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CORRELATION OF HISTOMORPHOLOGICAL PATTERNS OF PROSTATIC DISEASES WITH PROSTATIC SPECIFIC ANTIGEN

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ABSTRACT

Introduction: *Prostatic disease is a common presentation in our environment with a wide range of histomorphological patterns and a diverse range of Prostatic Specific Antigen (PSA) values. Correlation of the histomorphological patterns with PSA would enable a baseline data for which clinicians can manage patients effectively*

Methodology: *This was a retrospective cross-sectional study of 2 years duration. The bio-data, serum PSA and other relevant information were retrieved from the patient's case files. All tissue blocks were retrieved, reprocessed to obtain a fresh slide, and histologically examined and reported. Cancers detected were graded histologically according to the Gleason system using the following Gleason categories 1-5 and the International Society of Urological Pathologists (ISUP grading system. The data were analyzed using the Statistical Package for Social Sciences (SPSS) ® version 21.0 for Windows. Simple descriptive statistics were used to characterize the sociodemographic and clinical parameters.*

Results: *A total of 251 prostate biopsies were received during the study period however only 197 (78.5%) biopsies fulfilled the inclusion criteria for this study. The age range of participants was from 46 – 91 years. From the study population, 2% had PSA values within the normal range of ≤4ng/ml while 98% had ≥4ng/ml. Malignant lesions*

constituted 57.4% of the population and all had a diagnosis of adenocarcinoma. Benign prostatic hyperplasia was the second most common lesion accounting for 21.8%. More than half of the patients with PSA from 11ng/ml to 100ng/ml were diagnosed with cancer. At values ≥100ng/ml, 52% of the cases had a diagnosis of CAP. There is a statistically significant association between PSA level and the histomorphological spectrum of prostatic diseases that is positive and moderate. The commonest grade of cancer among the study population according to ISUP group grading is grade 5.

Conclusion: *This study concludes that PSA findings cannot predict the histological grade of prostate cancer but can predict the likelihood of a prostatic disease being cancerous. Prostatic biopsies should be done for all patients for proper grading of the prostatic adenocarcinoma which has prognostic value.*

Keywords: *Prostate cancer, Gleason scores, Benign prostatic hyperplasia*

INTRODUCTION

The prostate gland is a functional conduit that allows urine to pass from the urinary bladder to the urethra and adds nutritional secretions to the sperm to form semen during ejaculation. The normal adult prostate weighs approximately 30g. Microscopically, the prostate is composed of glandular epithelium and fibromuscular stroma. The range of diseases affecting the prostate includes prostatic nodular hyperplasia, infections, non-infectious inflammatory conditions, intraepithelial neoplasia, adenocarcinoma, mesenchymal tumors, basal cell hyperplasia and carcinoma as well as hematologic malignancies [1].

Prostate cancer is the most common male genital cancer worldwide and it is responsible for 20% of all newly diagnosed male cancers. Incidentally, it is commonly seen in the older age group. The incidence rate is noted to be high in Nigeria but varies amongst regions[2]. Prostatic specific antigen (PSA) is a glycoprotein and organ-specific marker secreted exclusively by the prostatic epithelium and used in the evaluation of prostatic diseases. It is tissue-specific but not disease-specific as it is elevated both in prostatic instrumentation and non-neoplastic diseases[3,4]. It is currently used as the first-line screening tool for prostatic cancer [5]. The upper limit of the normal range for PSA values is generally 4.0 ng/ml; levels between 4

and 10 ng/mL are considered borderline and more than 10 ng/mL is considered high[6]. Its widespread use has led to a marked increase in the number of non-palpable cancers diagnosed by needle biopsy as it has been noted to increase with malignancies[1, 6].

Gleason's grading is the most widely used grading method of prostatic adenocarcinoma and it is one of the most powerful prognostic indicators and diagnostic tools currently[5]. Though there are several studies supporting the theory that PSA is higher in malignancies than in benign lesions, there is conflicting information concerning the correlation of such malignancies with their respective Gleason's grade. Where such a correlation exists, it, therefore, implies that a higher PSA will translate to a higher Gleason's score.

Studies have been done outside and within the country to elucidate the impact of serum PSA on prostatic lesions and its correlations with Gleason's score. Such a study has not been done in the south-south region of the country. This study hopes to find the association between PSA and the spectrum of histological lesions in patients presenting to the University of Port Harcourt Teaching Hospital (UPTH) and extrapolate the findings to the larger environs.

This study, therefore, assessed the degree of correlation between the histological spectrum of prostatic diseases and PSA as well as the correlation between the PSA and the Gleason score in cancer of the prostate. It also determined the histomorphological spectrum of prostatic diseases, the relationship between serum PSA levels and histological findings of prostatic diseases, and the Gleason's grade of all prostatic adenocarcinomas seen at the University of Port Harcourt teaching hospital.

METHODOLOGY

Study Site: The University of Port Harcourt Teaching Hospital is a tertiary referral center and as such receives patients from within and outside the state. Hence such findings over 2 years would be representative of the population. The urology clinic of the University of Port Harcourt attends to over a hundred prostatic lesions yearly. These patients are requested to do a serum PSA and a biopsy as the baseline investigation.

Study design: This was a retrospective cross-sectional study of 2 years from January 2020 to December 2021. All cases of prostatic biopsies and prostatectomies received at the Anatomical Pathological Department of the University of Port Harcourt Teaching Hospital during the study period with

corresponding preoperative serum PSA taken were included while cases where serum PSA was not available were excluded.

Methods: The biodata, serum PSA and other relevant information were retrieved from the patient's case files. All tissue blocks were retrieved and reprocessed to obtain a fresh slide. Every slide was freshly examined histologically and reported and findings were noted for all variables using a proforma. Cancers detected in the biopsy cores were graded histologically according to the Gleason system using the following Gleason categories 1-5 and the ISUP grading system.

The estimation of PSA was done quantitatively by the immunoassay method. Standard reference values were considered for the age of the patient.

The data were analyzed using the Statistical Package for Social Sciences (SPSS) ® version 21.0 for Windows. Simple descriptive statistics were used to characterize the sociodemographic and clinical parameters.

The histological diagnosis, Gleason score, and serum PSA data were statistically analyzed and results were presented in tables.

RESULTS

A total of 251 prostate biopsies were received during the study period however only 197 (78.5%) biopsies fulfilled the inclusion criteria for this study. The age range of participants was from 46 – 91 years. Among participants whose biopsies returned positive, the mean age was 69.4 years as compared to 68.6 years among participants whose biopsies returned negative for prostate cancer (table 1).

Table 1: Age comparison based on Cancer Status

Classification	Frequency (n)	Min Age	Max Age	Mean ± SD	T-test	P-value
CAP	84	48	91	69.4 ± 9.9	-0.574	0.566
NON-CAP	113	46	91	68.6 ± 8.9		
TOTAL	197	46	91	69.0 ± 9.5		

There were two peak age ranges for the patients who underwent biopsies of 60 – 69 years and 70 – 79 years at 31% respectively while the lowest number of patients were less than 60 years at 16.8% (table 2).

Table 2: Frequency of age categories

		Frequency (n)	Percent (%)
AGE CATEGORIES	**<60 YEARS**	33	16.8
	60-69 YEARS	61	31.0
	70-79 YEARS	61	31.0
	80 AND ABOVE	42	21.3
	Total	197	100.0

A minor percentage of the study population had PSA values within the normal range of less than 4ng/ml (2%). From the study population, 98% had PSA values above the upper limit of normal which is considered as 4ng/ml, 3.6% had a PSA value of 5-10ng/ml and a significant percentage (38.1%) had PSA values greater than 100ng/ml (table 3)

Table 3: Frequency of PSA categories

		Frequency	Percent
PSA CATEGORY	**< 1**	1	0.5
	1 – 4	3	1.5
	5 – 10	7	3.6
	11 - 50	49	24.9
	51 - 100	62	31.5
	> 100	75	38.1
	Total	197	100.0

Malignant lesions constituted 57.4% of the population and all had a diagnosis of adenocarcinoma. The second most common lesion was BPH, accounting for 21.8% followed by BPH with prostatitis at 9.6%, high-grade PIN at 6.1% and atrophic prostate at 5.1% (table 4).

Table 4: Histomorphological spectrum of prostatic diseases

		Frequency	Percent
Histology	**CAP**	113	57.4
	BPH	43	21.8
	BPH WITH CHRONIC PROSTATITIS	19	9.6
	HIGH-GRADE PIN	12	6.1
	ATROPHIC PROSTATE	10	5.1
	Total	197	100.0

One patient had a PSA value below 1ng/ml with a diagnosis of CAP; 3 patients had a PSA value within 1-4ng/l with only one having a diagnosis of CAP, BPH with prostatitis and atrophic prostate each had a case. Half of the cases with PSA less than 4ng/ml were diagnosed with CAP. Seven patients had a PSA value within 5-10ng/ml with diagnoses of CAP (3 patients) and BPH with prostatitis (4 patients). From PSA of 11ng/ml and above, more than half of the patients were diagnosed with cancer. At ≥100ng/ml, 52% of the cases had a diagnosis of CAP. Fisher's exact test for association revealed a statistically significant association between PSA level and the histomorphological spectrum of prostatic diseases that is positive and moderately strong ($\chi^2 = 31.345$; $p = .024$) as highlighted in table 5. Thus at values above 11ng/ml, the patient is more likely to have a prostatic adenocarcinoma.

Table 5: Relationship between PSA levels and histopathological spectrum of prostatic diseases

PSA	**HISTOMORPHOLOGICAL SPECTRUM**

LEVEL	ATP	BPH	BPHWP	HGPIN	CAP	Total	χ^2	p-value
< 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	1 (100.0)	[f]31.345	.024*
1 – 4	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	1 (33.3)	3 (100.0)		
5 – 10	0 (0.0)	0 (0.0)	4 (57.1)	0 (0.0)	3 (42.9)	7 (100.0)		
11 – 50	0 (0.0)	10 (20.4)	4 (8.2)	6 (12.2)	29 (59.2)	49 (100.0)		
51 – 100	3 (4.8)	14 (22.6)	4 (6.5)	1 (1.6)	40 (64.5)	62 (100.0)		
> 100	6 (8.0)	19 (25.3)	6 (8.0)	5 (6.7)	39 (52.0)	75 (100.0)		
Total	10 (5.1)	43 (21.8)	19 (9.6)	12 (6.1)	113 (57.4)	197 (100.0)		

AP = Atrophic prostate; BPH = Benign prostate hyperplasia; BPHWP = Benign prostate with prostatitis; HGPIN = High grade prostatic intra-epithelia neoplasia

f = fishers exact; * = significant at p < .05

The commonest grade of cancer among the study population according to ISUP group grading is grade 5 (45.1%) followed by grade 4 (22.1%), then grade 1 (15.9%), grade 2 (12.4%), and grade 3 (4.4%) as shown in table 6.

Table 6: Prevalence of prostate adenocarcinoma by ISUP grades.

		Frequency	Valid Percent
ISUP GRADE	**GRADE 1**	18	15.9
	GRADE 2	14	12.4
	GRADE 3	5	4.4
	GRADE 4	25	22.1
	GRADE 5	51	45.1
	Total	113	100.0

A chi-square test conducted to test for the association between PSA level and ISUP grades showed a statistically non-significant relationship (χ^2 = 17.331; p = .825) (table 7).

Also, a Kruskal-Wallis H test conducted to ascertain the correlation between PSA value and ISUP grades showed a statistically non-significant relationship (table 8). Hence no significant relationship was noted between PSA levels and ISUP grade groups.

Table 7: Association between PSA level with ISUP grades

PSA LEVEL	ISUP GRADES						χ^2	p-value
	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5	Total		
<1	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)		
1-4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	1 (100.0)		
5-10	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (66.7)	3 (100.0)	[f]17.331	0.825
11-50	5 (17.2)	5 (17.2)	3 (10.3)	5 (6.1)	11 (13.0)	29 (100.0)		
51-100	7 (17.5)	4 (10.0)	2 (5.0)	10 (25.0)	17 (42.5)	40 (100.0)		
>100	5 (12.8)	4 (10.3)	0 (0.0)	10 (25.6)	20 (51.3)	39(100.0)		
Total	18 (15.9)	14 (12.4)	5 (4.4)	25 (22.1)	51 (45.1)	113 (100.0)		

f = fishers exact

Table 8a: Correlation between PSA value and ISUP grades

Spearman's Rho correlation			
	ISUP GRADE/ PSA	Correlation Coefficient	0.153
		Sig. (2-tailed)	0.105
		N	113

Table 8b: Test for normality of data

Tests of Normality						
VARIABLE	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	Df	Sig.
PSA VALUE	0.453	197	0.000	0.101	197	0.000

Tests of Normality						
	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
ISUP GRADE	0.257	113	0.000	0.770	113	0.000

DISCUSSION

In this study, the age of participants ranged from 46-91 years with the peak ages of prostatic diseases in the 7th and 8th decade. Similar peaks of the 7th and 8th decade have been reported by indigenous studies[7, 8] as well as foreign studies [3, 4, 9]. Also, no patient presented before the age of 40 years which is supported by indigenous studies [7]. This can be explained by the fact that most patients in our environment have poor health-seeking behavior presenting first to unorthodox traditional centers before seeking medical help years after the initial symptoms.

The spectrum of prostatic diseases in this study span from atrophic prostate, BPH, BPH with chronic prostatitis, high-grade PIN, and adenocarcinoma. Adenocarcinoma is the commonest lesion within the study period accounting for 57.4% and is closely followed by BPH which accounts for 21.8% and BPH with prostatitis at 9.6%. This is similar to an indigenous study that reported 58.9% adenocarcinoma[2]. However, some other studies have recorded prostatitis [1] and BPH [3, 6, 9,10] as the commonest lesions. Antibiotics are sold over the counter in our locality without a doctor's prescription. Thus only patients with symptoms that have not responded to antibiotics treatment will present years after self-treatment. It is also worthy of note that there is currently no organized screening program for prostate cancer or targeted health

promotion hence the late presentations. All the malignant cases in this study were adenocarcinomas with this collaborated in other studies[3, 4].

The PSA values of prostatic diseases are greatly diverse in this study. We noted that the majority of the cases had increased PSA values irrespective of benignity or malignancy. This is because disruption of the normal architecture of the prostate causes a release of PSA into the circulation which is dependent on the extent of the underlying pathology. We noted 97.9% of the study population had a PSA value >4ng/ml. We also noted 1 malignant case had a PSA <1ng/ml likewise a malignant case between 1-4ng/ml. This is also a similar finding in Shah et al which reports 90% of malignant cases had >4ng/ml and 85% of malignant cases had >10ng/ml[6]. Kumari et al reported an increased PSA >4ng/ml in 65.5% of the study population and 93.8% of CAP3; Yousfani et al report 100% of cases above 4ng/ml10 while Kocak C. recorded 66.2% of malignant cases having >10ng/ml[5].

When serum PSA levels in benign and malignant cases were compared using Fisher's exact test for association, it revealed a statistically significant association between PSA level and the histomorphological spectrum of prostatic diseases that is positive and moderately strong ($\chi 2 = 31.345$; $p = .024$; Cramer's $V = .221$). This implies that though serum PSA is increased for both benign and malignant lesions, the possibility of finding malignant lesions with increasing PSA values is strong. This is buttressed by several studies which recorded similar findings[2,6,9.] In patients with PSA<4 ng/mL and a normal digital rectal examination (DRE) or an abnormal DRE result, the incidence of prostate cancer ranges from 4% to 9% and from 10% to 20%, respectively[7]. In this study, 50% of the study population below 4ng/ml had a diagnosis of CAP. This may be explained by the fact that presentation in this environment to a tertiary health facility is more likely for patients with florid symptoms of malignancy. Hence a significant number of malignant cases may be missed if based solely on PSA levels.

The mean age of diagnosis of prostatic carcinoma in the present study was 68.53years which is similar to a study by Sazzad et al with 64.78 years[1] was recorded, Udoh et al with 68.22years [8] and Muhammed et al with 68.53years[7].

The commonest grade of cancer among the study population was Gleason grade group 5 followed by grade group 4. This may be explained by the fact that there is no

organized screening program in our environment hence late presentations are common. This is evident in indigenous studies by Mohammed et al and Udoh et al, who reported 38.1% for grade group 4[7]; and grade groups 4 and 5 combined as 60%[8] accounting for the commonest grades. Shah et al report the commonest grades as grade 5(45%) and 4(30%)[6]. This is contradicted by Buch et al who reports grade group 2 as the commonest[4].

The correlation done between PSA and ISUP grade groups showed a non-statistically significant relationship. This is in keeping with previous works by Mohammed et al[7] though contradicted by Udoh et al which showed a positive and statistically significant relationship that implied that PSA increases with higher grades of prostatic adenocarcinoma [8].

CONCLUSION

This study concludes that the mean age for prostatic lesions and adenocarcinoma of the prostate in our environment is 67.82 years and 68.53 years respectively. Adenocarcinoma grade group 5 is the commonest prostatic presentation. There is a positive and strong association between serum PSA and prostatic diseases but none between PSA and ISUP grade grouping. Thus PSA findings cannot predict the histological grade of prostate cancer but can predict the likelihood of a prostatic disease being cancerous. We, therefore, recommend that prostatic biopsies be done for all patients for proper grading of the prostatic adenocarcinoma which has prognostic value.

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