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Original Article

Correlation Between Pre Biopsy Serum Prostate Specific Antigen Level and Gleason Score in Patients Diagnosed with Prostate Adenocarcinoma: A Hospital Based Study

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ABSTRACT

Prostate Specific Antigen (PSA) is a non-invasive biomarker in the management of prostate adenocarcinoma. Due to its low specificity, its diagnostic role is controversial in prostate adenocarcinoma. Gleason score is considered as most powerful predictor of prostate carcinoma. PSA in combination with Gleason grading system improves the detection of pathological stage of prostate adenocarcinoma. **Objective:** To determine the degree of correlation between pre biopsy serum PSA level and Gleason score in patients diagnosed with prostate adenocarcinoma. **Methods:** Retrospective cross sectional study was conducted in Chemical Pathology and Histopathology department, Sheikh Zayed Hospital, Rahim Yar Khan between July 1, 2021 and September 31, 2022. A total of 51 histopathologically confirmed cases of prostate adenocarcinoma with documented Pre biopsy PSA level and Gleason score were included in the study. Serum PSA level correlation is compared with Gleason score, Gleason Pattern and Gleason Grade. p-value ≤0.05 taken as significant. **Results:** Mean age for prostate carcinoma patients was 65.71±10.062 years. Mean pre biopsy serum PSA level in study subjects was 40.31±37.52ng/ml. Of the total 51 study subjects, 27 (52.94%) were having Gleason score 7 suggestive of moderately differentiated tumor. Among these, 15(55.6%) were having serum PSA level between 10.01-50.00ng/ml. Statistically significant good correlation of serum PSA with Gleason score, Gleason pattern and Grade was established with p value <0.05. **Conclusion:** It was concluded that there is good degree of positive correlation between pre biopsy PSA level and Gleason score in patients with Prostate adenocarcinoma.

INTRODUCTION

Adenocarcinoma of prostate is one of the most prevalent carcinoma and is becoming a leading cause of mortality among aging males [1]. Around two-third cases of prostate cancer diagnosed in men over 65 years of age [2]. Prostate specific antigen (PSA) is kallikrein-related serine protease that is released by normal epithelial cells of prostate as well as cancer cells [3]. The use of PSA as a noninvasive screening biomarker can enhance the detection of carcinoma at earlier stage and thus the number of metastatic patients can be reduced [4]. PSA is prostate specific but it is not prostate carcinoma specific thus its use as diagnostic tool for prostate adenocarcinoma is controversial due to its elevation in other lesions and procedures such as benign prostatic hyperplasia, urinary tract infection, acute and chronic prostatitis, digital rectal examination, urethral instrumentation and ejaculation [5]. The levels of PSA are race and age adjusted and elevated levels of PSA in progressive carcinoma can be used as prognostic tool [6]. Prostate biological behavior can be predicted by using Gleason scoring and grading system. According to International Standards of Urological Pathology (ISUP) guidelines, it is recommended that the Gleason scores ≤6, 3 + 4 = 7, 4 + 3 = 7, 8 and 9-10 reported as five ISUP Gleason Grades (1-5) respectively [7]. Gleason scoring system is based on degree of glandular differentiation with five patterns of growth on the basis of

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their increasing aggressiveness. A lower Gleason score is assigned to well differentiated tumor and higher is assigned to poorly differentiated or anaplastic tumor. Clinical staging of the prostate adenocarcinoma is based on DRE (digital rectal examination), PSA testing and Gleason score [8, 9]. The correlation between pre biopsy PSA level and Gleason score is evaluated in this study to see the significance of PSA in advanced cancer detection and tumor pathologic grade by assessing the degree of correlation between serum PSA and Gleason score. Implication will be that higher the level of serum PSA, higher the patients having higher Gleason score and high Gleason score is associated with poor prognosis. PSA in combination with Gleason grade and clinical stage improves the pathological stage prediction in prostate carcinoma

METHODS

Retrospective cross-sectional study conducted in department of chemical pathology and histopathology, Sheikh Zayed Hospital, Rahim Yar Khan from July 1, 2021 to September 30, 2022. Non-probability consecutive sampling technique was used. Male ≥45 years of age, histopathologically confirmed cases of prostate adenocarcinoma with documented Gleason Score, Gleason Pattern, International Standards of Urological Pathology (ISUP) Gleason Grade and pre biopsy PSA level were included in study. The cases with missing data or not documented Gleason score and pre biopsy PSA level were excluded. All data was anaonymized and no additional testing was performed, so there was no requirement of ethical approval. A total of 51 subjects satisfying the inclusion criteria were included in the study. Data were retrieved from laboratory information management system of department of chemical pathology and histopathology, Sheikh Zayed Hospital Rahim Yar Khan. Patient's data such as Age, pre biopsy serum PSA level, Gleason pattern, Gleason score and Gleason Grade were recorded on a predesigned proforma. Data was analyzed using SPSS version 23. Continuous variables such as Age, Gleason pattern, Gleason score, serum PSA level presented in terms of mean and SD. Gleason pattern expressed in terms of frequency and percentage. Cross tabulation also generated. Pearson correlation coefficient was applied to test the correlation between serum PSA and Gleason score, Gleason pattern, Gleason Grade. Chi square test used for analysis of significance. P-value ≤0.05 taken as significant.

RESULTS

Of the total 51 confirmed cases of prostate adenocarcinoma, mean age was 65.71±10.062 years with maximum cases n=21 (41.2%) between 66-75 years age group (Table 1). Mean PSA level was 40.31±37.52ng/ml with maximum cases n=18 (35.3%) having PSA level between 10.01-50.00 ng/ml (Table 1). Distribution of study subjects with respect to Age, PSA level, Gleason score, Gleason Pattern and Gleason Grade is illustrated in table 1.

Variable	Mean±SD	Subgroup	Frequency	Percentage
Age (Years)	65.71±10.062	45-55	10	19.6%
		56-65	14	27.5%
		66-75	21	41.2%
		>75	6	11.8%
Serum PSA level (ng/ml)	40.31±37.52	<10.00	15	29.4%
		10.01-50.00	18	35.3%
		50.01-100	7	13.7%
		>100.00	11	21.6%
Gleason Score	7.35±1.016	6	8	15.7%
		7	27	52.9%
		8	8	15.7%
		9	6	11.8%
		10	2	3.9%
Grade Group	2.90±1.300	1	8	15.7%
		2	13	25.5%
		3	14	27.5%
		4	8	15.7%
		5	8	15.7%

Table 1: Distribution of study subjects with respect to Age, PSA level, Gleason Score, Gleason Grade

Cross tabulation of serum PSA categories with respect to Age, Gleason score, Gleason Pattern and Gleason Grade is illustrated in table 2. There was statistically significant positive correlation of serum PSA with Gleason score (r=0.579, p=0.001), Gleason pattern (r=0.674, p=0.000), Gleason Grade (r=0.680, p=0.000) and there was statistically insignificant negative correlation of serum PSA with age (r=-0.174, p=0.222) as shown in (Table 2).

Variable	Subgroups	PSA level(ng/ml)				Pearson correlation coefficient	p-value
		<10.00	10.01-50.00	50.01-100.00	>100		
Age (years)	45-55	2	3	0	5	-0.174	0.222
	56-65	5	5	1	3		
	66-75	7	6	5	3		
	>75	1	4	1	0		
Gleason score	6	8	0	0	0	0.579	*0.001
	7	7	15	1	4		
	8	0	1	3	4		
	9	0	2	2	2		
	10	0	0	1	1		
Gleason pattern	3+3	8	0	0	0	0.674	*0.000
	3+4	7	7	0	0		
	4+3	0	8	1	4		
	4+4	0	1	3	4		
	4+5	0	2	2	2		
	5+5	0	0	1	1		
	1	8	0	0	0		
	2	7	6	0	0		

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Grade Group	3	0	9	1	4	0.680	*0.000
	4	0	1	3	4		
	5	0	2	3	3		

Table 2: Cross tabulation of serum PSA categories with respect to age, Gleason score, Gleason Pattern and Gleason Grade.
*Correlation is significant at p<0.05(2-tailed)

ISUP Grade Group 1 → Gleason score≤6 Gleason → pattern≤3+3 → discrete well formed glands

. ISUP Grade Group 2 → Gleason score 7→ Gleason pattern 3+4 → discrete well-formed glands with lesser component of poorly formed fused glands

. ISUP Grade Group 3→Gleason score 7→ Gleason pattern4+3 → poorly formed fused glands with lesser component of well-formed glands

. ISUP Grade Group 4 → Gleason score 8→ Gleason pattern 4+4 → only poorly formed fused glands

. ISUP Grade Group 5→Gleason score 9,10 → Gleason pattern 4+5, 5+4, 5+5→lack of gland formation (or with necrosis) with or without poorly formed glands

Frequency of age distribution of study subjects is illustrated in figure 1 showing that minimum number of study subjects (n=6) having >75 years of age and maximum number of study subjects (n=21) were between 66-75 years of age.

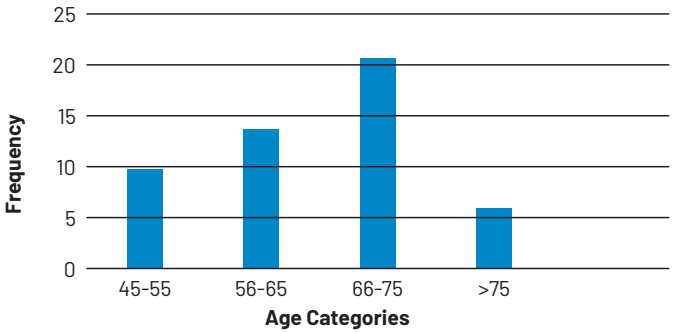

Figure 1: Frequency of Age distribution

Figure 2 illustrate the distribution of study subjects with respect to serum PSA level and it shows that minimum number of study subjects (n=7) were having serum PSA level between 50.01-100.00ng/ml while maximum number of study subjects (n=18) were having PSA level between 10.01-50.00ng/ml.

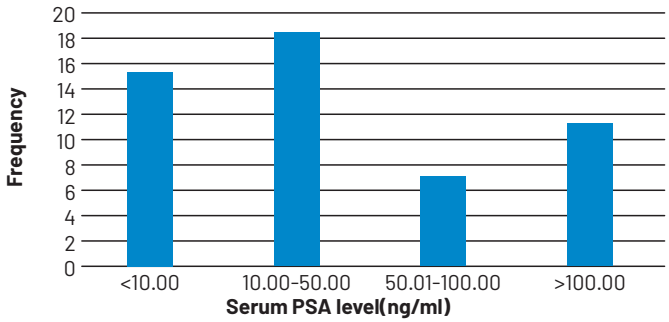

Figure 2: Frequency of Serum PSA level distribution

Figure 3 illustrate the distribution of study subjects with respect to Gleason score and it shows that minimum number of study subjects (n=2) were having Gleason score 10 while maximum number of cases (n=27) were having Gleason score 7.

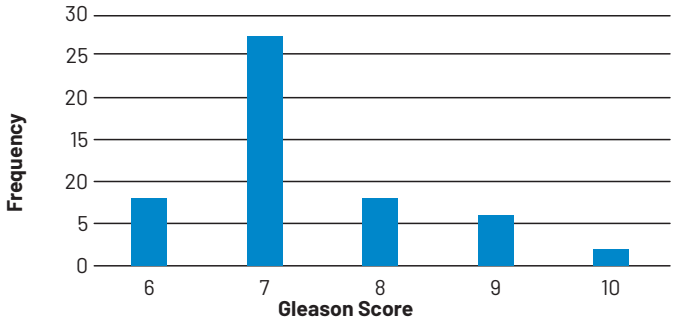

Figure 3: Frequency of Gleason score distribution

DISCUSSION

Of the total of 51 study subjects confirmed cases of prostate adenocarcinoma, age range was 45- 85 years with mean age 65.71±10.062 years. Maximum number of cases n=21(41.2%) were between 66-75 years. Mean PSA level was 40.31±37.52ng/ml with maximum cases n=18(35.3%)having PSA level between 10.01-50.00ng/ml. Our study revealed no statistically significant correlation between age and serum PSA level in prostate carcinoma with p value (0.222). NgwuPE *et al* demonstrated in their study that the mean age of study subjects diagnosed with prostate adenocarcinoma was 71.3±8.7years and mean PSA level was 52.3±37.5ng/ml with p value <0.001 [10]. According to a study conducted by Okolo C.A. *et al*, mean PSA level was 207.9±221.3ug/l with 55% of patients having PSA values >100ug/l [11]. Temel MC *et al* demonstrated the strong positive correlation of ISUP Gleason grade with age and total PSA level with p value <0.05 [12]. Our study revealed that all study subjects with Gleason score 6 were having serum PSA level <10.00ng/ml. A total of 27 study subjects with Gleason score 7, maximum number of cases n=15(55.6%) were having serum PSA level between 10.00-50.00ng/ml. Of the total 8 subjects having Gleason score 8, maximum number of cases n=4 (50%) were having serum PSA level >100ng/ml. Of the total 6 study subjects with

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Gleason score 9, 2 (33.33%) were having serum PSA level 10.01-50.00ng/ml, 2 (33.33%) were having serum PSA level between 50.01- 100.00ng/ml and 2(33.33%) were having serum PSA level >100.00ng/ml. There was a good degree of correlationbetween serum PSA and Gleason score with r=0.579, p value 0.001. Lojanapiwat B. *et al* demonstrated in their study that there is strong correlation between PSA level and tumor aggressiveness [13]. According to a study conducted by Pinsky P F *et al*, it is concluded that PSA level has association with Gleason score and clinical stage when analysed by univariate analysis but no association established in case of multivariate analysis [14]. Iwamoto H. *et al* demonstrated in their study that PSA is useful predictor of prognosis at level between 20-70ng/ml and prognostic value reaches a plateau at level above 70ng/ml [15]. Goldberg H *et al* have demonstrated in their study that aggressive prostate tumors have Gleasonscore 8-10 with PSA level >20ng/ml requiring different treatment modalities [16]. Izumi K *et al* demonstrated in their study that the patients with serum PSA level <3.5ng/ml were havingadvanced disease than the patients between 3.5-10ng/ml [17]. Masic S *et al* demonstrated in theirstudy that low risk prostate carcinoma is associated with low PSA values and high risk prostate carcinoma is associated with high PSA values with statistically significant difference P <0.05 [18]. Partin AW *et al* demonstrated in their study that PSA level >20ng/ml were having more cases ofmetastatic tumor than the cases with PSA values between 4-10ng/ml [19]. Bantis A *et al* in their study concluded that PSA level in combination with Gleason score enhancesthe prediction of advanced cancer. PSA level more than 20ng/ml and Gleason score 8 or more areassociated with metastatic tumor [20, 21]. Of the total 51 study subjects, 8 were having Gleason pattern 3+3 with serum PSA level <10.00ng/ml in all subjects (100%). Total 14 (27.45%) were having Gleason pattern 3+4 with 7(50%) having PSA level <10.00ng/ml and 7(50%) were having PSA level 10.01- 50.00ng/ml. A total 13(25.49%) were having Gleason pattern 4+3 with 8 having PSA level between 10.01- 50.00ng/ml, 1(7.69%) between 50.00-100.00ng/ml and 4(30.76%) having PSA level >100.00ng/ml. Total 8 (15.68%) study subjects were having Gleason pattern 4+4 with 1(12.5%) having PSA level between 10.01-50.00ng/ml, 3(37.5%) having between 50.01-100.00ng/ml and 4(50%) having >100.00ng/ml. 6(11.76%) were having Gleason pattern 4+5 and 2(3.92%) were having 5+5. 1(50%) subject with Gleason pattern were having PSA level between 50.01-100ng/ml and 1(50%) were having >100.00ng/ml (Table 2). Kamel *et al* demonstrated in their study that patients with Gleason pattern 4+3 have higher level of serum PSA than with 3+4 [22]. Of the total 51 study subjects, 8(15.68%) were having grade 1 tumor with all of these having serum PSA level <10ng/ml. 13 (25.49%) were having Grade 2 carcinoma with 7(53.84%) were having PSA level <10.00ng/ml and 6(46.15%) were having PSA level between 10.00- 50.00ng/ml.14(27.45%) were having grade 3 carcinoma with 9(64.2%) having PSA level between 10.00-50.00ng/ml and 4(28.57%) were having PSA more than 100.00ng/ml. 8(15.68%) were having grade 4 tumor with 4(40%) subjects having PSA more than 100.00ng/ml and 8(15.68%) were having grade 5 tumor with 3(37.5%) having serum PSA >100.00ng/ml (Table 2). Aihara M. *et al* illustrated in their study that Gleason Grade 3 is major contributor of serum PSA level than other grades of tumor [23]. Other causes of raised PSA values such as benign prostatic hyperplasia, urinary tract infection, acute and chronic prostatitis, urethral instrumentation, digital rectal examination and ejaculation were not ruled out due to retrospective study. f/ total PSA should have been performed in grey zone patients with serum PSA level between 4.00-10.00ng/ml. Age and race adjusted reference limits should have been used for the interpretation of serum PSA results.

CONCLUSIONS

On the basis of our study, strong positive correlation between pre biopsy serum PSA level and Gleason score was found. Higher level of PSA predicts the aggressive and worst histopathological grading.

Conflicts of Interest

The authors declare no conflict of interest

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