**J. Bio-Sci. 30(1): 79-89, 2022 (June)** **ISSN 1023-8654**
http://www.banglajol.info/index.php/JBS/index
**DOI:** https://doi.org/10.3329/jbs.v30i1.63103

# THE ROLE OF FREE PROSTATE-SPECIFIC ANTIGEN IN THE DIAGNOSIS OF PROSTATE CARCINOMA: A CROSS-SECTIONAL STUDY IN RAJSHAHI, BANGLADESH

**Md. Azizul Islam[1&2], S M Shahinul Islam[1*] and Md. Jawadul Haque[2]**

*[1]Institute of Biological Sciences, University of Rajshahi, Rajshahi-6205, Bangladesh*
*[2]Rajshahi Medical College, Rajshahi, Bangladesh*

## Abstract

The prevalence of prostatic carcinoma is the outcome of several factors including improved awareness the general population of the significance of carcinoma of the prostate and progresses in diagnostic approaches. The PSA is a probable prostate cancer tumor marker, although it cannot distinguish prostate cancer from BPH solely. To assess the usefulness of free, total, and free/total PSA ratios in differentiating BPH and prostate cancer has been studied under this research work. The work was carried out at RMCH during April 2021 to March 2022, 350 purposively selected urology outpatients and inpatients at RMCH were studied cross-sectional study. Trans-rectal ultrasound (TRUS) and serum PSA levels were analyzed along with Digital rectal examination (DRE). A digital guided prostatic biopsy using a monopty biopsy gun confirmed the diagnosis. Data analysis was done in SPSS 26 software program. Prostatic cancer was more prevalent in men aged 70-80, whereas BPH was more common in men aged 60-70 ($p = 0.00032$). Histopathology revealed 95 prostate cancer patients, 82 with PSA >4 ng/ml and 85 patients had f/t PSA ratio>0.16. BPH was found in 255 individuals. 139 BPH patients had total PSA >4 ng/ml and 245 BPH patients had f/t PSA ratio ≤0.16. Total PSA had sensitivity and specificity of 86.32% and 45.49%, respectively, lower than f/t ratio. The (Positive predictive value) PPV and accuracy was significantly higher in f/t ratio than total PSA. Along with total PSA, free and free/total PSA ratio may help detect prostate cancer early and distinguish BPH from prostate cancer.

***Key words:*** Carcinoma prostate, Benign prostatic hyperplasia, Prostate specific antigen, Transrectal ultrasonography, Digital rectal examination, Transurethral Resection of Prostate

## Introduction

The prostate is the biggest male accessory gland and is involved in male fertility. It is located near the bladder's neck and surrounds the urethra. The gland secretes several substances required for spermatogenesis. Steroid and peptide hormones are required for prostate gland healthy growth. Both growth factors and hormones affect the prostate. It's born weighing a few grams and matures to about 20 g (Kumar and Majumder 1995). The National Cancer Institute states the prostate gland enlarges along with age. BPH, the most frequent benign tumor in men, rises with age and causes excessive urination by pushing on the bladder and urethra. But it doesn't convert into prostate cancer (Advanced Urology 2021). There were 2,441 new instances of prostate cancer (1.6%) and 1,289 deaths (1.2%) due to the disease (Sung et al. 2021, WHO 2020). Recent study showed growing cancer mortality in Bangladesh due to low literacy, lack of cancer information, and economic hardship (Yazad 2022). The prostate is the sole organ that produces PSA (Kuriyama et al. 1980). PSA is a known biomarker for tumor recurrence (Moradi et al. 2019). PSA, a protein

*Author for correspondence: shahinul68@gmail.com

generated by prostate gland cells, may circulate in two ways: coupled with protease inhibitors α-1 Chymotripsin or α-2 Macroglobulin or alone an "fPSA" travels alone. The PSA test measures both free and bound PSA, unlike the free-PSA test. Conditions other than prostate cancer may elevate PSA like prostatitis, prostate enlargement, and aging. Those with a high PSA have a 75% chance of not having prostate cancer (Harvard Health Publishing 2009). Serum PSA levels are associated with disease development, but the accuracy of PSA testing for diagnosis is debatable (Moradi et al. 2019). PSA may be used to diagnose both benign and malignant prostate illnesses, making it a clinically equivocal test. But PSA testing alone cannot distinguish between prostate cancer and benign diseases, early clinical studies did not exhibit PSA testing's full therapeutic potential (Woodrum et al. 1998). A biopsy is often used to diagnose cancer in men. A biopsy is less painful than surgery, although it may cause some discomfort. Rather of biopsying every patient with a high PSA, urologists assess fPSA in those with a PSA between 4-10 ng/ml. Men having a tPSA in the range and an fPSA under 10% should be biopsied. More likely than not, they have prostate cancer (Harvard Health Publishing 2009). PSA measurement is a non-invasive diagnostic technique for early identification of prostatic cancer. For the diagnosis of prostate cancer, percent fPSA is preferred over tPSA (Asafudullah et al. 2009). For better prostate cancer screening and future research, the study's purpose was to see the role of fPSA and f/t PSA in correctly identify prostate cancer versus BPH and reduce needless biopsies. The research work has been undertaken following the objectives- to assess the role of tPSA, fPSA and f/t PSA levels in diagnosing BPH and prostatic carcinoma and to determine the ability of the serum PSA free/total ratio to diagnose prostate cancer and BPH.

## Materials and Methods

This research was carried out on a descriptive and analytical cross-sectional observational study. The research was conducted between April 2021 to March 2022 in Rajshahi Medical College Hospital (RMCH) in Bangladesh on outpatients and inpatients in the urology department. Here, 350 patients with symptoms of the lower urinary tract, such as frequent urination, urgency, reluctance, poor flow, incontinence, and nocturia, excessively big or nodular prostate detected by digital rectal examination suspected for BPH or prostate cancer were studied in men aged 50 and older. Inclusion criteria of this study were male patients above 50 years of age with enlarged prostate, digital rectal examination findings of enlarged or hard prostate and the presence of lower urinary tract symptoms such as frequency, urgency, hesitancy, poor flow, incontinence, nocturia. Exclusion criteria included: painful prostate on digital rectal examination, prior TURP history (acute or chronic), heart attack, and patients who were critically unwell. Patients were asked to sign a consent form for examinations and testing. The baseline study consisted of a patient's history, physical assessment and serum PSA (tPSA and fPSA). An ultrasonogram of the prostate was conducted to determine prostatic volume. A patient's 5cc venous blood was measured for PSA (free and total) prior to any prostatic intervention. For determination of PSA, from each patient, 5 cc venous bloods were taken before any prostatic manipulation. Clinically suspicious patients of BPH or carcinoma prostate were sent for serum PSA (Free, total and f/t ratio) estimation before any prostatic manipulation. Serum separated from the clot within 3 hours from the time of collection and stored at 2-8°C. Total PSA was assayed by Micro particle Enzyme Immunoassay (MEIA). Total PSA, free PSA and free/total ratio of PSA were measured in all cases in the immunology department of Rajshahi Medical Colllege, Rajshahi. Patient, with serum total PSA >10 ng/ml regardless of free/total ratio and patient with serum PSA 4-10 ng/ml in whom free/total PSA ratio <0.l6 were selected for biopsy. Rest of all done histopathological examination after TURP. DRE was done to observe the prostate to be firm (rubbery), nodular, or hard. High PSA or suspected DRE required transrectal ultrasound. TRUS was done to identify any hypoechoic or isoechoic lesion. Patients who declined TRUS-guided biopsy were given a digitally guided biopsy. Biopsy samples were collected in preservative-filled containers (10% formalin). The samples were subsequently sent to the Dept. of Pathology, Rajshahi Medical

College. After rigorously checking and rechecking the data, the student's unpaired' test or the chi-square test was used for statistical analysis. The p-value for significance was chosen at ($p<0.05$).

## Results

The total study population was 350 patients aged <60 to >80 years, according to <60 years 5% was prostate carcinoma and 4% was BPH, 60-70 years 21% was prostate carcinoma and % was BPH, 70-80 years 42% was prostate carcinoma and 45% was BPH and >80 years 32% was prostate carcinoma and 8% was BPH. Fig. 1 demonstrated the age distribution of the prostatic carcinoma and BPH patients. P value was found ($p = 0.00032$) and it was statistically significant.

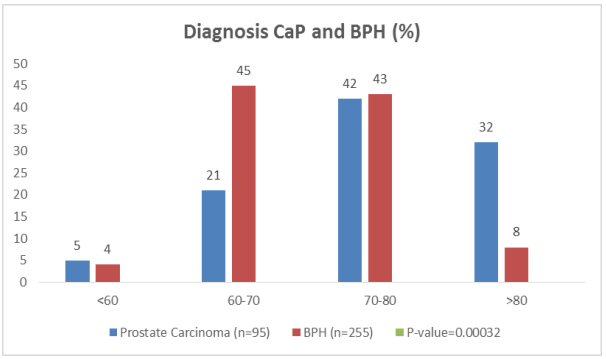
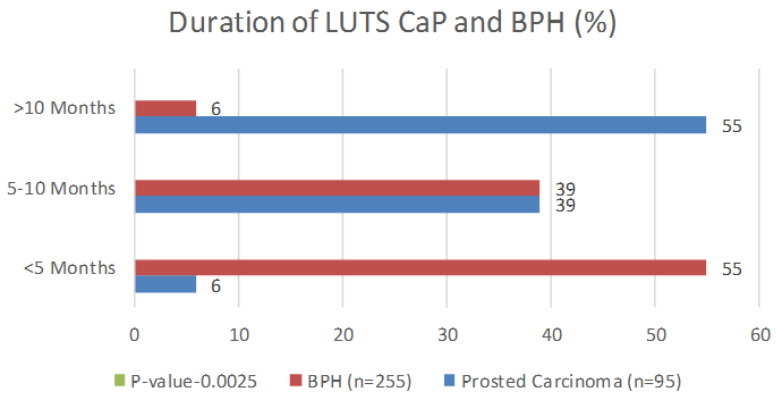



**Fig. 1:** Age distribution between BPH and CaP (n = 350).

Fig. 2 demonstrates the comparison of lower urinary tract symptoms (LUTS) between prostatic carcinoma and BPH. Study population was 350 patients, based on >10 months 6% was BPH and 55% was prostate carcinoma, 5-10 months 39% was BPH and 39% was prostate carcinoma and 5 months 55% was BPH and 6% was prostate carcinoma and here the p-value ($p = 0.00025$) showed significant.




# Student's t-Test was employed to analyze the data and level of significance was ($p<0.05$).

**Fig. 2:** Comparison of duration of LUTS between BPH and CaP (n = 350).

Table 1 demonstrates to comparison of clinical presentation between BPH and CaP. The total study population was 350 patients (prostate carcinoma = 95, BPH = 255) patients, according to low back pain 21% were prostate carcinoma, 6% were BPH and p-value 0.0071. Based on weight loss, 42% were prostate carcinoma, 10% were BPH and p-value 0.0258. According to hematuria, 22% were prostate carcinoma, 1% were BPH and p-value 0.0412. And when no targeted clinical presentation 15% were prostate carcinoma, 83% were BPH.

**Table 1:** Comparison of clinical presentation between BPH and CaP (n = 350).

| Clinical presentation | Diagnosis | | p-value |
|---|---|---|---|
| | Prostate carcinoma (n = 95) (%) | BPH (n = 255) (%) | |
| Low back pain | 21% | 6% | 0.0071 |
| Weight loss | 42% | 10% | 0.0258 |
| Hematuria | 22% | 1% | 0.0412 |
| No targeted clinical presentation | 15% | 83% | |

The percentage of hypoechoic lesions in prostatic cancer (74%) was greater than in BPH (20%) ($p<0.05$) (Fig. 3). Table 2 showed that positive DRE was greater in prostate cancer (84%) than BPH (2%) ($p=0.000$). Prostatic carcinoma had a volume of less than 50 ml in 76% of cases, whereas BPH had a volume of less than 50 ml in 75%. Prostatic carcinoma had a smaller mean volume (40.8±6.1 ml) than BPH (45.3±2.7 ml) ($p = 0.0432$) (Fig. 3). Figures in the parentheses denote corresponding percentages. Here data was analyzed using $x^2$ Test and the level of significance was 0.05. The Fig. 4 showed in the parentheses denotes corresponding % ages where the student's t-Test was employed to analyze the data and level of significance was 0.05.

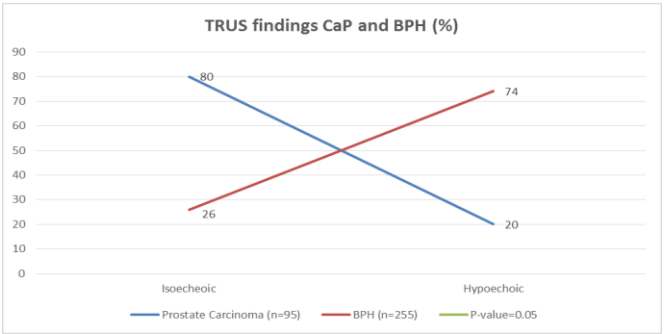



**Fig. 3:** Association of TRUS findings between BPH and CaP (n = 350).


**Fig. 4:** Association of volume of prostate in diagnosis of BPH and CaP (n = 350).

Table 2 demonstrates the association of DRE findings between BPH and CaP. The total study population was 350 patients (Prostate carcinoma = 95, BPH = 255) patients, according to DRE when it was positive 80(84%) were Prostate carcinoma and 4(2%) were BPH. And when it was negative 15(16%) were Prostate carcinoma and 251(98%) were BPH and both P value was found 0.000.

**Table 2:** Association of DRE findings between BPH and CaP (n = 350).

| DRE | Diagnosis | | p-value |
|---|---|---|---|
| | Prostate carcinoma (n = 95) (%) | BPH (n = 255) (%) | |
| Positive | 84% | 2% | 0.000 |
| Negative | 16% | 98% | |

Data shows the accuracy of fPSA to detect BPH and CaP. The total study population was 350 patients (prostate carcinoma = 95, BPH = 255) patients, according to free serum PSA level (ng/ml) when it was > 0.934, 70 were prostate carcinoma, 60 were BPH and total was 130. And when it was ≤0.934, 25% were prostate carcinoma, 195 were BPH and total was 220. And total result, 95 were prostate carcinoma, 255 were BPH and total was 350 (Table 3).

**Table 3:** Accuracy of fPSA to detect BPH and CaP (n = 350).

| Free serum PSA level (ng/ml) | Diagnosis | | Total |
|---|---|---|---|
| | Carcinoma prostate (n = 95) | BPH (n = 255) | |
| > 0.934 | 70 | 60 | 130 |
| ≤ 0.934 | 25 | 195 | 220 |
| Total | 95 | 255 | 350 |

Table 4 demonstrates the accuracy of total serum PSA to detect BPH and CaP. The total study population was 350 patients, according to total serum PSA (ng/ml) when it was >4, 82% were prostate carcinoma, 139 were BPH and total was 221. And when it was ≤4, 13% were prostate carcinoma, 255 were BPH and total was 350. And total result, 95 were prostate carcinoma, 255 were BPH and total was 350 (Table 4).

**Table 4:** Accuracy of total serum PSA to detect BPH and CaP.

| Total serum PSA (ng/ml) | Diagnosis | | Total |
|---|---|---|---|
| | Carcinoma postate (n = 95) | BPH (n = 255) | |
| > 4 | 82 | 139 | 221 |
| ≤ 4 | 13 | 116 | 129 |
| Total | 95 | 255 | 350 |

Table 5 demonstrates the accuracy of F/T PSA ratio to detect BPH and CaP. The total study population was 350 patients, according to F/T PSA ratio when it was >0.16, 85 were carcinoma prostate, 10 were BPH and total was 95. And when it was ≤ 0.16, 10 were prostate carcinoma, 245 were BPH and total was 255. And total result, 95 were prostate carcinoma, 255 were BPH and total was 350.

**Table 5:** Accuracy of free/total PSA ratio to detect BPH and CaP.

| F/T PSA ratio | Diagnosis | | Total |
|---|---|---|---|
| | Carcinoma postate (n = 95) | BPH (n = 255) | |
| >0.16 | 85 | 10 | 95 |
| ≤ 0.16 | 10 | 245 | 255 |
| Total | 95 | 255 | 350 |

The data demonstrates the comparison of accuracies between total and F/T serum PSA ratio. The total study population was 350 patients (prostate carcinoma = 95, BPH = 255) patients, according to sensitivity 86.32% were total, 89.47% were F/T ratio and p-value were 0.768943 and in specificity, 845.49% were total, 96.08% were F/T ratio and p-value 0.000324. In PPV 37.10% were total, 89.47% were F/T ratio and p-value was 0.768943 and in NPV 89.92% were total, 96.08% were F/T ratio and p-value was 0.768943. In false +ve 62.90% were total, 10.53% were F/T ratio and p-value was 0.000021, In false -ve 10.08% were total, 3.92% were F/T ratio and p-value was 0.000321 and in overall accuracy 56.57% were total, 94.29% were F/T ratio and p-value was 0.012546 (Table 6).

**Table 6:** Comparison of accuracies between total and F/T serum PSA ratio.

| Components of validity test (%) | Serum PSA | | |
|---|---|---|---|
| | Total | F/T ratio | p-value |
| Sensitivity | 86.32 | 89.47 | 0.768943 |
| Specificity | 45.49 | 96.08 | 0.000324 |
| PPV | 37.10 | 89.47 | 0.003104 |
| NPV | 89.92 | 96.08 | 0.658763 |
| False +ve | 62.90 | 10.53 | 0.000021 |
| False -ve | 10.08 | 3.92 | 0.000321 |
| Overall accuracy | 56.57 | 94.29 | 0.012546 |

**Discussion**

Between April 2021 to March 2022, this cross-sectional study included 350 LUTS patients aged over 50 who were treated at the Urology Department of Rajshahi Medical College Hospital, Rajshahi, Bangladesh. The study included 255 BPH patients and 95 prostate cancer patients. Comparable research revealed 9 patients (8.4%) had no abnormal results on histology, 69 patients (64.48%) had benign illnesses, and 29 patients (27.1%) had prostate cancer (Haroun et al. 2011). Prostate cancer was more prevalent in males aged 70-80, but BPH was more common in men aged 60-70. In both cases, older median ages of 76.5±8.5 years and 66.8±4.7 years were found. Prostate cancer patients had higher low back discomfort (21%), weight loss (42%), and hematuria (22%). Almost three-quarters (73%) of BPH patients had vague symptoms. LUTS symptoms lasted 5-10 months in 74% of prostate cancer patients, but only 55% of BPH patients. In Nigeria, 640 people were studied prospectively, and 545 had BPH, whereas 95 had clinical cancer. The median age of cancer patients was 62.2 years, whereas BPH patients were 66.1 years. Most patients had been showing indications of prostatism for a year or more. The study also found that approximately two-thirds of men with prostate cancer had paraplegia or paresis at the time of diagnosis, with or without urine retention. Symptoms included back discomfort, numbness in the lower limbs, and lack of coordination (Dawam et al. 2000). The most frequent clinical symptoms were nocturia (97.2%), followed by frequency (89.0%), weak stream (82.4%), straining (79.7%), incomplete emptying (63.4%), urgency (51.7%), terminal dribbling (49.3%), and hesitancy (49.3%) (Awaisu et al. 2021). These studies are quite similar with the present findings under the present study. The link between prostate cancer, BPH, and LUTS has been studied extensively. These studies, however, rely on observational data and so are subject to ascertainment bias. As a result, no one can agree on the exact nature of the link between LUTS and cancer risk (Engel et al. 2012). The study found that 70% of men with prostate cancer and BPH had a prostate volume under 50 ml (Finne et al. 2002). The mean standard deviation volume of the prostate was greater in BPH patients (45.3±2.7) than in prostate cancer patients (40.8±6.1), which is consistent with a Swedish study that indicated prostate volume influences cancer chances (Finne et al. 2002). A study found that the benign group had a larger median

prostate volume (46 cc) than the malignant group in 456 men with elevated PSA after one benign sextant biopsy (36 cc). They also found no malignancy in any prostates larger than 70 cc (Zackrisson et al. 2003). Transrectal ultrasonography (TRUS) is a commonly utilized imaging modality for the examination of the prostate. It is noninvasive and noninvasive (Mitterberger et al. 2010). Prostatic carcinoma had a higher percentage of hypoechoic lesions (74%) than isoechoic lesions (26%) in this study, suggesting an advanced stage of the illness. The TRUS test found that 20% of BPH patients had hypoechoic and 80% had isoechoic outcomes ($p<0.05$). The study also revealed that positive DRE was more prevalent in prostate cancer (84%) than BPH (2.0%). In a Croatian study, 33% of prostate cancer patients had TRUS testing. 31.8% of the tumors were isoechoic, whereas 60.6% were hypoechoic (Spajic et al. 2007). To assess the clinical significance of PIN in prostatic tumors, Korean researchers studied 50 BPH and 100 pathologically confirmed prostate cancers. During the DRE, prostatic nodules were palpable in 53% of prostate cancer patients. In a study, 37% of prostate cancer patients had hypoechoic areas on TRUS images were found by (Kamoi et al. 2008). They found hypoechoic areas in 12 BPH patients. They concluded that DRE nodules and hypoechoic TRUS areas are highly selective for prostate cancer (Lee et al. 1993). Our results are supported by both of the research cited above. fPSA is predicted to be 10-30% of tPSA. Normal men have a higher fPSA proportion than prostate cancer men (PCa). A study indicated that normal prostate tissue had higher mean fPSA than those with benign and malignant prostate diseases (Haroun et al. 2011). In this study, the sensitivity of tPSA and fPSA to tPSA ratio was not found to differ, although the specificity was significantly lower in case of tPSA (45.49%) compared to free/tPSA (96.08%) ($p<0.000324$). The PPV was also much lower in the former group (37.10%) than that in the latter group (89.47%) ($p<0.003104$), whereas NPV was nearly same in both tPSA and free to tPSA in ratio. The % age of false positive was significantly higher when tPSA was used to diagnose the disease compared to when free to tPSA was used as a diagnostic tool ($p<0.000021$). A larger positive predictive value reduces unnecessary biopsies, saving time and money (Higashihara et al. 1996). In this research, the positive predictive value for fPSA (53.85%) was higher than the positive predictive value for tPSA (37.10%). In a group of patients with tPSA levels ranging from 4.0 to 10.0 ng/L, found that a 25% fPSA cutoff detected 95% of cancers while sparing 20% of biopsies (Catalona et al. 1999). The concentration of fPSA was found to be lower- in the CaP patients when compared to the equivalent values in the BPH patients, according to the findings of another research (Magklara et al. 1999). In this research, among the 255 BPH patients studied, 116 had tPSA levels below 4 ng/ml and 139 had tPSA levels over 4 ng/ml. In 95 cases of prostate cancer, 13 had tPSA levels less than 4 ng/ml and 82 had tPSA levels more than 4 ng/ml. The optimal threshold was 4 ng/ml. It showed 86.32% sensitivity, 45.49% specificity, 37.10% positive predictive value, and 56.57% accuracy in differentiating prostatic cancer from BPH (BPH). The sample had a high percentage of false positives (62.90%) and false negatives (10.08%). In the present study, 54% of 255 BPH patients and 86% of 95 carcinoma patients had tPSA values more than 04 ng/ml. This study found that tPSA increases faster in prostate cancer than in BPH. Thus, total PSA (PSA) may be used to detect prostate cancer early. But tPSA alone cannot detect prostate cancer. When comparing the overall PSA concentrations of the two groups of patients, no statistically significant differences were identified in a study (Christensson and Bjork 1993). According to the findings of a research, the serum PSA levels of 4 ng/ml as the upper normal limit are not substantially trustworthy for the high-risk group or for

the early identification of prostate cancer (Dawam et al. 2000). As PSA is paired with fPSA, the positive predictive value is increased in a statistically meaningful way when compared to when PSA is used alone (Awaisu et al. 2021). Christensson and Bjork (1993) observed that men with prostate cancer had a lower ratio of free to tPSA than those with BPH. In this study, 10 prostate cancer patients and 245 BPH patients had F/T PSA ratios below 0.16. The sensitivity of free/total serum PSA (at a cut-off value of 0.16 ng/ml) was 89.47%, while the specificity was 96.08%. The test has an 89.47% PPV and a 96.08% NPV, according to the findings. The test showed 10.53% false positives and 3.92% false negatives. Klinger found that the free-to-tPSA ratio was more accurate than tPSA in predicting cancer (Klinger 1998). Recker et al. (1998) found that the free/total ratio had 87% sensitivity and 52% specificity on 333 consecutive individuals. At all sensitivity levels evaluated, the free to tPSA ratio was more specific than tPSA (91%). The findings showed that at a tPSA threshold of 4ng/ml, the sensitivity, specificity, and positive predictive value were 88%, 57%, and 40%. At the same sensitivity of f/t PSA, the specificity and PPV were 66% and 44%, respectively (Recker et al. 1998). Wolff et al. (1996) also found that f/tPSA was more accurate than tPSA in discriminating between patients with Ca prostate and those with BPH. Males with a tPSA in the “gray area” and an fPSA above 25% are more possibly having a benign disorder than cancer, therefore a biopsy is unnecessary. As a consequence, this study supports earlier studies.

**Limitations of the study**

In this research, the sample size was quite small, which may not represent the whole population. The research used purposeful sampling, which may have skewed the results. Not all samples were biopsied using the same procedure, resulting in a biased outcome.

**Conclusion**

In conclusion the benign prostatic hyperplasia showed a higher free/total ratio of serum prostate-specific antigen levels than prostate cancer, which is supported by this research. Because of this, free PSA, free/total ratios, along with total PSA may be utilized for screening reasons. Based on our experience, the comparison of accuracies between total and F/T serum PSA ratio, the values of Sensitivity, Specificity and Overall accuracy had been (86.32%, 45.49% and 56.57%) respectively. We consider that f/tPSA is no longer a definitive test for diagnosing prostatic cancer. Our observations on the sensitivity of tPSA and fPSA to tPSA ratio was not found to differ, even though the specificity was significantly lower in case of tPSA (45.49%) in contrast to free/tPSA (96.08%). Our observations on the behavior of free prostatic-specific antigen in the diagnosis of prostate carcinoma patients.

**Conflict of interest:** The authors hereby declare no conflict of interest regarding the publication of this article.

**References**

Advance Urology, American Cancer Society, Different Symptoms of BPH vs. Prostate Cancer (2021), https://advancedurology.com/advanced-blogging/different-symptoms-of-bph-vs-prostate-cancer/

Asafudullah SM, Salam MA, Badruddoza SM and Rahman MK (2009). Free PSA is a better tumor marker than serum total PSA in diagnosis of prostatic carcinoma. Journal of Teachers Association, 22(1): 30-35.

Awaisu M, Ahmed M, Lawal AT, Sudi A, Tolani MA, Oyelowo N, Muhammad MS, Bello A and Maitama HY (2021). Correlation of prostate volume with severity of lower urinary tract symptoms as measured by international prostate symptoms score and maximum urine flow rate among patients with benign prostatic hyperplasia. African Journal of Urology, 27(1): 1-7.

Calatayud DG, Neophytou S, Nicodemou E, Giuffrida SG, Ge H and Pascu SI (2022). Nano-theranostics for the sensing, imaging and therapy of prostate cancers. Frontiers in Chemistry, 10.

Catalona WJ, Partin AW, Slawin KM, Brawer MK, Flanigan RC, Patel A, Richie JP, De Kernion JB, Walsh PC, Scardino PT and Lange PH (1999). Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: A prospective multicenter clinical trial. The Journal of Urology, 161(1): 353-354.

Christensson A and Bjork T (1993). Nilsson O, Dahlen U, Matikainen MT, Cockett AT, Abrahamsson PA, and Lilja H: Serum prostate-specific antigen complexed to alpha-lantichymotrypsin as an indicator of prostate cancer. J Urol, 150: 100-105.

Dawam D, Rafindadi AH and Kalayi GD (2000). Benign prostatic hyperplasia and prostate carcinoma in native Africans. BJU International, 85(9): 1074-1077.

Engel C, Loeffler M, Steinke V, Rahner N, Holinski-Feder E, Dietmaier W, Schackert HK, Goergens H, von Knebel DM, Goecke TO and Schmiegel W (2012). Risks of less common cancers in proven mutation carriers with lynch syndrome. Journal of Clinical Oncology, 30(35): 4409-4415.

Finne P, Auvinen A, Aro J, Juusela H, Määttänen L, Rannikko S, Hakama M, Tammela TL and Stenman UH (2002). Estimation of prostate cancer risk on the basis of total and free prostate-specific antigen, prostate volume and digital rectal examination. European Urology, 41(6):619-627.

Haroun AA, Hadidy AS, Awwad ZM, Nimri CF, Mahafza WS and Tarawneh ES (2011). Utility of free prostate specific antigen serum level and its related parameters in the diagnosis of prostate cancer. Saudi Journal of Kidney Diseases and Transplantation, 22(2): 291.

Harvard Health Publishing (2009). What is the difference between PSA and free PSA? Available from: https://www.health.harvard.edu/blog/what-is-the-difference-between-psa-and-free-psa-20091001114

Higashihara E, Nutahara K, Kojima M, Okegawa T, Miura I, Miyata A, Kato M, Sugisaki H and Tomaru T (1996). Significance of serum free prostate specific antigen in the screening of prostate cancer. The Journal of Urology, 156(6): 1964-1968.

Kamoi K, Okihara K, Ochiai A, Ukimura O, Mizutani Y, Kawauchi A and Miki T (2008). The utility of transrectal real-time elastography in the diagnosis of prostate cancer. Ultrasound in Medicine and Biology, 34(7): 1025-1032.

Klinger E (1998). The search for meaning in evolutionary perspective and its clinical implications. Lawrence Erlbaum Associates Publishers.

Klingler HC, Woo H, Rosario D, Cutinha PE, Anderson J, Ward AM and Chapple CR (1998). The value of prostate specific antigen (PSA) density and free: total PSA ratio in selecting patients with a normal digital rectal examination and intermediate total PSA levels for further investigation. British J Urology, 82: 393-397.

Kumar VL and Majumder PK (1995). Prostate gland: structure, functions and regulation. International Urology and Nephrology, 27(3): 231-243.

Kuriyama M, Wang MC, Papsidero LD, Killian CS, Shimano T, Valenzuela L, Nishiura T, Murphy GP and Chu TM (1980). Quantitation of prostate-specific antigen in serum by a sensitive enzyme immunoassay, Cancer Research, 40(12): 4658-4662.

Lee H, Terreros D and Bahk JY (1993). Clinical significance of prostatic intraepithelial neoplasia. Korean Journal of Urology, 581-8.

Magklara A, Scorilas A, Catalona WJ and Diamandis EP (1999). The combination of human glandular kallikrein and free prostate-specific antigen (PSA) enhances discrimination between prostate cancer and benign prostatic hyperplasia in patients with moderately increased total PSA. Clinical Chemistry, 45(11): 1960-1966.

Mitterberger M, Horninger W, Aigner F, Pinggera GM, Steppan I, Rehder P and Frauscher F (2010). Ultrasound of the prostate. Cancer Imaging, 10(1): 40.

Moradi A, Srinivasan S, Clements J and Batra J (2019). Beyond the biomarker role: Prostate-specific antigen (PSA) in the prostate cancer microenvironment. Cancer and Metastasis Reviews, 38(3): 333-346.

Recker F, Kwiatkowski MK, Piironen T, Pettersson K, Goepel M and Tscholl R (1998). Free-to-total prostate-specific antigen (PSA) ratio improves the specificity for detecting prostate cancer in patients with prostatism and intermediate PSA levels. British Journal of Urology, 81(4): 532-538.

Spajic B, Eupic H, Tomas D, Stimac G, Kruslin B and Kraus O (2007). The incidence of hyperechoic prostate cancer in transrectal ultrasound–guided biopsy specimens. Urology, 70(4): 734-737.

Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. A Cancer Journal For Clinicians, 71(3): 209-249.

Wolff JM, Borchers H, Effert PJ, Habib FK and Jakse G (1996). Free-to-total prostate-specific antigen serum concentrations in patients with prostate cancer and benign prostatic hyperplasia. British Journal of Urology, 78(3): 409-413.

Woodrum DL, Brawer MK, Partin AW, Catalona WJ and Southwick PC (1998). Interpretation of free prostate specific antigen clinical research studies for the detection of prostate cancer. The Journal of Urology, 159(1): 5-12.

World Health Organization (2020). Country-specific, Incidence Mortality Cervix, Breast Lip, Oesophagus Gallbladder Lip, Oesophagus Cervix, Breast Lung Computed, Prevalence Index, Human Development, Bangladesh, 745: 9-10.

Yazad M (2022). 20 lakh cancer patients in Bangladesh: Health Minister. Available from: https://www.risingbd.com/english/national/news/85088.

Zackrisson B, Aus G, Lilja H, Lodding P, Pihl CG and Hugosson J (2003). Follow-up of men with elevated prostate-specific antigen and one set of benign biopsies at prostate cancer screening. European Urology, 43(4): 327-332.

Zhigang Z, Jieming L, Su L and Wenlu S (2007). Serum insulin-like growth factor I/free prostate specific antigen (IGF-I/fPSA) ratio enhances prostate cancer detection in men with total PSA 4.0–10.0 ng/ml. Journal of Surgical Oncology, 96(1): 54-61.

*(Manuscript received on 22 April 2022; Revised on 18 May 2022)*