ORIGINAL ARTICLE

Association of Gleason score with PSA Values and Serum Testosterone Levels Measured Prior To Prostate Biopsy

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ABSTRACT

Objective: To analyse the association of prostate cancer (PCa) Gleason score evaluated upon prostate biopsy with clinical PSA values, total and free testosterone (TT and FT, respectively) levels measured prior to biopsy.

Study Design: A descriptive study.

Place and Duration of Study: Department of Urology, Sultan Abdulhamid Han Education and Research Hospital, from July to December 2019.

Methodology: A total of 85 patients were included and classified into non-PCa (group 1) and PCa (group 2) groups according the results of prostate biopsy pathology. Age, digital rectal examination (DRE) findings; prostate volume (PV); free/total prostate specific antigen (PSA) ratio (f/tPSA); PSA density (PSA-D) and total PSA (tPSA), free PSA (fPSA), TT and FT levels of the two groups were evaluated. Associations of the ISUP grade of patients in group 2 with age, DRE findings for PCa; PV; PSA-D; f/tPSA and tPSA, fPSA, TT and FT levels were analysed.

Results: Mean patient age was 63.00 (57.50–70.00) years. Mean age, significant DRE findings for PCa, tPSA levels and PSA-D were significantly higher in group 2 ($p < 0.05$), whereas PV was significantly higher in group 1 ($p < 0.05$). The ISUP grade of patients in group 2 was significantly and positively correlated with age and tPSA levels ($p < 0.05$). ISUP grade was significantly and positively correlated with significant DRE findings for PCa ($p < 0.05$). However, ISUP grade was negatively correlated with PV and f/tPSA ($p < 0.05$). No significant difference was observed between the two groups in terms of TT and FT levels ($p > 0.05$).

Conclusion: TT and FT levels evaluated before prostate biopsy did not provide any additional benefit in predicting Gleason score grade before biopsy.

Key Words: *Prostate biopsy, prostate cancer, ISUP grade, Gleason score, total testosterone, free testosterone*

How to cite this article: Temel MC, Ediz C, Akan S, Ozer E, Yilmaz O. Association of Gleason score with PSA Values and Serum Testosterone Levels Measured Prior To Prostate Biopsy. *J Coll Physicians Surg Pak* 2020; **30(04)**:399-402. DOI: https://doi.org/10.29271/jcpsp.2020.04.399.

INTRODUCTION

Prostate cancer (PCa) is the most common non-cutaneous cancer in men in the United States.[1] It is responsible for 10% of all cancer-related deaths and is the second most common malignancy after lung cancer. Approximately 75% of diagnosed PCa cases are patients aged ≥65 years, and the disease incidence increases with age.[2] Androgens and androgen receptors are important for prostate growth and development as well as PCa development.[3] Porcaro *et al*. reported a positive correlation between basal total testosterone (TT) levels and ISUP grade reported at diagnosis.[4] In a collaborative analysis of 20 prospective studies, men with low circulating free testosterone (FT) levels were likely to be at a lower risk of overall PCa.[5]

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Received: March 14, 2020; Revised: April 30, 2020; Accepted: May 08, 2020
DOI: https://doi.org/10.29271/jcpsp.2020.04.399

Moreover, some parameters such as patient age, digital rectal examination (DRE) finding, total prostate specific antigen (tPSA) level, PSA density (PSA-D) and free/total PSA (f/tPSA) ratio are associated with PCa risk and Gleason grade.[6-10] Thus, Gleason score (GS) for PCa is affected by various parameters.

The association between GS and androgen levels has only been retrospectively evaluated in the past.

The aim of this study was to prospectively analyse the association of ISUP grade with clinical PSA values and testosterone levels evaluated prior to prostate biopsy and to define the parameters that worsen ISUP grade, if any.

METHODOLOGY

Patients who were admitted to the Urology Outpatient Clinic of Sultan Abdulhamid Han Education and Research Hospital between July 2019 and December 2019 with complaints of lower urinary tract symptoms and for whom a prostate biopsy decision was made due to significant DRE findings for PCa and/or tPSA elevation based on physical examination and other evaluations were included. This prospective descriptive study was approved by the local Ethics Committee and conducted according to the principles of World Medical Association Declaration of Helsinki 'Ethical Principles for Medical Research Involving Human Subjects.

Patients aged ≥50 years who underwent prostate biopsy due to the presence of significant DRE findings for PCa and/or tPSA elevation were included in the study. Exclusion criteria were non--consent to participate in the study; age <50 years; urinary system infection that may affect patient's hormonal parameters (tPSA, fPSA, TT and FT levels; f/tPSA ratio and PSA-D); recent invasive urinary system intervention and presence of any additional pathology such as testicular/pituitary/hypothalamic defect, diabetes, obesity (BMI >30 Kg/m^2), severe cardiovascular disease or metabolic syndrome. A total of 85 patients who met these criteria were included in the study.

Table I: Comparison of age; PV; f/tPSA; PSA-D and tPSA, fPSA, TT and FT levels between groups 1 and 2.

Parameter	Pathology	n	Median (interquartile range)	p-value
Age (years)	Group 1	52	59.50 (56.50–68.00)	0.001*
	Group 2	33	65.00 (61.00–73.00)	
Prostate volume (cc)	Group 1	52	48.50 (40.00–62.00)	0.002*
	Group 2	33	36.00 (30–48.00)	
Total PSA (ng/mL)	Group 1	52	5.16 (3.94–7.14)	0.022*
	Group 2	33	6.72 (5.09-11.78)	
Free PSA (ng/mL)	Group 1	52	0.98 (0.68–1.73)	0.291
	Group 2	33	1.19 (0.76–1.73)	
Free/total PSA ratio	Group 1	52	0.19 (0.17–0.25)	0.058
	Group 2	33	0.17 (0.12–0.23)	
PSA density (ng/mL/cc)	Group 1	52	0.10 (0.09–0.15)	0.001
	Group 2	33	0.21 (0.15–0.34)	
Total testosterone (ng/dL)	Group 1	52	456.39 (373.82–535.85)	0.223
	Group 2	33	561.60 (403.97–612.00)	
Free testosterone (ng/dL)	Group 1	52	9.63 (6.92–12.82)	0.256
	Group 2	33	8.97 (6.75–10.30)	

*Values are presented as median (interquartile range). *p < 0.05.*
Median TT levels in groups 1 and 2 were 456.39 (373.82–535.85) and 561.60 (403.97–612.00) ng/dL, respectively. Median FT levels in groups 1 and 2 were 9.63 (6.92–12.82) and 8.97 (6.75-10.30) ng/dL, respectively. Comparative analysis between the two groups revealed no difference in terms of TT and FT levels (p > 0.05, Table I). Results of comparison of age; PV; f/tPSA; PSA-D and tPSA, fPSA, TT and FT levels are shown in Table I. Linear regression analysis with ISUP grade as the dependent variables and age; PV; f/tPSA; PSA-D and tPSA, fPSA TT and FT levels as the independent variables revealed a significant positive correlation of ISUP grade with age and tPSA levels (p = 0.003 and p <0.001, receptively; Table II) and a significant negative correlation of ISUP grade with PV and f/tPSA levels (p <0.001 and p = 0.048, receptively; Table II).

Table II: Linear regression analysis with ISUP grade as the dependent variables and age; PV; f/tPSA; PSA-D and tPSA, fPSA TT and FT levels as the independent variables.

Parameter	Median (interquartile range)	β value	p-value	95% confidence interval for β
				Lower to upper
Age (years)	63 (57.50-70.00)	0.196	0.003*	−0.01 to 0.04
Prostate volume (cc)	45.00 (32.5–59.35)	−0.342	<0.001*	−0.02 to 0.01
Total PSA (ng/mL)	5.59 (4.00–8.53)	1.39	<0.001*	0.04 to 0.11
Free PSA (ng/mL)	1.06 (0.72–1.73)	−0.37	0.19	−0.19 to 0.04
Free / total PSA ratio	0.18 (0.15–0.25)	−0.15	0.048*	−3.80 to 0.02
PSA density (ng/mL/cc)	0.12 (0.09–0.22)	−0.27	0.15	−1.58 to 0.25
Total testosterone (ng/dL)	486.67 (383.73–593.59)	0.09	0.18	0.00 to 0.00
Free testosterone (ng/dL)	9.44 (6.86–11.41)	−0.07	0.25	−0.05 to 0.01
Digital rectal examination findings	Odds Ratio: 2.63	0.97	0.003*	1.40 to 4.92

**p <0.05*

Age, significant DRE findings for PCa (presence of nodules and diffuse stiffness, amongst others); prostate volume (PV) measured by transrectal ultrasonography; tPSA, fPSA, TT and FT levels; f/tPSA ratio and PSA-D were evaluated, and the results were prospectively entered into a data collection system. Blood samples required to test these parameters were obtained between 8 and 10 am just before prostate biopsy. Thus, biopsy was not affected by DRE. No restriction was imposed on patients' sexual activities to evaluate hormonal levels. The patients were classified into non-PCa (group 1) and PCa (group 2) groups according to the results of prostate biopsy pathology. Both groups were statistically compared in terms of the aforementioned parameters. The correlations of ISUP grade with the measured parameters were evaluated by linear regression analysis, with ISUP grade as the dependent variable and age; PV; f/tPSA; PSA-D and tPSA, fPSA, TT and FT levels as independent variables. In addition, binary logistic regression analysis was performed to investigate the association between DRE findings and ISUP grade, with the presence/absence of significant DRE findings for PCa was used as the dependent variables and ISUP grade as the independent variable. GS was classified according to the current 2014 ISUP grading system.

One day before prostate biopsy, oral administration of 500 mg levofloxacin and 400 mg etodolac was initiated and continued for five days. On the day of biopsy, rectal enema (250 mL) was performed prior to prostate biopsy. The procedure was performed with the patient in the left lateral position with flexed thighs. The procedure was performed under ultrasound guidance using a 7.5-MHz biplanar probe. Biopsy was performed on an outpatient basis in a room equipped with all materials necessary for emergency intervention. Sedation and anaesthesia were not achieved. Ten minutes before the procedure, periprostatic nerve blockade was performed using perianal intrarectal lidocaine gel. Injections were delivered at the angle between the seminal vesicle and prostate on each side using 5 cc of 2% lidocaine. The 12 quadrant prostate biopsies were performed by multiple experienced urologists.

Statistical analysis was performed using SPSS for Windows 22.00. Shapiro–Wilk test was used to assess normal data distribution. Qualitative variables were expressed as frequency and percentage, and Chi-square test was applied. Quantitative variables were expressed as median (interquartile range). All variables were non-normally distributed. Therefore, Mann–Whitney's *U*-test was used to evaluate all non-normally distributed variables. Pearson correlation, linear logistic regression and binary logistic regression analyses were performed to assess the correlations amongst variables. Pearson correlation analysis was applied as a preliminary study for linear regression analysis (data not included here), and meaningful results were obtained with linear regression analysis. Binary logistic regression analysis was used to assess the correlation between the presence/absence of significant DRE findings for PCa and ISUP grade. Simple linear regression analysis was to assess the correlations of ISUP grade with age; PV; f/tPSA; PSA-D and tPSA, fPSA, TT and FT levels. A p <0.05 was considered statistically significant in all analyses.

RESULTS

Mean (range) patient age was 63.00 (57.50–70.00) years. Median PV was 45.00 (32.50–59.35) cc. Median tPSA and fPSA levels were 5.59 (4–8.53) and 1.06 (0.72–1.74) ng/mL, respectively. Median f/tPSA ratio was 0.18 (0.15–0.25), and median PSA-D was 0.12 (0.09–0.22) ng/mL/cc. Median TT and FT levels were 486.67 (383.73–593.59) and 9.44 (6.86–11.41) ng/dL, respectively.

Furthermore, 33 patients (38.82%) showed significant DRE

findings for PCa and 52 (61.18%) did not. According to the results of prostate biopsy pathology, 52 patients (61.18%) were included in the non-PCa (group 1) and 33 (38.82%) in the PCa (group 2) group.

Median patient age was 59.50 (56.50-68.00) years in group 1 and 65.00 (61.00–73.00) years in group 2. Moreover, 19 (22.4%) and 14 (16.5%) patients showed significant DRE findings for PCa in groups 2 and 1, respectively. The rate of detecting significant DRE findings for PCa was significantly higher in group 2 than in group 1 ($p = 0.005$). Binary logistic regression analysis was performed with the presence/absence of significant DRE findings for PCa as the dependent variable and ISUP grade as the independent variable, which revealed a significant positive correlation between ISUP grade and the presence of significant DRE findings for PCa ($p = 0.003$).

Median PV was 48.50 (40.00–62.00) cc in group 1 and 36.00 (30–48.00) cc in group 2. PV was significantly higher in group 1 ($p = 0.002$). Median tPSA level was 5.16 (3.94–7.14) ng/mL in group 1 and 6.72 (5.09–11.78) ng/mL in group 2. Median PSA-D was 0.10 (0.09–0.15) ng/mL/cc in group 1 and 0.21 (0.15–0.34) ng/mL/cc in group 2. Age, tPSA level and PSA-D were significantly higher in group 2 ($p = 0.001$, $p = 0.022$ and $p = 0.001$, respectively). No statistically significant difference was observed in terms of fPSA levels and f/tPSA between the two groups ($p = 0.058$, Table I).

DISCUSSION

PCa is the second most common cancer in men and the fifth most common cause of mortality worldwide.[11] Prostate development and growth are closely associated with androgenic stimulation. The association between serum TT levels and PCa has become increasingly clear in the recent years. In a cohort study conducted in the USA, Muralidhar *et al.* reported that older men are more likely to have high-grade PCa or show a high risk of developing PCa.[8] Meanwhile, Alibhai *et al*. attributed even a slight increase in PCa stage and grade at the time of diagnosis to possible delayed diagnosis in older men rather than advanced age.[12] In the present study, a significant positive correlation was observed between age and GS. However, considering the results of regression analysis in which the shared effect of all the above-mentioned parameters on GS was investigated, our results are consistent with those of Alibhai *et al*.[12]

By examining the relationship between PCa and DRE, Carvalhal *et al*. reported that the positive predictive value of significant DRE findings for PCa was significant in men with low serum tPSA levels; this value was 5%, 14% and 30% in men with tPSA levels of 0–1.0, 1.1–2.5 and 2.6–4.0 ng/mL, respectively, and all diagnosed cancers were clinically localised. They also reported that most of these detected cancers were clinically significant and treatable.[6] In the present study, a significant positive correlation was observed between the presence of significant DRE findings for PCa and ISUP grade; therefore, our results are consistent with those of Carvalhal *et al*.[6]

Mir *et al*. investigated the relationship between PCa and PV and, based on multivariate analysis, reported that PV measured using transrectal ultrasonography was negatively correlated with high grade tumour rate determined by pathological examination following transrectal needle biopsy or radical prostatectomy.[13] In another study, Caliskan *et al.* reported that smaller prostates are more likely to compose higher percentage of high-grade prostate cancer, local advanced disease and Gleason upgrading.[14] Consistent with the results of both studies, we observed a significant negative correlation between PV and ISUP grade in multivariate regression analysis in the present study.

PSA forms represent an important adjunct to DRE for the detection of PCa.[15] Fang *et al.* investigated the association between PCa and PSA forms and reported that serum tPSA levels were positively correlated with postoperative GS.[16] According to the results of multivariate regression analysis in the present study, there was a significant positive correlation between tPSA levels and ISUP grade ($p < 0.05$). f/tPSA ratio is specifically used in "grey zone" patients.[17] In a study by Elabbady and Khedr, men with PCa and low f/tPSA ratio were at an increased risk of showing a high GS (7–10) and those with high f/tPSA ratio were more likely to show a low GS.[18] According to the present data, there was a significant negative correlation between f/tPSA ratio and ISUP grade ($p < 0.05$), which is consistent with the study of Elabbady and Khedr.

Drobková *et al.* evaluated androgen presence and PCa and reported that serum TT was not a significant predictive factor for pathological GS and stage.[19] In the present study, there was no significant difference in TT levels between the non-PCa and PCa groups based on the results of pathological evaluation. Furthermore, no positive or negative correlation was observed between TT levels and ISUP grade. In another study on such patients, Morote *et al.* reported that PCa risk and tumour aggressiveness were not associated with serum TT and FT levels.[20] In the present study, no significant relationship was observed between FT levels and PCa risk or risk of increase in ISUP grade ($p < 0.05$). In addition, there was no statistically significant difference between the two groups in terms of FT levels ($p < 0.05$).

Patients' serum hormonal levels were based solely on circulating levels, which may be a limitation of the present study. Data on patients' comorbidities were collected in this study, and comorbidities that could affect hormone levels were excluded; however, no additional evaluation was performed by an expert endocrinologist. Nonetheless, all patient parameters were measured in the same laboratory at a single centre.

CONCLUSION

In patients who underwent prostate biopsy, age, DRE findings for PCa and tPSA levels were positively correlated with increased PCa and ISUP grade risks. However, there was a negative correlation of ISUP grade with PV and f/tPSA ratio. In addition, PSA-D was significantly higher in patients with PCa than in those without PCa based on pathology results. No association of TT and FT levels with the presence of PCa or increase in ISUP grade was observed. In case of suspicion of PCa, prior consideration and evaluation of parameters such as patient age, DRE findings, tPSA, f/tPSA, PV and PSA-D can guide the decision for biopsy. Evaluation of TT and FT levels prior to prostate biopsy offers no additional clinical benefit.

ETHICAL APPROVAL:

This prospective descriptive study was approved by the local Ethics Committee of Haydarpaşa Numune Training and Research Hospital (HNEAH-KAEK 2019/143).

PATIENTS' CONSENT:
Informed consent is obtained from patients to publish the data concerning this study.

CONFLICT OF INTEREST:
Authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
EC: Contributed to the conception and design of the study.
EC, TMC, OE, AS: Collected the data.
EC, YO, AS: Drafted and revised the manuscript.
EC, AS, TMC, OE: Participated in preparing tables and performing statistical analysis.

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