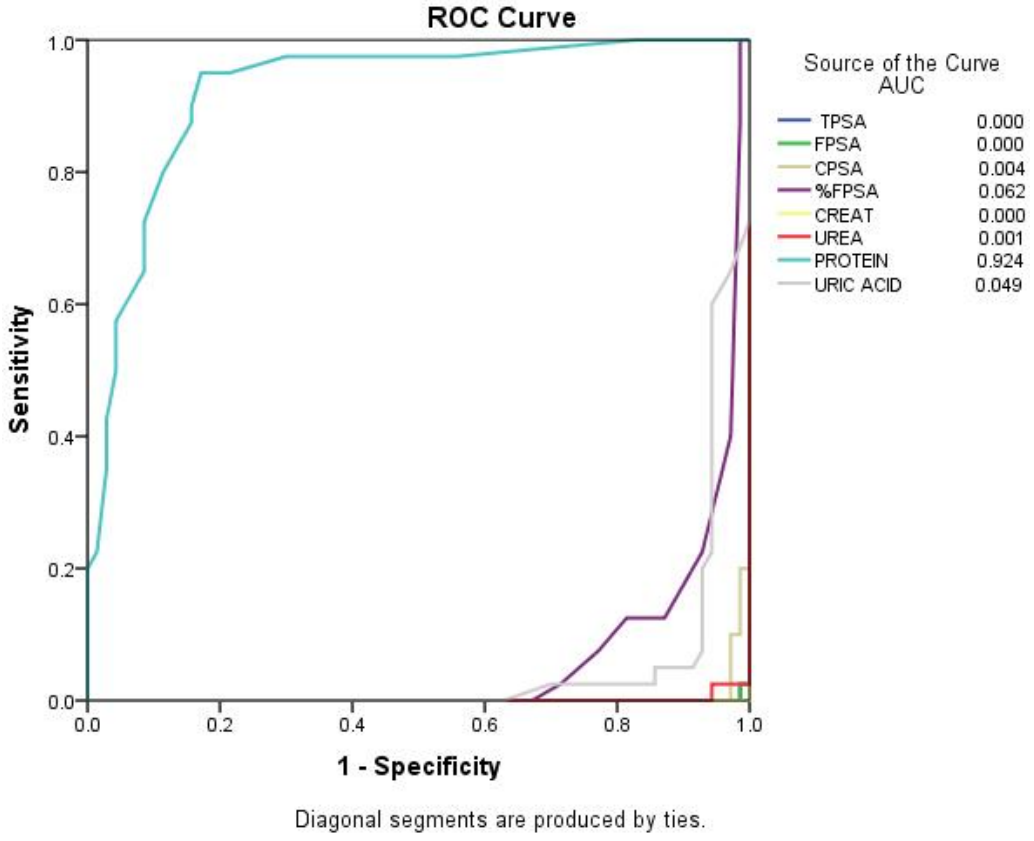

Fig. 3. ROC of tPSA, cPSA, fPSA, %fPSA, creatinine urea, protein and uric acid in control subjects

RI confirms the report that %fPSA is often used as a tool for detection of prostate cancer [55]. Some other studies have also reported that the use of the f/tPSA or cPSA test among men with PSA levels between 2 and 10 ng/ml can reduce the number of unnecessary biopsies while maintaining a high cancer detection rate [27,26].

The present study observed significantly higher serum creatinine, urea and Uric acid levels in Pca subjects with RI compared with controls. The serum creatinine, urea and uric acid levels were also significantly higher in PCa with RI than the counterpart without RI and the increase is very marginal. This is consistent with previous reports [35- 37]. Joshi et al. reported that increased urea/or creatinine is associated with early detection of prostate cancer [36] while Dantoni et al. in their prospective study observed that higher baseline serum creatinine concentrations were strongly related to higher risk of prostate cancer [35]. Creatininemia, depending on the laboratory assay methods used, has been defined with thresholds ranging from 1.5–2.0 mg/dL [55 - 58]. Previous studies have also shown that serum creatinine is a measure of renal function after adjusting for confounding factors such as age, sex, muscle mass, intake and absorption of dietary creatine and creatinine [56-58].

However, our study reported that mean values of tPSA, cPSA and urea were significantly higher in ages 51-60 years compared with the corresponding value in ages 61-70 years in PCA subjects with RI while creatinine and uric acid levels were significantly lower in ages 51-60 years compared with ages 61-70 years. This suggests that PCa progresses with age which might lead to renal dysfunction at older age if not diagnosed and treated. The elevated values of creatinine and urea in PCa subjects with RI may also be attributed to the drugs the subjects used in the treatment of prostate cancer. Similar studies in other countries have reported the median serum creatinine concentrations ranging from 1.11 – 1.18mg/dL for men aged between 40 -74 years [59- 61].

The significant positive correlation between cPSA, creatinine and urea in the present study shows association between PCa and renal impairment. The present study neither categorized PCa nor staged the degree of renal impairment. However, poor prognosis reported in some prostate cancer patients may be due to poor renal function and increased creatinine levels. Some researchers while assessing a potential PCa staging and prognostic maker also noted that high creatinine concentrations predicted advanced prostate carcinoma and survival rate [62 - 68].

The significantly higher uric acid levels in PCa subjects with RI compared with subjects without RI and controls suggests decreased excretion of uric acid by the kidneys in subjects with renal impairment which resulted to an increase in serum uric acid level. Our study observed uric acid value > 7.2mg/dl in Pca subjects with RI showing that they have aggressive Pca which may progress to chronic kidney disease. The present study is consistent with a previous report [69]. Other studies have reported that hyperuricemia is independently associated with a decline in renal function [70,71]. This may suggest that renal dysfunction co-exists with elevated serum uric acid showing that uric acid should be taken into consideration as a link between renal dysfunction and prostate cancer. Some other reports have also shown that elevated serum uric acid is associated with high risk of prostate cancer [72-74]. These authors in their reports identified an association of elevated SUA with the risk for development of prostate cancer over a period of ten years following baseline measurement. Also a SUA level above 358 μM was found by binary regression analysis to be an independent and significant prospective risk factor for incident of prostate cancer [73]. A larger prospective studies conducted on both male and female European cohorts also confirmed that high SUA (>6.71 mg/dl in men and >5.41 mg/dl in women) measured at baseline was an independent risk factor for death from all cancers compared to high normal SUA (4.6 mg/dl) [74].

Receiver operating curve in the present study shows that tPSA and cPSA had significantly higher diagnostic accuracy than fPSA and %fPSA in the prediction of PCa associated with RI and PCa without RI. Creatinine, urea and uric acid had significantly higher diagnostic accuracy than protein in the prediction of RI associated with PCa. Only Uric Acid had significantly higher diagnostic accuracy than creatinine, urea and protein in the prediction of PCa without RI. The present study is consistent with works done by other researchers [45,54,75-76].

5. CONCLUSION

Total PSA and cPSA had significantly higher diagnostic performance than fPSA and %fPSA in

the prediction of PCa associated with RI while Creatinine, urea and uric acid had significantly higher diagnostic accuracy in the prediction of RI associated with PCa within the age range of 50-61 than 61-70 years. Similarly, tPSA and cPSA had higher diagnostic performance in the prediction of PCa without RI while Uric acid had significantly higher diagnostic accuracy than creatinine, urea and protein in the prediction of PCa. Routine use of these markers in early screening, diagnosis and monitoring of prostate cancer from 50 years is strongly recommended to minimize complication and progression of PCa to RI as the age advances. More prospective longitudinal study using improved and advanced indexes such as prostate health index (PHI), pro-enzyme prostate specific antigen (%p2PSA) and Gleason score would go a long way in categorizing the degree and stages of PCa vis-à-vis renal impairment in the study area.

CONSENT

All authors declare that 'written informed consent was obtained from the patient.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the ethics committee Federal Medical Centre, Lokoja, Nigeria and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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