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Original Research

Predictive Value of Prostate-Specific Antigen Density on Tumour Grade in Diagnosis of Prostate Cancer: A Hospital-Based Cross-Sectional Study.

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Abstract

Background: Prostate cancer is the most common urologic malignancy in men, it is witnessing a huge burden in developing countries. Prostate-specific antigen has served as a tool in diagnosis and prognostication. To improve its sensitivity, Prostate-specific antigen density is being used to discriminate between benign and malignant conditions to avoid the incidence of unnecessary biopsy. Similarly, it is important to establish the importance of Prostate-specific antigen density in prognostication to help in treatment stratification. The aim of this study, therefore, is to assess the relationship between Prostate-specific antigen density and tumour grade using the Gleason score.

Methodology: This study was a prospective cross-sectional study carried out between 2015-2016. It involved 191 consecutive patients who were either asymptomatic or symptomatic with elevated prostate-specific antigen (PSA)/abnormal digital rectal examination findings or both. They had a Prostate volume assessment and digitally guided prostate biopsy. Prostate-specific antigen density was calculated, and histopathology reports were evaluated. Data were analysed using SPSS version 20.0. Pearson correlation coefficient and test of ANOVA were used to assess the relationship between prostate-specific- antigen and Gleason score while a scatterplot was used to determine the relationship between prostate-specific antigen and prostate volume. The level of significance was set at $p< 0.05$

Results: All patients in this study were Nigerians, mean age of the study population was 68.2$\pm$ 9.4 years. The median PSA for patients with prostate cancer was 76.9ng/ml and 14.5ng/ml for patients with benign disease, the difference was statistically significant ($p<0.001$), and median prostate volume was 84.5mls while the median PSAD was 0.25. PSAD for Gleason score 2-4,5-7,8-10 was 0.4,0.8 and1.1 respectively which was statistically significant using a test of ANOVA ($p=0.001$). Pearson correlation coefficient revealed a statistically significant correlation between Prostate-specific antigen and Gleason score ($r= 0.375$, $p=0.024$). Using Fisher's exact test there was a statistically significant difference between PSAD for benign prostatic disease and carcinoma of the prostate, $p<0.001$.

Conclusion: The study revealed that Prostate-specific antigen density has a statistically significant predictive value for tumour grade using Gleason score, however no statistically significant correlation was observed between prostate-specific antigen and prostate volume in prostate cancer.

Keywords: *Gleason Score, PSAD, Prostate Cancer, Tumour Grade*

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Introduction:

Prostate cancer is the most common urologic malignancy in men over 50 years old [1, 2]. It is the second leading cause of death from cancer after lung cancer[3]. The chance of any man being diagnosed with prostate cancer is 1 in 10.[3] The incidence of prostate cancer rises with age, 30% in men >50 years of age and 60-80% in men >80 years of age.[4] The incidence rate of the disease varies widely between countries and ethnic populations, the lowest yearly incidence rate occurs in Asia (1.9 per 100,000 in China) and the highest in North America (especially in African Americans, 249 per 100,000)[5] and Scandinavia. Nigerian males have been shown to have a high incidence of prostate cancer as documented in the study done by Osegbein Lagos, which revealed an incidence of 127 per 100,000 men.[6] Similarly, Dawam in Zaria reported that carcinoma of the prostate occurs in 1 in 7 cases of prostatic disease, with prostatic disease accounting for 10% of surgical admissions.[7] Eke and Sapira in Port Harcourt went on to record an incidence of 114 per 100,000 men.[8] Prostate cancer in men has witnessed an increasing burden in the developing world, as life expectancy increases due to improvement in public health and socioeconomic indices,[9] as reflected in a more recent study done in Ife, Nigeria by Badmus et al, where the incidence of carcinoma of the prostate was 182 per 100,000 men.[10]

Prostate-specific antigen (PSA) has been characterised as the most useful serum marker for the detection and management of prostate cancer, however, it is well-recognised that serum PSA is also found to be elevated in many benign prostatic diseases, such as benign prostatic hyperplasia (BPH), prostatitis and after manipulations of the prostate.[11] For practical and clinical purposes, PSA is organ-specific but not disease-specific as demonstrated by substantial overlap in values between men with benign versus malignant prostate diseases.[12] However, PSA has had a major impact on screening, early diagnosis of prostate cancer, monitoring of established disease and as a general prognostic index.[13] The specificity of an elevated PSA is often considered too low for prostate cancer diagnosis, thus men presenting with prostate disorders are most likely to have a biopsy for histological investigation to confirm or rule out cancer.[13] The Gleason histological system is widely used for prostatic adenocarcinoma and it is believed to be an important factor for prognosis. Based on primary and secondary patterns, the Gleason score has been validated as a useful prognosticator.[14] In 2014, the International Society of Urological Pathology consensus conference recommended some changes to the Gleason scoring system, these grades include a Gleason score of 6 or less in Grade I, Gleason 3+4=7 in Grade II, Gleason 4+3=7 in Grade III, all Gleason 8 in Grade IV and all Gleason 9 and 10 in Grade V.[15] In predicting aggressiveness of prostate cancer, prognostic nomograms are in use which utilize PSA level, Gleason score and clinical staging, particularly in borderline cases. These include the Partin tables and the Cancer of the Prostate Risk Assessment (CAPRA) score.[16] Prostate-Specific Antigen Density (PSAD) introduced in the early nineties by Benson et al[17], has been shown to be a better predictor of prostate cancer than PSA but its application has been inconsistent over the years.[18] The tendency to detect clinically significant prostate cancer has been demonstrated severally with the use of PSAD. The integration of PSAD into active surveillance has been shown to improve enrolment criteria and reduce the rate of upgrading and reclassification down to 17.5%[19,20]. This study therefore aims to establish the relationship between prostate volume and prostate-specific antigen and the predictive value of PSAD in determining tumour grade using the Gleason score.

Methodology

Study setting

This study was conducted in the urology unit of a Tertiary Hospital from April 2015 – June 2016. Benin is the capital of Edo state located in the South-South geopolitical zone of Nigeria.

Study population

The study involved patients referred to the urology outpatient clinic, who were either asymptomatic with elevated Prostate-specific antigen (PSA) or presented with lower urinary tract symptoms. They were evaluated for prostate carcinoma with digital rectal examination (DRE) and prostate-specific antigen (PSA). All patients with established clinical suspicion of prostatic carcinoma on account of PSA >4ng/ml and abnormal DRE were referred for prostate biopsy and constituted the study population.

Study design

The study was a prospective cross-sectional study.

Inclusion criteria

The inclusion criteria were: Male patient ≥ 50years who had: Abnormal digital rectal examination findings; Pre-treatment PSA level > 4ng/ml and gave informed consent

Exclusion criteria

The following criteria were used to exclude or discontinue any patient from the study. Urethral instrumentation within the past 3 weeks; Indwelling urethral catheter; a previous diagnosis of carcinoma of the prostate (CaP); patients with urinary tract infection/prostatitis and patients who refused to give informed consent

Ethical consideration

The approval of the ethics and research committee of UBTH was obtained before the commencement of the study. Informed consent was obtained from all patients before enrolment into the study. Also, investigations for the purpose of the study were carried out at no extra cost to the patients. These included serum total PSA. Respondents were informed of their right to decline participation or even opt out of the study whenever they deemed necessary, and patient selection was within set inclusion criteria.

Study procedures

Eligible patients, after a thorough medical history, had a detailed physical examination which included a DRE. Digital rectal examination was considered abnormal when the gland exhibited nodules, asymmetry, irregularity or fixity of overlying rectal mucosa. A venous blood sample was taken for pre-treatment total PSA and free PSA determination. Collected samples were kept at 4^{o}c after centrifugation by a laboratory scientist within 24 hours of analysis or at -25^{o}c when analysis was done after 24 hours. PSA level was determined by the enzyme-linked fluorescent assay (ELFA), using Biomerieux mini VIDAS immunoassay system analyser (2010), which is an automated multi-parametric immunoassay system. A PSA value of > 4ng/ml was considered elevated. Patients with abnormal DRE and/ or PSA >4ng/ml were recruited and had transabdominal ultrasound scans done to determine the prostate volume of the study

population prior to biopsy and patients were subsequently subjected to digitally guided prostate biopsy. A researcher-administered semi-structured proforma was used for data collection which included biodata, observations made on history and clinical examination. Laboratory and radiological tests were also recorded.

All patients had a course of ciprofloxacin and metronidazole antibiotics for 5 days which commenced the night before the biopsy. Patients on aspirin or non-steroidal anti-inflammatory agents had to discontinue the drugs for at least 10 days before biopsy.

Biopsy procedure

All patients had to undergo a digitally guided transrectal prostate biopsy on an outpatient basis. Patients were instructed to empty their bowels on the morning of the biopsy prior to presentation without laxatives. With the patient in the left lateral position and both knees flexed, 20mls of 2% xylocaine gel was instilled into the rectum before the biopsy. An 18G trucut biopsy needle in a spring-loaded Bard monopty ^{R} biopsy gun (Bard urological, Covington GA) was then introduced into the rectum with the aid of the gloved index finger.

Under digital guidance, sextant biopsies were obtained for each patient [from the apex, mid portion, and base of each lateral lobe]. Specimens were collected in a bottle containing 10% formalin and sent for histopathology analysis. All patients were allowed to go home after observation for about an hour following the biopsy. The patients were instructed to report back to the hospital if any complications such as prolonged haematuria, rectal bleeding and fever occurred. Patients were also followed up with telephone calls to ascertain if there were any complications. At the histopathology laboratory, formalin-fixed paraffin-blocked tissues were cut on a microtome to the thickness of 4 microns, and tissue sections stained with hematoxylin-eosin(H&E) were examined by a histopathologist dedicated to this study. Gleason's grade and score were assigned by the pathologist.

Statistical analysis

Statistical analysis was done using the IBM SPSS (Statistical Package for the Social Sciences) software version 20.0. Data that are numerically distributed such as age (years) were expressed as mean ± standard deviation and median when the data is skewed. Data that are categorical were expressed as frequencies and percentages.

To establish the relationship between prostate-specific antigen density (PSAD) and tumour grade, a Pearson’s correlation coefficient was also used. Exploratory data analysis was done to identify the underlying Gleason score distribution amongst outcome variables. The test of statistical significance was done using the independent t-test and analysis of variance (ANOVA). The level of significance was set at $p < 0.05$.

Results

A total of two hundred and one patients who satisfied the inclusion criteria were recruited for this study. Only 191 (95%) patients presented for prostate biopsy, after clinical evaluation.

Patients’ characteristics

All patients in this study were Nigerians with an age range between 50-85 years. About a third of the study population, which accounts for 67 patients were between 60 and 69 years followed by the 70-79year age range accounting for 25.7% of the study population. Seventy-seven (40.3%) of the study

population were diagnosed with adenocarcinoma of the prostate. The mean age of the study population was 68.2± 9.4 years, while the mean age of patients diagnosed with CaP and benign prostatic disease was 68.9±9.4 years and 67.7±9.2 years, respectively. The difference in the mean age of the patient population with CaP and benign prostatic disease was statistically insignificant (p= 0.394).

Most (93%) of the patients who formed the study population had exposure to formal education (93%). As shown in Table 1

Table 1: Patients' characteristics

Variable	Frequency (n = 191)	Percentage (%)
Age group (years)*		
50 – 59	43	22.5
60 – 69	67	35.1
70 – 79	49	25.7
≥80	32	16.8
Level of education		
None	14	7.3
Primary	77	40.3
Secondary	58	30.4
Tertiary	42	22.0

***Mean ± standard deviation = 68.2 ± 9.4 years**

PSA parameters

The PSA range of the study population was 0.27-840ng/ml, the median PSA of patients with CaP was 76.9ng/ml, while for patients with benign prostatic disease, the median PSA was 14.5ng/ml. The difference in mean PSA value between these two groups of patients was statistically significant (p<0.001).

Median prostate volume on ultrasound was 84.50ml IQR =56.00-115.00 and median PSA density was 0.25 and IQR= 0.13-0.79 as shown in Table 2

Table 2: Median and Interquartile range values of PSA parameters

PSA parameter	Median*	Interquartile range (IQR)
PSA total (ng/ml)	21.77	10.0 – 61.00
Prostate volume (mls)	84.50	56.00 – 115.00
PSA density	0.25	0.13 – 0.79

***Median value used because the values were not normally distributed**

Range of PSA for benign prostatic disease (0.27-53.27) ng/ml

Range of PSA for CaP (3.8-840) ng/ml

Correlation between Prostate Volume and Total PSA

There was a weak negative correlation between prostate volume and total PSA (r= -0.02), which was not statistically significant (p=0.845) as shown in Figure 1. The correlation (r) = -0.02 (p=0.845).

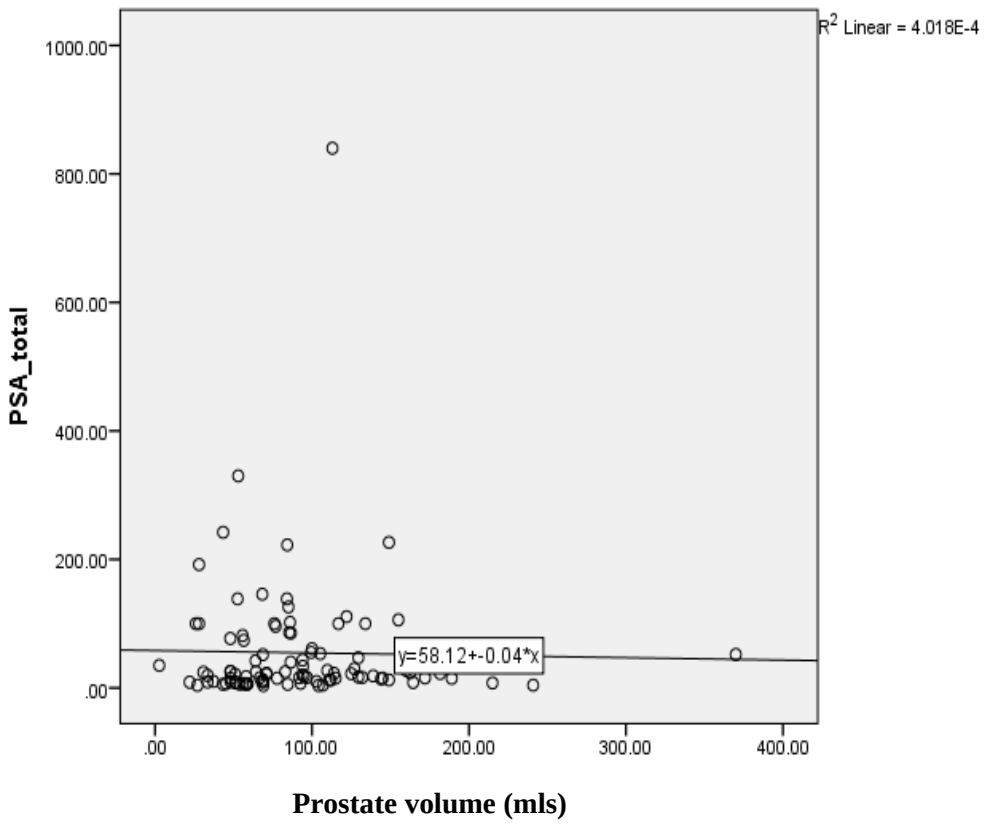

Figure 1: Correlation between Prostate volume (mls) and total PSA (ng/ml) (Scatter plot)

Range of prostate volume for benign prostatic disease (40-370) mls, mean prostate volume (98±55.53).

Range of prostate volume for CaP (27-320) mls, mean prostate volume (92.61±63.69), P=0.536

The PSA density of Gleason's score, 2-4, 5-7, and 8-10 were 0.4, 0.8 and 1.1 respectively. The difference in PSAD of the various Gleason's scores was statistically significant, p=0.001 as shown in Table 3

Table 3: Association between Gleason score and PSA density

Gleason score	Prostate vol. (mean± SD)	Median PSA density
2-4	103.2±70.8	0.4 (0.04-0.75)
5-7	109 ± 74.0	0.8 (0.02-7.43)
8-10	67.1 ± 32.3	1.1 (0.18-6.85)
p-value*	0.021	0.001*

F-test (ANOVA). *Significant. SD = standard deviation

The regression line on the scatter plot shows a weak correlation between PSAD and Gleason score. Pearson correlation coefficient (r=0.375) which was statistically significant p=0.024 as shown in Figure 2.

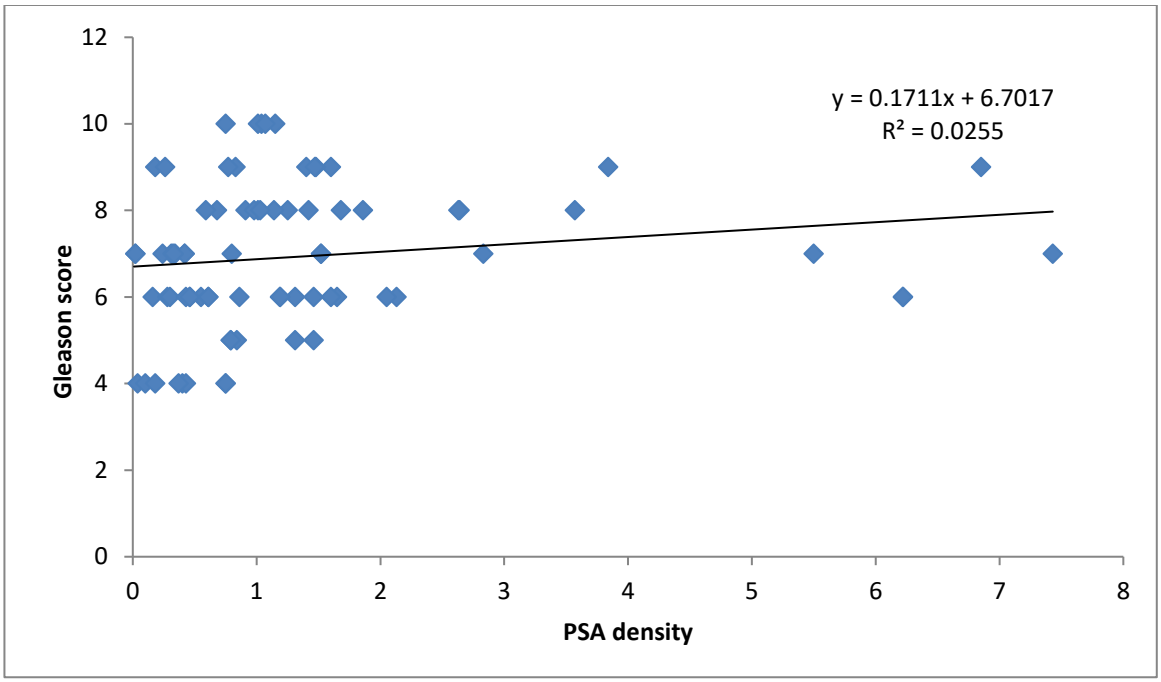

Figure 2: PSA density and Gleason score, r=0.375, p=0.024

Tumour Characteristics

A higher percentage (51.9%) of the study population with adenocarcinoma had Gleason's score 5-7 (moderately differentiated adenocarcinoma) as shown in Table 4

Table 4: Tumour grade of the study population

Variable (Gleason score)	Frequency (n = 77)	Percentage (%)
2-4	8	10.4
5-7	40	51.9
8-10	29	37.7

Tumour Characteristics and PSA Values

The Seventy-seven patients with adenocarcinoma of the prostate had a percentage Free-to-total PSA of ≤25 while the 102 with benign prostate disease had a percentage Free-to-total PSA >25 which was statistically significant (p<0.001).

Seventy-three (94.8%) of the patients with adenocarcinoma of the prostate had PSAD >0.15. Similarly, the only patient with high-grade prostatic intra-epithelial neoplasia (HGPIN) also had PSAD >0.15. However, 65(57.5%) of the patients with benign prostatic disease had PSAD ≤0.15 which was found to be statistically significant (p<0.001) as shown in Table 5

Table 5: Tumour types, and mean PSA density

Tumour type	PSA density		p-value*
	≤0.15	>0.15	
Benign	65 (57.5)	48 (42.5)	<0.001
Malignant	4 (5.2)	73 (94.8)	
HGPIN	0 (0.0)	1 (100.0)	

***Fisher's exact test**

Discussion

Carcinoma of the prostate is the most frequent malignancy of adult Nigerian males with a significant health burden. The advent of PSA has had a major impact on screening, diagnosis, prognosis and monitoring of treatment response in established diseases. A recent innovation has witnessed the use of the ratio of free-to-total PSA and PSAD to improve screening and diagnosis. Histopathologic pattern following prostate biopsy remains the gold standard of diagnosing CaP [25], while Gleason grade/score has been validated as a tool in treatment stratification and prognostication.[21]

In this study, the age range was 50-85 years, with a mean age of 68.2 years. The mean age of patients with CaP was 68.9 years while patients with benign prostatic disease had a mean age of 67.7 years; the difference in age between these two groups was statistically insignificant. The mean age of patients with CaP was in consonance with several other studies in which patients with CaP were in their 7th decade of life, amongst which is Dawam in Zaira who reported a mean age of 62.2 years[7]. Okolo et al[22], also reported a mean age of 68.5 years and in a more recent study, Ezenwa et al[23] and Ojewola et al[24] reported a mean age of 64.4 and 67.4 years, respectively.

The range of serum total PSA of the study population revealed a difference between cancer and benign prostatic disease, the difference in mean total PSA between the two groups was found to be statistically significant. The finding in this study is in consonance with a recently published study that reported a statistically significant difference in PSA ($p<0.001$) for adenocarcinoma of the prostate (79.2ng/ml) and benign prostatic disease (16ng/ml).[25] Similarly, the study by Agyei-Frempong et al[26], reported a significantly higher mean total PSA in the group of patients with CaP (65.4ng/ml) compared to patients with BPH (17.9ng/ml). Udeh et al[27], also recorded similar findings in their study, in which the difference in mean PSA values between prostate cancer patients (49.86ng/ml) and BPH patients (13.71ng/ml) was statistically significant (p value= 0.002). The statistically significant higher PSA value in CaP patients is supported by the fact that prostate cancer tissue contributed more to an increased PSA value than benign prostatic diseases [28], even though there is an overlap in values between CaP and benign prostatic disease.[12] The median prostate volume in this study was 84.5mls. This volume was similar to documented findings in previous studies by Badmus et al[29]. Similarly, Obiesie et al[30] also recorded large prostate volume in a study carried out to assess the correlation between prostate volume and symptom severity score in patients with benign prostatic hyperplasia. Reasons adduced for large prostate volume in blacks include increased sexual activity.[31] The study assessed the relationship between prostate volume and

prostate-specific antigen. The findings noted no statistically significant correlation between prostate volume and PSA as shown in figure 1. This may have been due to the fact that cancer results in distortion of the basement membrane of prostate gland epithelium leading to the release of PSA into the circulation and hence elevated PSA irrespective of prostate volume.[28] However, several studies including those done in Nigeria have proven a positive correlation between serum PSA and prostate volume, even though most of these studies were amongst patients with BPH.[32-34]

Prostate-specific antigen density (PSAD) was correlated with Gleason score/ tumour grade, it was demonstrated in this study, and it was demonstrated that there was a positive correlation between PSAD and Gleason score which was statistically significant (r= 0.375, p=0.024). This is demonstrated by the scatter plot as shown in figure 2. Prostate-specific antigen density increases with increasing tumour aggressiveness as shown in Table 3 which was statistically significant (p=0.001) using test of ANOVA. In a retrospective study, Saidi et al[35] demonstrated that PSAD correlated positively with the Gleason score (r=0.234) which was statistically significant (p<0.05). Similarly, Wang et al[36] also demonstrated that PSAD positively correlated with tumour grade (r=0.804, p=0.0057). In a more recent study, Udeh et al[28] demonstrated a similar finding in which they established a positive correlation (r=0.3097, p= 0.001)

which was statistically significant. In a recently published series conducted in Dhaka, there was a positive correlation between PSA density and Gleason score[37]. The same findings were noted by Sfoungaristos et al[38] in their study which recorded a statistically significant correlation between PSA density and Gleason score.

Furthermore, this study also revealed that PSAD as a predictor of tumour type on histology was statistically significant using a cut-off of 0.15 with a p-value which was <0.001. This is supported by previous studies which documented the predictive value of PSAD in discriminating between benign prostatic hyperplasia (BPH) and carcinoma of the prostate.[7,28] This underscores the usefulness of PSAD in the detection of prostate cancer.

Conclusion

The outcome of this study, therefore, has shown a predictive value of Prostate-specific antigen density (PSAD) on tumour grade using the Gleason score. Hence, it implies that it could be exploited as a useful tool in tumour stratification and prognostication as it also discriminated between prostate cancer and benign prostatic hyperplasia. The study has also shown that prostate-specific antigen does not correlate with prostate volume in those with prostate cancer as it does with benign prostatic hyperplasia.

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