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Correlation of Serum PSA with Gleason Score and Gleason Group Grade in Patients with Prostate Adenocarcinoma at Sokoto North-Western Nigeria

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Abstract: Introduction: Prostate Specific Antigen (PSA) is the first-line test in the screening of prostate cancer, its increase depends on differentiation of tumour cells. Gleason grading is one of the most powerful predictors of biological behaviour and when combined PSA with Gleason score and clinical stage. It improves the prediction of the pathological stage for prostate carcinoma. The aim of this study was to determine the association between serum PSA concentration and the new (2016 modified) Gleason grade group of tumour among patients with adenocarcinoma of the prostate. **Materials and Methods:** This is a retrospective, study of all diagnosed prostate adenocarcinoma over a 4 year period (January 2014 to December 2017) in the Department of Histopathology, Usmanu Danfodiyo University Teaching Hospital. Biodata and other relevant information were retrieved for the study. **Result:** One hundred and eighteen prostate adenocarcinoma were diagnosed within the study period. The peak age group was 61-70years accounting for 48.3%. The youngest age was 47years and the oldest age was 96 years. Poorly differentiated adenocarcinoma accounted for 48.3%, well-differentiated accounted for 27.2%, moderate to poorly differentiated 17.8% and moderately differentiated accounted for 6.7%. According to the 4 tier group grading system. The group grade 5 with serum PSA above 50.0ng/ml accounted for 43.5% while the same group grade with serum PSA less than 4.0ng/ml accounted for 4.3%. The mean serum PSA was 43.18 ± 40.22 with the range from 1.10 to 270.ng/ml. **Conclusion:** This study shows that there is a weak positive correlation that is not statistically significant between serum PSA levels and newly introduced (2016) Gleason group grade of prostatic carcinoma.
Keywords: Serum PSA, Gleason Score, grade, modified, Prostate adenocarcinoma.

Introduction

Prostate cancer (PCa) is the second commonest diagnosed malignancy and the second leading cause of cancer mortality in men [1]. It account for 7.1% of all cancer cases with an estimate of 18.1 million new cancer cases and 9.6 million cancer deaths in 2018 [1]. The development of Prostate cancer is usually accompanied by a rise in the concentration of serine protease prostate-specific

antigen (PSA). Screening with prostate-specific antigen (PSA) has led to an increasing number of prostate cancer diagnoses, especially in younger men and at an earlier cancer stage [2]. Prostate-specific antigen is produced by normal epithelial cells lining the prostatic glands, hyperplastic epithelial cells and malignant epithelial cells in the prostatic adenocarcinoma. There is destruction of the cell wall integrity which leads to release of PSA into circulation.

Prostate-specific antigen (PSA) is the most useful tumour marker in the diagnosis and first-line test in screening [3]. The increase in serum PSA depends on differentiation of tumour cells and the biology of tumours cells. The poorly differentiated prostatic tumours will have low serum PSA levels compared to well-differentiated tumours [2]. The combination of serum PSA with Gleason score improves the prediction of clinical-stage for prostate carcinoma [3]. The diagnosis requires clinical history, physical examination including the digital rectal examination (DRE), serum PSA estimation and transrectal ultrasound (TRUS), and TRUS-guided needle biopsies of the prostate.

The clinical diagnosis of prostate cancer based on digital rectal examination (DRE) and serum PSA was neither specific nor sensitive. Thus, histopathology of tissue analysis is the gold standard in the diagnosis of prostate cancer. The diagnosis is based on histopathological examination of tissue obtained from the prostate gland such as needle core biopsies, TURP chips and open suprapubic prostatectomy specimens. The histopathological reports must contain Gleason grading and score which were an independent predictor of tumour behaviour and determining the treatment options [4]. The Gleason scoring system is a reflection of tumour architecture proposed by Donald Gleason in 1966 and modified in 2005 [5]. It is divided into five categories (grade 1-5) with increasing tumour aggressiveness and decreasing tumour differentiation. The Gleason score is gotten by adding up the first dominant and the second dominant tumour architecture to obtain a final score. Modified Gleason score have been correlated with serum prostate-specific antigen (PSA) levels, tumour volume on biopsy and pathological stage [6]. The grading scheme has gained almost universal acceptance among anatomical pathologists and urologists [7]. The aim of this study is to correlate serum PSA with Gleason score in prostate cancer at Sokoto, North West of Nigeria.

The aims and objective of this study are

1) To determine the age of the patients with prostate adenocarcinoma.
2) To determine the Gleason score of patients with prostate adenocarcinoma.
3) To determine the correlation between Gleason score and the serum PSA.
4) To determine the correlation between Group grade system and the serum PSA.

Materials and Methods

This was 4year retrospective review of all cases of prostate adenocarcinoma seen in the Department of Histopathology, Usmanu Danfodiyo University Teaching Sokoto between January 2014 and December 2017. All the cases of prostate adenocarcinoma diagnosed were retrieved from the surgical pathology register. The patients' biodata; histology diagnosis, Gleason grade, Gleason score and pre-treatment serum PSA was obtained from the pathology request cards and reports. Other relevant clinical history and preoperative PSA levels were collected from patients' folder. Indications for biopsy were relevant clinical history, elevated PSA, and or abnormal features of the prostate on digital rectal examination (DRE). The specimens were fixed in 10% neutral buffered formalin and processed routinely through dehydration, clearing, infiltrated with paraffin wax for paraffin-embedded tissue sectioning and stained with Haematoxylin and Eosin stain. The slides prepared were reviewed, Gleason grade and Gleason score of prostate adenocarcinoma were done.

Adenocarcinoma was assigned one of the five grades [8]:
Group grade 1 (score 2-6) < 7
Group grade 2 (score 3+4) =7
Group grade 3 (4+3) =7
Group grade 4 (4+4,5+3,3+5) =8

Group grade 5(4+5, 5+4 and 5+5)= 9-10.
Adenocarcinoma was also graded according to 4 tier grading system as follows [9];
Well-differentiated with Gleason score 2-6
Moderately differentiated with Gleason score 3+4
Moderate to poorly differentiated with Gleason score 4+3
Poorly differentiated to undifferentiated carcinoma with Gleason score 8-10.

Serum PSA levels were measured by Chemiluminescence Immunoassay technique using Siemens AdviaCentaur®CP Immunoassay system. Serum PSA level <4.0ng/ml was considered normal. Gleason score and Group grade were then correlated with serum PSA levels. All Cases of benign prostatic hyperplasia and prostate adenocarcinoma without corresponding serum PSA were excluded from the study.

Results

One hundred and eighteen patients had a trans rectal ultrasound-guided biopsy of the prostate with the diagnosis of adenocarcinoma and Gleason score assessed over the study period. The average age of the patients was 68 years ± 8years. The peak age group was 61-70years old which accounted for 48.3% (57). The youngest age was 47years and the oldest age was 96 years (Table 1). About 74.6% (88) of patients presented with lower urinary tract symptoms (LUTS), 11.9% (14) presented with LUTS and acute urinary retention, 10.2% (12) of patients presented with LUTS, lower back pain and inability to walk while LUTS with obstructive uropathy accounted for 0.8% (1). About 2 cases had other complaints which include weakness of bilateral lower limbs swelling, anorexia and weight loss which accounted for 1.6% (Table 2).

The mean serum PSA was 43.18 ± 40.22 with the range from 1.10 to 270.ng/ml. Only 1 (0.8%) of the respondents had a normal serum prostate-specific antigen (PSA) while the majority of the 73 (61.9%) had serum PSA between 11.0ng/ml to 50.0ng/ml (Table 3). Poorly differentiated adenocarcinoma accounted for 48.3%, well-differentiated accounted for for27.2%, moderate to poorly differentiated 17.8% and moderately differentiated accounted for 6.7% according to the 4 tier group grading system (Figure 1).

The Gleason score with group grade 4 was the commonest accounted for 38.1%, 27.2% for group grade 1,17.8% group grade 3, 10.2% group grade 5 and the group grade 2 accounted for 6.7% (Figure 2). The group grade 1 prostate adenocarcinoma with serum PSA above 50.0ng/ml accounted for 14.3% while the same grade with serum PSA between 5-10.0ng/ml accounted for 10.7%. The group grade 5 with serum PSA above 50.0ng/ml accounted for 43.5% while the same group grade with serum PSA less than 4.0ng/ml accounted for 4.3% (Table 4).

The association between prostate-specific antigen and age was found to be significant as all the patients above the age of 80 were found to have had more than 10.0ng/ml in their serum PSA (Table 4). There is a weak positive correlation found between S.PSA and Gleason score with group grade5 and poorly differentiated adenocarcinoma but this was not statistically significant (Table 5).

Table 1. Presentation of respondents by age groups (N=118)

Age Groups	Frequency	Percentage
≤ 50	2	1.7
51–60	18	15.3
61–70	57	48.3
71–80	35	29.7
≥81	6	5.1
Mean±SD	**68.53±8.56**	
Range	**47–96**	

Table 2. Symptoms in respondents

Variables	Frequency	Percentage
LUTS	88	74.6
LUTS & AUR	14	11.9
LUTS, Low back pain and inability to walk	12	10.2
LUTS & haematuria	1	0.8
LUTS & Obstructive uropathy	1	0.8
Others	2	1.6
LUTS (lower urinary tract symptoms) and AUR (Acute urinary retention)		

Table 3. Serum Prostate Specific Antigen (PSA) of respondents

PSA Groups	Frequency	Percentage
0– 4	1	0.8
5–10	6	5.1
11–50	73	61.9
≥51	38	32.2
Mean ± SD	**43.18±40.22**	
Range	**1.10–270**	

Table 4. Association between Prostate-specific antigen and Gleason score with age

Variables	Prostate-specific antigen (PSA)				χ^2	P
	0–4 (%)	5–10 (%)	11–50 (%)	> 50 (%)		
Age Groups					17.121[y]	**0.047**
≤ 50	0 (0.0)	0 (0.0)	2 (100.0)	0 (0.0)		
51–60	0 (0.0)	1 (5.6)	12 (66.7)	5 (27.8)		
61–70	1 (1.8)	4 (7.0)	31 (54.4)	21 (36.8)		
71–80	0 (0.0)	1 (2.9)	25 (71.4)	9 (25.7)		
≥ 81	0 (0.0)	0 (0.0)	3 (50.0)	3 (50.0)		
4 tier Grade score					14.869[y]	0.095
Well differentiated	0 (0.0)	4 (12.5)	24 (75.0)	4 (12.5)		
Moderately differentiated	0 (0.0)	0 (0.0)	5 (62.5)	3 (37.5)		
Moderate to poorly differentiated	0 (0.0)	0 (0.0)	16 (76.2)	5 (23.8)		
Poorly undifferentiated	1 (1.8)	2 (3.5)	28 (49.1)	26 (45.6)		
Gleason score					16.359[y]	0.175
Grade group 1	0 (0.0)	4 (12.5)	24 (75.0)	4 (12.5)		
Grade group 2	0 (0.0)	0 (0.0)	5 (62.5)	3 (37.5)		
Grade group 3	0 (0.0)	0 (0.0)	16 (76.2)	5 (23.8)		
Grade group 4	1 (2.2)	1 (2.2)	22 (48.9)	21 (46.7)		
Grade group 5	0 (0.0)	1 (8.3)	6 (50.0)	5 (41.7)		
[y]=Yates corrected chi-square.						

Table 5. Correlation between prostate-specific antigen and age, 4 tier Gleason and Gleason group grade

PSA	AGE	4 tier Gleason	Gleason Group 5
Pearson Correlation	-0.012	0.156	0.162
Sig. (2-tailed)	0.896	0.091	0.080

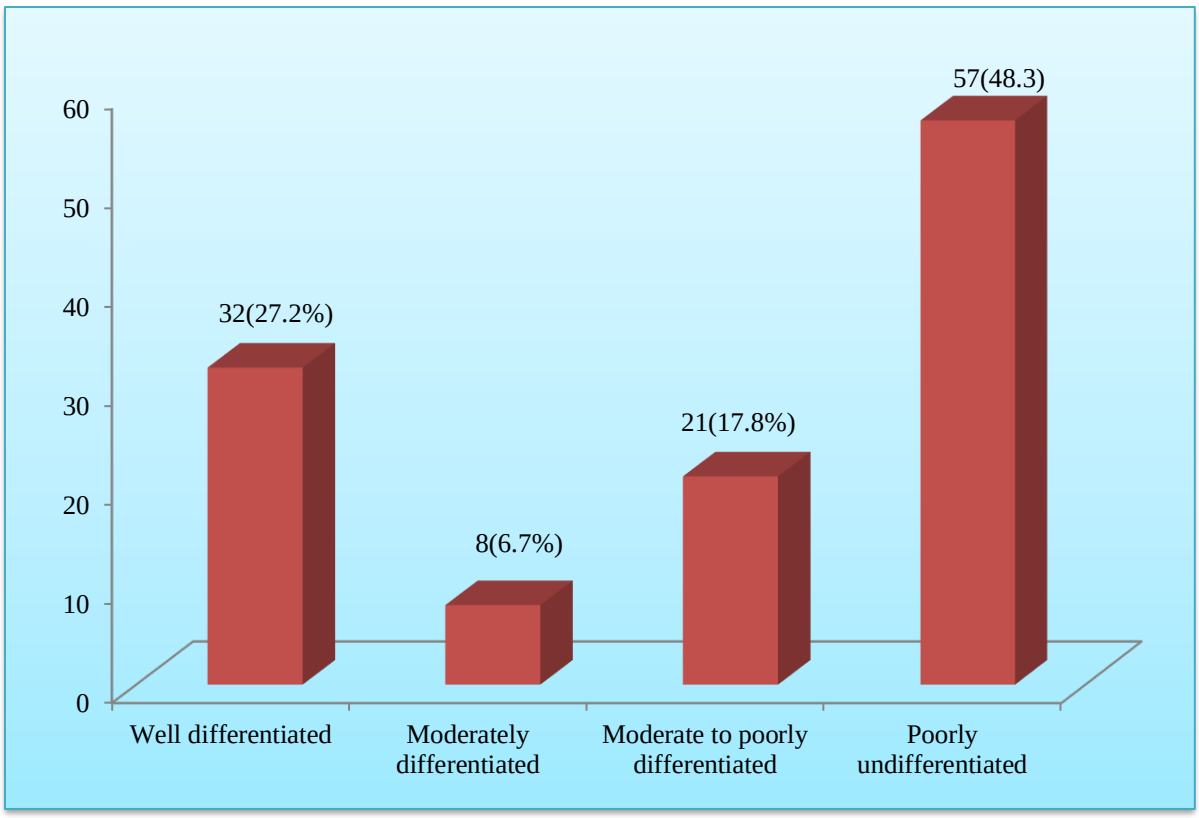

Figure 1. 4 tier group grading system for prostate adenocarcinoma

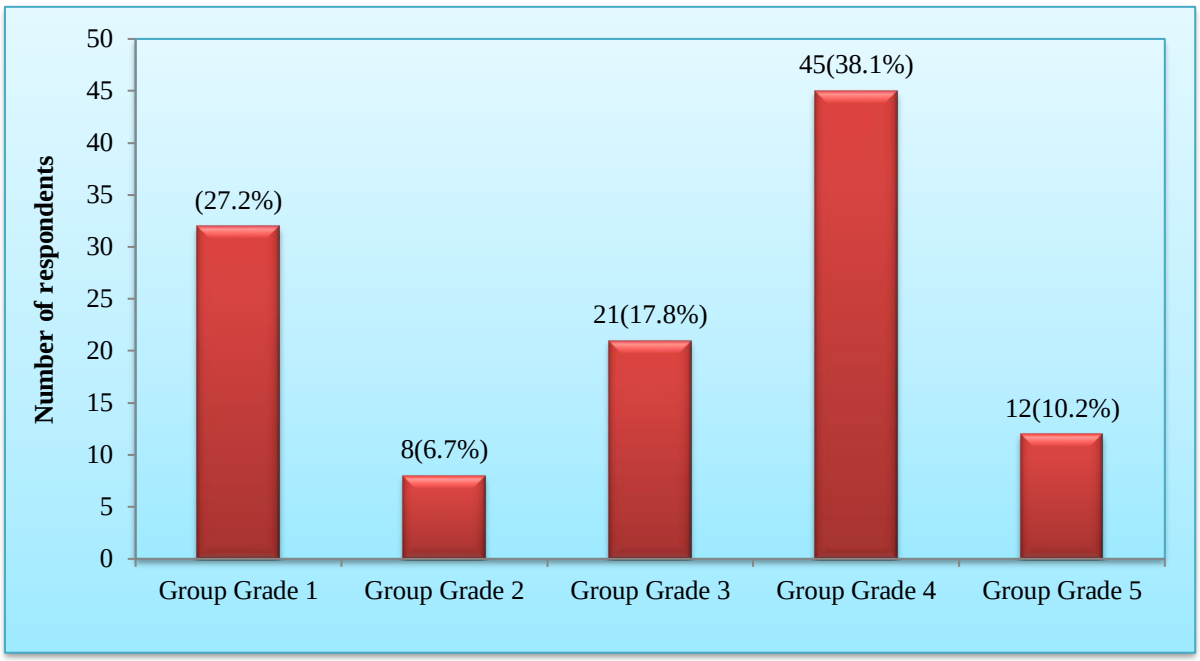

Figure 2. Gleason Grade score

Discussion

Patients were aged predominantly between 60–70 years. The mean age at diagnosis in this study was 68yrs, the youngest patient was 47years and the oldest was 96 years. This is comparable with studies done by Deepika, Abubakar, Jackson and Okolo et al. [10, 11, 12, 13]. In current study prostate cancer was seen among two patients younger than 50 years, these are in keeping with studies done by Abubakar et al. [11] and Jackson et al. [12] both of which showed three patients were below the age of 40 and 50 years respectively. These findings confirm that prostate cancer is a disease of elderly men, although young men are not excluded. However, Prostate cancer occurred a decade earlier in

our patients as compared to their White counterparts in Europe and America where it mainly presents in the eighth decade [14]. This probably reflects the profound effects of genetic and environmental factors with the natural history of Prostate cancer [15]. More than 74.6% of patients in this study presented with lower urinary tract symptoms, this corroborates with the findings from previous studies in Nigeria [11, 12]. However, 11.9% of our patients presented with acute urinary retention, in contrast, to study from Odubanjo et al [16] at Lagos which accounted for 2.9%. This might be due to low level of awareness, knowledge and lack of accessibility to secondary and tertiary health centres or was accessible but they cannot afford the cost of interventions among our patients in the North West.

The symptoms of metastases such as low back pain, paraparesis and paraplegia, abdominal swelling were also found to be common in the current study and this is in keeping with previous studies [16, 17, 18]. The mean serum PSA concentration in our studies was 43.18±40.22ng/mL (range 1.10–270ng/mL). These are comparable to the values reported by Abubakar et al [11] in Zaria, Odubanjo et al [16] in Lagos but lower than the values reported by Okolo et al [11] and Abbiyesuku et al [20] among men with Prostate cancer from other parts of Nigeria. Lower mean serum PSA concentration was reported by Rasool et al [21] among Pakistani men with Prostate cancer (PCa) and by Moul et al [22] among White men with PCa in the US. The variations in serum PSA among different ethnic groups may be attributable to genetic factors [15] while the variations among Blacks may be due to the several other coexisting conditions other than Prostate cancer leads to elevation of serum PSA which includes include benign prostatic hyperplasia, prostatitis, urinary tract infection, and instrumentation [13].

The present study shows that 94.1% had elevated Serum PSA above 10.0ng/ml while 0.8% with S.PSA less than 4.0ng/mg and this is concordance with study by Abubakar et al [11]. However, Deepika et al [10] reported that 84.3% of patients with S.PSA above 10.0ng/ml, 5.9% below 4.0ng/ml while Zivkovic et al [23] showed that 80.0% with S.PSA above 10.0ng/ml, and 2.5% below 4.0ng/ml. These findings were closely related to study from Odubanjo et al [16] and may be explained by the fact that most doctors recommend prostate biopsy in patients with a serum PSA concentration of ≥4.0 ng/mL and arbitrary grading/stratification of S.PSA without the standardized universal scheme. In patients with S.PSA<4 ng/mL and a normal DRE or an abnormal DRE result, the incidence of prostate cancer ranges from 4% to 9% and from 10% to 20%, respectively [24]. Many prostate cancers are missed with this cut-off. The Gleason score with group grade 4 was the commonest accounted for 38.1%, 27.2% for group grade 1, 17.8% group grade 3, 10.2% group grade 5 and the least group grade 2 accounted for 6.7%. However, Abubakar et al [11] reported that Gleason grade group 1 was the commonest in their study with 32.2%, while grade groups 2, 3, 4, and 5 had 6.2%, 14.0%, 29.9%, and 18.0% respectively. This contrasted sharply with studies in many centres in Nigeria [13, 16, 19] and with studies among Black population in the US [25]. However, this may be explained by the fact that the other studies were all not based on the new (2016) Gleason grade group used in this study [26]. Majority of our patients with poorly differentiated adenocarcinoma accounted for 48.3% based on 4 tier grading scheme which was concordant with the study by Deepika et al [10]. However, there is a paucity of data on the majority of the study done in Nigeria and developed countries because they do not consider a 4 tier grading system in the assessment of prostate cancer.

The current study revealed a weak positive correlation between the serum PSA value, the Gleason group grade system and 4 tier grading of prostate cancer. This was found not to be statistically significant. This is in keeping with previous works by Deepika et al [10] and Nnabugwu et al [26].

Conclusion

This study shows that in patients with prostatic adenocarcinoma, there is a weak positive correlation that is not statistically significant between serum PSA levels and newly introduced (2016) Gleason group grade of prostatic carcinoma. We recommend additional studies to be conducted to further

investigate the clinical utility of the correlation between Serum PSA with new grade group system and 4 tier grading system in prospective clinical trials. This will further enhance the prognostication and estimation of the risk of disease progression.

Conflict of Interest: The authors declare that they have no conflicts of interest.

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