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Original Research

The Role Of Serum Prostate Specific Antigen And Prostatic Volume In The Diagnosis Of Prostate Cancer; A Hospital-Based Study.

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Abstract

Introduction: Prostate cancer is a type of cancer that affects men in most parts of the world. After lung cancer, PCa is the second most common cause of death by cancer.PCa is a type of adenocarcinoma. Adenocarcinoma is a type of cancer that develops in epithelial cells that secrete fluids and mucus. Prostate cancer is characterized by slow growth, and it mostly remains in the prostate gland, though some forms of PCa are very aggressive and can metastasize very quickly to nearby organs. PCa is an example of a heterogenous cancer, with the clinical cause of the disease varying greatly. The gland can be categorized into four zones: peripheral zone (PZ), central zone (CZ), transition zone (TZ) and anterior fibromuscular zone (stroma). The peripheral zone is the largest and makes about 70% of the total gland in men. 70 to 85% of PCa occur in this zone. The transition zone is the innermost zone and makes up 5% of the total gland. Benign Prostatic Hyperplasia (BPH) growth occurs in this zone. Age, dietary changes and environmental factors influence the incidence of PCa. A prostate biopsy is considered as the benchmark test for diagnosis of PCa, but the invasive nature of the procedure makes it highly inconvenient to the patient, hence, it is not widely used as a screening test. PSA is the most used biomarker in PCa screening but, it is limited in its ability to exclude benign tumors from malignant tumors. PSA increases with age which has led to the development of age specific PSA ranges.For men in their fourth and fifth decades, the normal range is 0.6 to 0.7ng/ml, for men who are 60 years and above the normal range is 1.0 to 1.5ng/ml, but the cutoff value for PSA is 4.0ng/ml. PSA levels are also elevated in other conditions such as BPH, and prostatitis. Hence, PSA lacks specificity in diagnosis of PCa. To improve detection of PCa, other parameters derived from PSA such as PSA density (PSAD) have been introduced.

Method: Serum PSA total was estimated by chemiluminescent immunoassay using the Access 2 immunoassay system. Prostate volume was measured by transabdominal ultrasound and the height, length and width of the prostate was measured. Prostate volume was calculated from these parameters by applying the ellipsoid formula. PSA density was calculated from serum PSA and prostate volume by using the formula: PSAD = serum PSA (ng/ml) / prostate volume (cc). Statistical analysis done on the data obtained using IBM's SPSS version 29.0 and Microsoft Excel 365

Results: It was observed that prostate volume and serum PSA total increase with age. Prostate volume and PSA showed a strong and significant correlation, with a**p** value of **0.001 (at p<0.05)** and a Pearson correlation of **r = 0.39**. similarly, PSA and PSAD have a strong and significant correlation, with a **p value** of **0.001 (at p<0.05**) and a Pearson correlation value of **r = 0.84**.

Conclusion: From the above result it was concluded that PSA density is sensitive than PSA total at predicting prostate cancer especially at PSA levels greater than 4ng/ml.

Keywords: baclofen, Carbamazepine, Trigeminal neuralgia

Introduction

Prostate cancer is a type of cancer that affects men in most parts of the world. After lung cancer, PCa is the second most common cause of death by cancer[1]. Cancer refers to uncontrolled cell proliferation. Normal body cells grow and multiply in the process of cell division, forming new cells that replace old and worn-out cells as per the requirements of the body. Cell division is a strictly controlled process, but sometimes the cells grow out of control resulting in the formation of tumors which can be cancerous or non-cancerous. In the process of metastasis, cancerous tumors spread from the prostate gland to nearby tissues and organs of the body. PCa is a type of adenocarcinoma[2]. Adenocarcinoma is a type of cancer that develops in epithelial cells that secrete

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fluids and mucus. These types of cells are mostly made of glandular tissues. Prostate cancer is characterized by slow growth, and it mostly remains in the prostate gland, though some forms of PCa are very aggressive and can metastasize very quickly to nearby organs. PCa that remains confined to the prostate gland usually poses very little thread and may require only minimal treatment to cure it when it is diagnosed early. PCa is an example of a heterogenous cancer, with the clinical cause of the disease varying greatly[3]. Ranging from a quiescent benign tumor which is mostly harmless, only seen accidentally by biopsy testing to highly aggressive tumors that spread very rapidly to nearby tissues and organs. It forms multiple tumor patterns which include glandular, cribriform, and trabecular cell patterns. This heterogenous nature of the disease made way for the development of an effective grading system for the classification of tumors based on cell morphology and arrangement patterns. The prostate gland is a gland that is found only in males, made of glandular and fibromuscular structures. It is a cone shaped structure located deep into the pelvis surrounded by the urethra and lies inferiorly to the bladder. The gland is made up of 5 lobes, an anterior, posterior, median and two lateral lobes[4]. Cancers mostly occur in the media and lateral lobes because they contain glandular tissues, and it is absent in the anterior and posterior lobes that is made predominantly of fibromuscular tissue. Superiorly it is divided into the base, mid-gland, and the apex, with the base being the largest part. The gland can be categorized into four zones: peripheral zone (PZ), central zone (CZ), transition zone (TZ) and anterior fibromuscular zone (stroma)[5], [6]. The peripheral zone is the largest and makes about 70% of the total gland in men. 70 to 85% of PCa occur in this zone. The transition zone is the innermost zone and makes up 5% of the total gland. Benign Prostatic Hyperplasia (BPH) growth occurs in this zone. The central zone makes up 25% of the gland and about 20 to 25% of PCa occur in this zone[7]. The prostate gland undergoes many variations as the male ages on. It has a size of (3×4×2) cm and weighs about 20g in males below 50years and increases to about 38.8g in men in their 80s[8]. This gland plays an important role in reproduction and produces an alkaline fluid that is an active component of semen. The development of the prostate gland is influenced by the hormone testosterone and in the absence of this hormone, the prostate does not develop.

Prostate cancer usually starts when a genetic mutation occurs in the glandular cells of the prostate, mainly in the peripheral zone. Most PCa are confined to the peripheral zone and is easily be detected through a Digital rectal examination (DRE)[9]. PCa being an adenocarcinoma mostly affects the glandular part of the gland. The tumor cells grow and form a nodule within the prostate gland tissue. The tumor can remain confined to the prostate gland or spread to other organs, mostly to the bones and lymph nodes.

Age, dietary changes and environmental factors influence the incidence of PCa[10]. It is clinically silent but when it manifests, symptoms are like those observed in BPH. For this reason, patients are sometimes diagnosed when PCa is already in the advanced stages and metastasis is present. This has led to the push for early screening to detect the disease before it advances to more severe stages. Disorders relating to the prostate are common in men after middle age. This includes Benign Prostatic Hyperplasia (BPH), prostatitis, and PCa[11]. The incidence of PCa is very high but it remains the only kind of cancer that if diagnosed early, can be treated completely. Symptoms of prostate cancer include lower abdominal pain, hematuria, difficulty in passing out urine, urine retention, constipation, bone pain, blood in semen and sometimes losing weight without trying[12].

An ideal screening test for PCa should produce one of two outcomes: Cancer is present, or cancer is absent but, this is not achievable in real practice[1]. A good screening test should be both sensitive (able to detect all true positive cases) and specific (detect all true negative cases). Organized screening of PCa has been shown to decrease death rate compared to opportunistic screening. Though organized screening is associated with decreased death rate, it is associated with a large chance of overdiagnosis. Opportunistic diagnosis has little or no influence on mortality but is also linked with a higher rate of overdiagnosis. Therefore, PCa screening is highly dependent on a balance between the ability to decrease death rate and reduce overdiagnosis and consequently reduce over treatment. A prostate biopsy is considered as the benchmark test for diagnosis of PCa, but the invasive nature of the procedure makes it highly inconvenient to the patient, hence, it is not widely used as a screening test[12]. The Gleason scoring system is the most predictive system used in grading prostate cancer during biopsy testing. The grading system takes into consideration the pattern of arrangement of the different cells in the gland and not the characteristics of a single cell. The arrangement of cells is graded from 1 to 5, with 1 representing a normal pattern of cell arrangement and 5 where the cells patterns are dominated by sheets of abnormal cells. The grading system considers two numbers and the total of both numbers. The first number represents the most dominant pattern of cell arrangement, and the second number depicts a minor pattern, with both being graded with a score of 1 to 5. A cancer is considered as low grade if it has a Gleason score of (3+3) = 6 and below. When the score is (3+4) = 7, it is categorized under intermediate grade cancer, indicating that most of the cells are of a Gleason grade 3 pattern and a few are more aggressive belonging to grade 4. A high-grade cancer is represented by a grade score of (4+3) = 7 and higher. Aggressiveness of the

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tumor increases from grade 1 to grade 5[13]. PSA is the most used biomarker in PCa screening but, it is limited in its ability to exclude benign tumors from malignant tumors. The estimation of serum PSA was approved by the Food and Drug Administration (FDA) in 1986 as a useful tool in tracking treatment progress of PCa and in the later years for the screening of asymptomatic patients[10]. PSA, also known as kallikrein-3 is a glycoprotein made in the prostate gland and plays a role in the movement of sperm cells and dissolves cervical mucus. PSA leaks into blood when the epithelial cells of the prostate gland are destroyed by tumor cells. Normal PSA values increase with age which has led to the development of age specific reference ranges for serum PSA[14]. For men in their fourth and fifth decades, the normal range is 0.6 to 0.7ng/ml, for men who are 60 years and above the normal range is 1.0 to 1.5ng/ml, but the cutoff value for PSA is 4.0ng/ml. PSA levels are also elevated in other conditions such as BPH, and prostatitis. Hence, PSA lacks specificity in diagnosis of PCa. To improve detection of PCa, other parameters derived from PSA such as PSA density (PSAD) have been introduced. PSAD is calculated by dividing serum PSA by prostate volume. Prostate volume (PV) is estimated using medical imaging techniques such as MRI (Magnetic Resonance Imaging), ultrasonography, and CT (computed tomography). Ultrasonography is the most used technique because it is harmless, portable, affordable and gives a real time image of the prostate[15]. Transrectal and transabdominal ultrasound are the most commonly employed. At the age of 50 to 54 years prostate volume is about 24cc and increases to about 38cc after 70years of age. PSA and prostate volume are used in differentiating between PCa and BPH. PSAD increases the diagnostic efficiency of PCa[16].

Benign prostatic hyperplasia is characterized by the proliferation of cells within the transition zone, resulting in an enlargement of the prostate gland. It mostly occurs in aging men and is hormone dependent[7]. By the age of 60 years, at least 50% of men develop BPH and above 85 years of age, close to 90% of men develop the condition. Lower urinary tract symptoms (LUTS) affect men of the older age group, and its prevalence increases to about 70% in men aged 80 years plus[11]. Though LUTS can be caused by other conditions such as infection, it is mostly caused by BPH. There is no evidence that BPH or prostatitis can cause PCa, but the possibility of man having one or both conditions and later developing into PCa cannot be totally ignored. Serum PSA lacks specificity between PCa and BPH. Aside from PSA, other parameters used in predicting PCa include Total PV, PSAD, free PSA to total PSA ratio, transition volume ratio to total prostate volume (TZV/TPV)[17]. These parameters are mostly not used in screening because of the high cost and time involved[16]. The main aim of this study is to evaluate the role of Serum prostate specific antigen and prostate volume in the effective diagnosis of PCa in the hospital.

Review of Literature

Prostate cancer (PCa) poses a global risk to the well-being of the male population[18]. Statistics show that PCa affects at least one in nine men at age above 65[19]. An update by India today suggests that 33,000 to 42,000 new PCa cases are diagnosed in India annually and a new lancet study has revealed that the number of cases diagnosed with PCa is said to double by the year 2040, skyrocketing from 1.4million in 2020 to 2.9million by 2040 and annual deaths predicted to rise by 85%. PCa is most common in developed countries and is estimated to be the fifth cause of death, with varying mortality rates across the globe. Less developed countries have the highest mortality rates due to PCa with respect to more developed regions. Highest rates are observed in populations of the Caribbeans, middle and southern parts of Africa[19]. The major risk factors of PCa are age, being of an African American decent, family history of PCa[20]. The rate at which it progresses to prostate cancer increases with age and environmental factors. Age is the most relevant risk factor of prostate cancer and by age 55 and above the chances of detecting prostate cancer increases. It is rarely diagnosed in men below the age of 40years[21]. Incidence of PCa differs among different ethnic groups. In the United States for example, incidence and mortality rate is higher in black men when compared to white men. The rates are relatively lower in Asians, American Indian natives, and Hispanic men[17]. The main reason behind this difference remains unclear but, many studies have suggested that the difference can be attributed to the stage of diagnosis and access to healthcare facilities. Family history is another factor that increases the risk of developing the disease. Men having a father, or a brother diagnosed with PCa are at a higher risk and the risk increases up to three folds if both father and brother are diagnosed with the disease. In the same way, a man whose brother or father died from PCa is at a higher risk of death by the same when compared to other men diagnosed with PCa with no prior family history of the disease[19]. It was observed in a study that amongst men diagnosed with PCa, high level of activity improves survival rate and reduces progression of the disease. Smoking increases risk of death and advancement of the disease. Early detection by estimation and immediate intervention have greatly fatality. It is the second leading cause of death and occurrence, and mortality rates vary on demography. Most prostate cancers fall in the category of adenocarcinomas and share some similar features with other epithelial cancers such as breast cancer and colon cancer[22]. Morphological changes that may lead to the development of PCa such as prostate enlargement occur early in life. Many studies have

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proven that early screening can reduce death rate by up to 20%. The main goal of screening is to identify the disease in a state that is treatable, thereby preventing death and long suffering[18]. Some autopsy studies have revealed histological evidence of developing the disease in men in their third and fourth decades of their lives. This risk doubles as they grow older. Biopsies from about 80% of men with PCa show evidence of benign prostatic hyperplasia (BPH) in the presence or absence of clinical manifestations. PCa and BPH are both observed in older men and their growth is hormone dependent. Some clinicians believe that PCa develops from BPH while others believe that BPH confers protection against the development of a PCa, with some studies revealing that a larger prostate decreases the chances of developing PCa[14]. An inverse relationship exists between prostate size and the incidence and aggressiveness of PCa. The different zones of the prostate gland have different embryogenic origins, anatomical and functional differences. When the prostate gland is scanned by magnetic resonance imaging, only the peripheral zone can be clearly differentiated from the rest of the gland, it is called the central gland and is different from the central zone. BPH originates from the transition zone. Recent studies have revealed that BPH growth results in changes within the peripheral zone that cause a significant tissue transformation. This soon results to thickening of the prostate capsule and it further progresses to fibrosis referred to as the surgical cap by many urologists because of a distinct plane that forms between the transition zone and the peripheral zone in large prostates, which is less visible in smaller prostates. BPH growth in the transition zone causes cell atrophy in the peripheral zone[7]. This is because the growing transition zone tissue exerts pressure on the peripheral zone, resulting in tissue injury thereby reducing blood flow which eventually results in cell death. Since 80% of PCa arise from the epithelial cells within the peripheral zone, atrophy of cells due to pressure from growing transition zone explains why there is an inverse relationship between prostate size and incidence of PCa. Symptoms of BPH are almost the same as those observed in prostate cancer[12]. A prostate biopsy remains the benchmark test for predicting PCa using the Gleason score grading system[23], [24]. The invasive nature of the procedure makes it highly inconvenient to the patient, hence, it is not widely used as a screening test[25]. As a result, a more convenient, simple, non-invasive, and sensitive technique is required to screen out patients with the disease. PSA is the most used biomarker in PCa but, it is limited in its ability to exclude benign tumors from malignant tumors[26].

Prostate specific antigen (PSA) is used in screening for PCa[9]. It has a low sensitivity of about 40%. It is used in men who are above middle age and men showing lower urinary tract symptoms (LUTS). The estimation of serum PSA was approved by the "Food and Drug Administration (FDA)" in 1986 as a useful tool in tracking the treatment progress of PCa and in later years for the screening of asymptomatic patients. Screening is done in men aged 50years and above and in men with a family history of PCa, screening starts at age 45[27]. Death has greatly decreased with the introduction of PSA screening, but a lot of controversies have sparked because of treatment based on PSA screening, with many studies highlighting the possibility of overdiagnosis and overtreatment and up to 60% of the diagnosed cases by PSA testing are said to be over diagnosed. PSA is an enzyme that is made by the prostate gland that breaks down a semen protein releasing sperm cells. When the epithelial cells of the prostate gland are degraded by tumor cells, PSA leaks into blood streams. PSA levels are also seen to be elevated in other conditions such as benign prostatic hyperplasia, prostatitis, prostate infection[28]. As a result, a high PSA level alone is not enough to make a definitive conclusion on prostate cancer. The low specificity of PSA has made room for many unnecessary invasive prostate biopsies. Most prostate biopsies show a negative PCa because increased PSA levels overlap with other prostate conditions. PSA testing is important in screening out high-risk patients from a larger population. It is most useful in men of middle age and above[29]. Higher levels of PSA usually require further tests for confirmation. When detected early, PCa can be cured but when it is diagnosed in the later stages when symptoms have occurred, metastasis is always present. Many tests that are based on estimation of biomarkers are assigned a cutoff value to differentiate a positive from a negative result. The cutoff value for PSA is 4.0ng/ml. Hence, patients with PSA values less than the cutoff value were not required to undergo further testing.

Prostate volume (PV) is used in diagnosis of BPH, management of lower urinary tract symptoms (LUTS) and in calculating PSA density, a parameter that is useful in managing PCa. Prostate volume is measured using medical imaging techniques including magnetic resonance imaging, ultrasound, and computed tomography[11]. Ultrasound is most used because it is harmless, portable, less expensive and enables the physician to visualize the prostate in real life. Transrectal ultrasound (TRUS) and abdominal ultrasound are the most employed types of ultrasounds in estimation of prostate volume. Traditionally, PV was measured manually on medical images by experts[30]. This resulted in variation between observers thereby increasing the percentage of error. Automated systems for estimating PV are important in eliminating the inaccuracies observed in manual estimation.

The ratio of PSA to PV is known as PSA density (PSAD). PSAD is used in PCa screening to level up the sensitivity and specificity of PSA[31]. It is effective and non-invasive and has been used in many studies to predict the outcome of a biopsy. PSAD is

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useful when serum PSA levels are in the range of 4ng/ml to 10ng/ml[32]. It can be used as an indicator to reduce the number of unwanted (unnecessary) biopsies. This requires a clear cut off value that can clearly differentiate between the benign and malignant form of the disease.

The peripheral zone being the largest part of the prostate (70%) is the zone where 80 to 85% of adenocarcinomas originate while 20 to 25% originate in the central zone. All BPH (100%) occur in the transition zone[5]. A study conducted by[33] explains that the estimation of serum PSA is of a greater significance in men with a smaller prostate. Another study suggests that a small PV can be a strong indicator of cancer in the PSA range of 2.0 to 9.0ng/ml. PV measurements are important in early detection and play a role in excluding the need for repeated biopsies. The level of BPH growth is a strong determinant of increase PSA concentrations[34]. BPH is characterized by prostate enlargement followed by LUTS. Close to 75% of men aged 50years and above develop symptoms arising from BPH. PSA levels are proportional to the volume of prostatic epithelium[35]. In BPH, PSA release increases about four times the normal level while in PCa, it increases to about 30 times. High PSA levels and a small prostate maybe indicative of PCa, while high PSA levels in a man with a larger prostate point towards BPH. A PSAD level greater than 0.15% can indicate a 25% risk of developing cancer. Variations in prostate size is an important factor that cannot be overlooked[9].

Materials and Methods

It is a cross-sectional and quantitative data study involving 85 participants, carried out in Tagore Hospital and Heartcare Center, Jalandhar, Punjab, India. Patients included for the study were both OPD and IPD patients, requesting for both serum PSA test and transabdominal ultrasound, and aged 40 years and above. Patients with extremely high serum PSA levels above 15.0ng/ml and patients going for either serum PSA test or transabdominal ultrasound but not both tests were excluded from the study.

Estimation of serum PSA

All blood samples were drawn prior to transabdominal ultrasound and other prostatic examinations. 4ml of whole blood was collected and allowed for 30minutes at room temperature for clot formation. Serum was then separated from the cells by centrifuging at 3000rpm for 5minutes using the Naya/Remi benchtop centrifuge. Serum PSA total was then estimated using the Access hybritech PSA immunoassay system, which uses a paramagnetic particle and chemiluminescent immunoassay.

Estimation of prostate volume

Prostate volume was measured by transabdominal ultrasound at urinary bladder volume. Prior to this procedure, all blood samples for serum PSA estimation were drawn. A sonogram is obtained with the Length(L), Height (H), and Width(W) of the prostate gland estimated. Prostate volume is calculated from these parameters by applying the ellipsoid formula.Prostate Volume = $L \times H \times W \times 0.52$.

Calculation of PSA density

PSA density was calculated from serum PSA and prostate volume by using the formula PSAD = serum PSA (ng/ml) / prostate volume (cc).

Statistical Methods

Descriptive statistics (average, standard deviations) were performed on the data obtained using Microsoft Excel 365. Test of significance and correlation was done using the Pearson's correlation on IBM's SPSS version 29.0 for a two-tailed analysis at $p < 0.05$.

Results and Observations The research involved 85 males between the age range of 40 to 86 years old. The mean age and standard deviation are 68.98 and 10.81 respectively. Obtained serum PSA values ranged between 0.009 and 12.42, with mean 3.02 and standard deviation of 2.74. Prostatic volume as estimated by transabdominal ultrasound was between 22cc and 76cc, having a mean of 40.69 with a corresponding standard deviation of 14.64. PSA density values derived from PSA and prostate volume was in the range of 0.004 to 0.56, mean as 0.076 and standard deviation of 0.087.

	minimum value	maximum value	Mean	standard deviation
Age	40	86	68.98	10.81
PSA	0.09	12.42	3.02	2.74
PV	22	76	40.69	14.64
PSAD	0.004	0.56	0.076	0.087

Table 1 Represents the minimum and maximum values, mean and standard deviation of all parameters considered in the research

Age distribution

The research included 85 males between the ages 40 to 86 years. The mean age being 68.98 with a standard deviation of 10. 81. Most of the patients were within the age range of 61 to 70 years, with a total of 30 patients making up 35.29% of the total population. Second to it is the age range of 71 to 80 years with a total of 25 patients, making up 29.41% of the total population. 13 patients were aged 81+ making up15.29% 0f the total population and the lowest number was found in the age group of 40 to 50 years with only 5 patients (5.88%).

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Age	Number of patients
40-50	5
51-60	12
61-70	30
71-80	25
81 +	13
Total	85

Table 2 Shows the distribution of the study population based on age

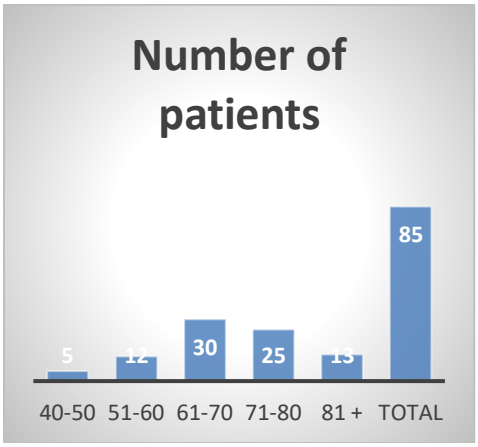

Figure 1 shows a graphical representation of the study population by age group.

PSA and age: The data from PSA values was divided into 3 main groups, less than 2.0ng/ml, between 2.0 and 4.0ng/ml and greater than 4.0ng/ml. A total of 39 patients had a serum PSA level less than 2.0ng/ml (45.88% of the total population). It was closely followed by 24 patients having a serum total PSA level greater than 4.0ng/ml, making up 28.24% of the total population. Most patients (15) with serum PSA levels less than 2.0ng/ml were in the age group of 61 to 70 years while 10 patients in the age range 71 to 80 years had serum total PSA value greater than 4.0ng/ml. In the age range of 40 to 60, no patient was recorded having a serum PSA value greater than 4.0ng/ml.

Age	PSA<2.0 ng/ml	PSA 2.0-4.0ng/ml	PSA>4.0ng/ml	Number of Patients
40-50	4	1	0	5
51-60	7	5	0	12
61-70	15	6	9	30
71-80	10	6	10	25
81 +	3	4	5	13
Total	39	22	24	85

Table: 3 Depicts the relationship between Age and serum PSA levels

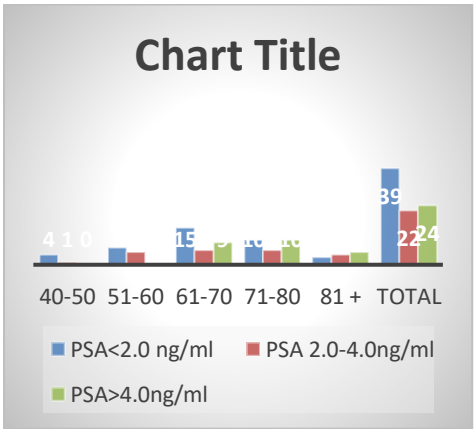

Figure: 2 Graphical representation of the distribution of serum PSA levels in the different age groups.

Age and Prostate volume

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As estimated using transabdominal ultrasound, PV values ranged from 22cc to 76cc with a mean ± standard deviation of 40.69 ± 14.64. Of the 85 patients evaluated, 51 (60%) had a moderately high (30 to 60cc) prostatic volume, while 24 patients (28.23%) had a normal prostatic volume less than 30cc and 10 patients (11.76%) with a very high prostatic volume going above 60cc. In the age range 61 to 70, 25 patients measured a moderately high prostatic volume while 7 patients falling in the age range of 71 to 80 had a very high prostatic volume. Zero patients between age 40 and 60 showed a very high prostatic volume.

Age	Normal (<30cc)	moderately high (30-60cc)	Very High (>60cc)	Number of Patients
40-50	2	3	0	5
51-60	6	6	0	12
61-70	4	25	1	30
71-80	10	8	7	25
81 +	2	9	2	13
Total	24	51	10	85

Table: 4 Distribution of prostatic volume with Age.

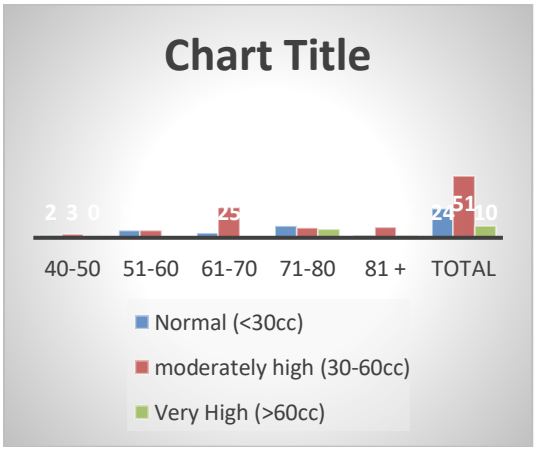

Figure: 3Distribution of prostatic volume within the different age intervals.

Prostate volume and serum PSA: A test of significance shows a p value of 0.001 (at $p<0.05$) and a Pearson correlation of r = 0.39 showing that prostate volume and PSA are significant and have a weak positive correlation. Prostatic volume and serum PSA are two useful parameters employed in differentiating between PCa and BPH. Both parameters increase with age. A scattered plot of prostatic volume and serumPSA confirms that there is a positive linear correlation between prostatic volume and serum PSA.

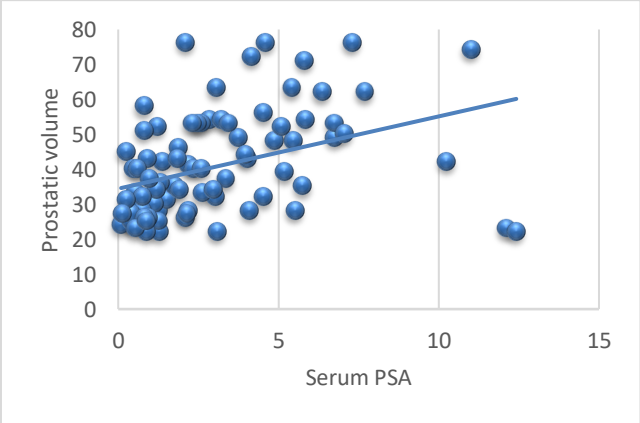

Figure: 4the scattered diagram depicts the relationship between serum PSA and prostatic volume.

Serum PSA and Prostate volume

Of all the 85 patients involved in this research, 6 (7.06% of the total study population) showed PSA density values greater than or equal to 0.15. Within the 6, 4 patients had a high serum PSA level with a corresponding prostatic volume below 30cc. A test of significance shows a p value of 0.001 (at $p<0.05$) and a Pearson correlation value of r = 0.84, this indicates that PSA and PSAD have a strong and significant correlation. A scattered plot of PSA and PSA density shows a strong positive correlation.

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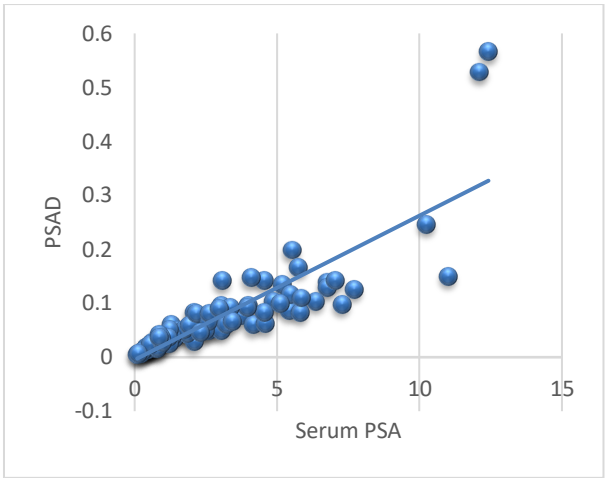

Figure: 5 Represents the relationship between serum PSA and PSA density.

Discussion

The results show that there exists a positive correlation between prostate volume and serum PSA, and both tend to increase with age. Serum PSA and PSA density have a significant correlation, with PSA density being more sensitive in predicting PCa.

Age is a significant factor in the development of PCa. As a man advances in age, the prostate grows bigger. This increase in prostate size results in a corresponding increase in serum PSA. The growth of the prostate gland is highly dependent on hormones (androgens). Between the age of 25 to 30 years, the prostate is about 20g. After age 40, the prostate can grow to a larger size.

Though PSA has a low diagnostic significance, it is still the most used screening test for PCa. Before the introduction of serum PSA, most men diagnosed with PCa were already at the metastasis stage at the time of diagnosis. After introducing serum PSA in PCa screening, the number of men presenting with metastasis at the time of diagnosis reduced. Also, about 75% of men with PCa have non palpable tumors which are detected only by biopsy testing guided by high PSA levels. But, because serum PSA is highly unspecific in diagnosis of PCa, conclusions based on high PSA levels alone result in overdiagnosis and overtreatment. This is because PSA levels have been shown to increase in other prostate conditions such as bacterial prostatitis and BPH. Serum PSA levels have been shown many researchers to increase with age, contributing greatly to the development of age specific serum PSA ranges[1], [28]. Research has confirmed that as a man ages on, the prostate gland increases in size[9]. This increase in prostate size results in a corresponding increase in production of PSA by the cells of the prostate gland and serum PSA is proportional to the volume of the prostatic epithelium.

PSA in blood exists in two forms: bound PSA and unbound (free) PSA. Bound PSA is linked to other proteins while unbound PSA circulates freely in blood. Total PSA includes both bound and unbound PSA. In people with non-cancerous prostate conditions such as BPH and prostatitis, the levels of free PSA are usually very high compared to PCa patients with a relatively lower unbound PSA level. Therefore, a high serum PSA level does not directly translate into PCa but, measuring the free PSA to total PSA ratio can offer more insights into predicting PCa.

Prostate volume alone has no significant diagnostic potential of PCa. But when employed alongside serum PSA, there is an improvement in prediction of PCa. Many literatures have stated that just like serum PSA, prostate volume also increases with age. According to research carried out by[37], when serum PSA levels fall between the range of 2 to 9ng/mml and showing a corresponding small prostatic volume, it becomes a strong predictor of PCa. This can be explained by the fact that prostate gland hyperplasia mostly occurs in the transition zone of the prostate, while prostate cancer occurs in the peripheral zone. A high serum PSA with no significant increase in gland size cancels out the possibility of having benign prostatic hyperplasia[34]. Prostatic volume therefore increases the diagnostic potential of serum PSA and prostatic volume estimation can result in early diagnosis of prostate cancer, thereby reducing the need for multiple biopsy testing. Benign prostatic hypertrophy is a strong determinant of increase in serum PSA levels. Therefore, prostatic volume estimation prevents overdiagnosis and consequently overtreatment by reducing the number of biopsy tests. Larger prostates are the result of BPH growth in the transition zone. This growth exerts pressure on the peripheral zone, leading to a reduction in blood flow and other drastic changes that finally result in cell atrophy. Some literatures suggest that prostate volume has little or no influence on the detection of PCa but in a recent study published by Yamashiro et al[7] concluded that a large prostate confers protection against development of PCa. Explaining their results suggested that since majority of PCa growth occurs in the peripheral zone and because it is well documented that large prostates are because of BPH growth in the transition zone. In the same study they established that there exists an inverse relationship between prostate size and the

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incidence and aggressiveness of PCa. Cell atrophy that occurs in the peripheral zone reduces PCa growth. Measuring total gland volume is of less significance in predicting PCa but, transition zone volume to total prostate volume ratio is significant in diagnosing PCa. The bigger the ratio, the higher the chances of diagnosing prostate cancer.

Hanafi et al[38] on exploring the relationship between prostate volume and PSA with body mass index in men aged 40 years and above, concluded that age and body mass index are positively related to prostate volume and PSA. But they found no correlation between prostate volume and PSA. Another study conducted by **Neziri** et al[39] in BPH patients concluded that PSA and prostate volume showed a significant correlation and the levels rising with age.

The sample size and variations in methods of estimation of both PSA and prostate volume can somehow contribute to the discrepancy observed. The result of each estimation is highly dependent on the sensitivity and specificity of the method employed. Prostate volume can be determined by magnetic resonance imaging, computed tomography, and ultrasonography. These methods have varying sensitivities and accuracy rates. Bladder volume also has a significant influence in the measurement of prostate volume and different results could be obtained at different bladder volumes[15], [40].

PSA density is a measure of the amount of PSA in blood with respect to prostate volume. The cut off value for PSA density used in this study is 0.15. At PSA density levels greater than 0.15, chances of detecting prostate cancer increases by 25%. Research findings suggest that a high serum PSA plus a corresponding small prostate volume maybe indicative of PCa while a high serum PSA followed by a high prostate volume maybe suggestive of BPH[11]. PSA density is a parameter derived from PSA and prostatic volume. PSA density is considered as a stronger determinant of prostate cancer[41], [42]. In many studies, PSA density has been used to predict the outcome of a biopsy test, thereby further reducing the number of unnecessary biopsies[43], [44]. The predictive value of PSA density requires that a clear cut off value be used that can differentiate between the benign and malignant forms of the disease[12].

A study by Nath et al[29] on 106 individuals with serum PSA in the range of 4.0 to 9.99ng/ml suggests that PSA density is useful in distinguishing between BPH and PCa, with 54 showing a positive biopsy with PSA density of 0.15 ± 0.01. Another study by Shrestha et al[44] on80 biopsies concluded that the diagnostic efficacy of PSA density is a better predictor of PCa at cut off value of 0.18. A large majority of PCa growth occurs in the peripheral zone. PSA density has a good predictive but, measuring peripheral zone PSA density as revealed by Wang et al[13] the highest predictive value of PCa.

Due to variations in prostate cancer characteristics in relation to family history, environmental and morphology, Nahvijou et al[1] proposed the implementation of a more personalized PCa screening method paying attention to individual PCa risk factors to improve screening efficacy.

Conclusion

From the results, it can be concluded that prostate volume and serum PSA have a significant positive correlation. Serum PSA alone is not sufficient in diagnosis of PCa. Increase in the production of serum PSA has been observed in other prostate conditions such as BPH and prostatitis. This reduces the sensitivity of serum PSA as a diagnostic tool for PCa. PSAD, which is a ratio of serum PSA and prostate volume is more significant at predicting prostate cancer especially in the PSA range of 4ng/ml to 10ng/ml.

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