J. Bio-Sci. 30(2): 67-77, 2022 **ISSN 1023-8654**
http://www.banglajol.info/index.php/JBS/index
DOI: https://doi.org/10.3329/jbs.v30i2.68914

PROSPECTIVE ANALYSIS OF PERCENT FREE PROSTATE-SPECIFIC ANTIGEN AS A BETTER PREDICTOR OF EARLY DIAGNOSIS OF PROSTATE CANCER

Md. Azizul Islam[1&2*], Md. Jawadul Haque[2], Md. Mokter Hossain[3] and S. M. Shahinul Islam[1*]

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

Abstract

Prostate-Specific Antigen (PSA) is a prostate cancer tumor marker, but furthermore, studies have revealed that many people with benign prostatic issues or other conditions have high PSA levels in their blood. As a result, various approaches have been suggested to boost prostate-specific antigen specificity. The aim of the study to determine whether the free-to-total PSA ratio (percent fPSA) is able to be utilized to discriminate between prostate cancer and benign prostatic hyperplasia. From December 2018 to November 2022, 260 males with Lower Urinary Tract Symptoms (LUTS) symptoms attended Rajshahi Medical College Hospital in Bangladesh were recruited purposively for a cross sectional study as per inclusion criteria. Digital Rectal Examination (DRE) and transrectal ultrasonography were performed along with age analysis. Before any manipulation, total PSA, free PSA, and percent free PSA were assessed. Transrectal ultrasound-guided biopsy or digitally guided biopsy was used to confirm the diagnosis. SPSS 26 was used to analyze the data. Among the 260 individuals, 105 were diagnosed with prostate cancer and the remaining 155 were diagnosed with benign prostatic hyperplasia. Patients with CaP were much older than those with Benign Prostatic Hyperplasia (BPH) (Mean±SD was 72±4.4 vs. 64±6.6 years, respectively) ($p = 0.00001$). The sensitivity, specificity, and positive predictive value of % free PSA (at cut off point 0.16) were greater (94%, 93%, 90% respectively) than those of total PSA (84%, 48%, 52% respectively). The proportion of false positives was lower in percent free PSA (10%) than in tPSA (19%). All of these considerations are critical in establishing the appropriateness of a screening test. In case of percent free PSA, the overall accuracy was 93%, significantly higher than tPSA (62%) ($p<0.005$). Thus, the free/total/ serum PSA ratio assists more accurately in differentiating BPH from prostate cancer. When compared to tPSA, the fPSA/tPSA and ratio enhance the discrimination between BPH and CaP comparable and are equally beneficial in lowering the incidence of unnecessary biopsies, but tPSA alone has less impact.

Key words: Benign prostatic hyperplasia, Free PSA, Lower urinary tract symptoms, Prostate cancer, Prostate specific antigen, Total PSA, Transrectal ultrasonography.

Introduction

Prostate cancer is the most common cancer in men; accounting for 32% of new cases in the United States (Wingo et al. 1997). Prostate-specific antigen (PSA) is the most practicable test for early detection of prostate cancer (Carlson et al. 1998). The PSA is a protein produced by prostate gland cells, both normal and cancerous, and is released into the bloodstream. The PSA test measures PSA levels in the blood. The FDA approved it in 1986 to track the progression of prostate cancer in men who had already been diagnosed

*Author for correspondence: shahin_ibsc@ru.ac.bd/ drazizbd@gmail.com

(Thompson et al. 2004). PSA blood concentrations are routinely used as a screening method to help detect prostate cancer early (Catalona et al. 1994, Islam et al. 2022). After 6-12 months, repeated biopsies of these individuals revealed that the original biopsy missed close to one-third had prostate cancer (Keetch et al. 1994). Again, some men with PSA levels below 4.0 ng/ml had prostate cancer, while many men with PSA levels between 4 and 10 ng/ml did not (Catalona et al. 1994) PSA does not differentiate between prostate and non-prostate cancer (Epstein et al. 1994). More than half of men with PSA levels over 10.0 ng/ml have advanced prostate cancer, whereas most men with somewhat elevated PSA levels have early-stage disease (Catalona et al. 1994). So, low PSA cutoffs (4.0 ng/ml) were required for screening to detect early prostate cancer that could be treated effectively. Due to significant false-positive rates, low PSA cutoffs result in unnecessary biopsies. The most common causes of false-positive PSA readings are BPH and prostatitis. (Catalona et al. 1995) The most prevalent benign tumor in older men, BPH, is seen in around 90% of individuals over the age of 85. Also, by age 80, one in every four American guys will need treatment for BPH (Stamey et al. 1987). The recommended tPSA threshold for prostate biopsy has recently been reduced from 4 to 2.5 ng/ml by urology and oncological organizations (Cannarella et al. 2021). The investigation found limited specificity in the serum PSA range of 2-10 ng/ml (Stamey et al. 1987). The Europian Randomized Study of Screening for Prostate Cancer (ERSPC) study revealed that for every 1,000 men examined, around 1.8 deaths from prostate cancer might be avoided (National Comprehensive Cancer Network 2011). Several strategies have been proposed to overcome these problems, including detecting PSA molecule forms, especially the percentage of fPSA. % fPSA (fPSA to tPSA ratio × 100) is now utilized as a reflex test to discriminate between benign from malignant prostate cancer in males with tPSA (tPSA) levels between 2 and 10 ng/ml (Mikolajczyk et al. 2002). Initial biopsy cut points have been demonstrated to preserve 530 of negative biopsies while maintaining a sensitivity of >90% using this difference in % fPSA distributions between these groups (Hugosson et al. 2019). Six hundred twenty-two individuals aged 50 to 75 years who had a non-suspicious DRE and a PSA result in the 4.0 to 10.0 ng/ml range were included in the first multicenter prospective % fPSA clinical study performed by Catalona et al. (1994). A 95 % sensitivity limit (25% fPSA) and a corresponding 20% specificity led the researchers to conclude that % fPSA, may be useful in distinguishing malignant from benign prostate disorder (Bruzzese et al. 2014). The main objectives of this study were to determine the free-to-total PSA ratio which is able to be utilized to discriminate between prostate cancer and benign prostatic hyperplasia patients with LUTS related to either BPH or prostate cancer.

Methodology

This study was a cross-sectional, observational study contained both descriptive and analytical components. The study comprised 260 purposively selected male patients over 40 years old with LUTS caused by BPH or prostate cancer between December 2018 and November 2022, Urology Outpatients and Inpatients Department of Rajshahi Medical College Hospital (RMCH) in Bangladesh. The inclusion criteria were an enlarged or nodular prostate in males revealed by Digital rectal exam, constant urination, and associated urinary symptoms (such as incontinence and nocturia). An exclusion criterion of this study was- age below 40 years, post-prostatectomy state, prostatic absences, chronic prostatitis, prostatic calcification. Before each exam or test, patients must have signed a written consent form. Patients with a tender prostate on DRE, previous trans urethral resection of prostate (TURP) history, or who were extremely ill were excluded. Using the patient's medical history, physical examination, which included a DRE, biochemical testing, urine analysis, and a serum PSA level (tPSA, fPSA, free/tPSA ratios), a baseline study was constructed for each patient. A careful evaluation of the patient's medical history and physical examination led to a diagnosis. DRE was done to identify whether the prostate was firm (rubbery), nodular, or hard. Patients with elevated PSA or suspected DRE had transrectal ultrasonography. An ultrasonography of the Prostate gland determined prostate volume. A monopty gun was used to perform digitally guided

biopsy for patients who refused TRUS to ultimately reveal prostate cancer. The biopsy criteria were F/t PSA ratios ≤1.6 and PSA values between 4 and 10 ng/ml. Biopsied samples were kept in 10% formalin containing container and sent to pathology department of Rajshahi Medical College. Each patient had 5 cc venous bloods taken before any manipulation. The serum was maintained at 2-8°C for three hours. The MPEI was used to measure tPSA. After reviewing and rechecking the data, SPSS version 26 was used to do statistical analysis, including student's 't' or chi-square tests. The level for statistical significance was set at 0.05.

Results

During the five-year trial period, a total of 260 patients with LUTS related to either BPH or prostate cancer that satisfied the study criteria were selected to participate in the study. The prevalence of prostate cancer at prostate biopsy was 40% (n = 105), while the prevalence of BPH was 60% (n = 155). The sensitivity, specificity, positive and negative predictive values, rates of false positives and false negatives, and overall accuracy of the tests were all evaluated in this study.

Prostate cancer was more widespread (67%) in the 70-80 age groups, with a Mean±SD of 72±4.4 years, while BPH was more prevalent (61%) in the 60-70 age groups, with a Mean±SD of 64±6.6 years, according to the study. There was a statistically significance in the age distribution of prostatic cancer and BPH patients (p = 0.00001).

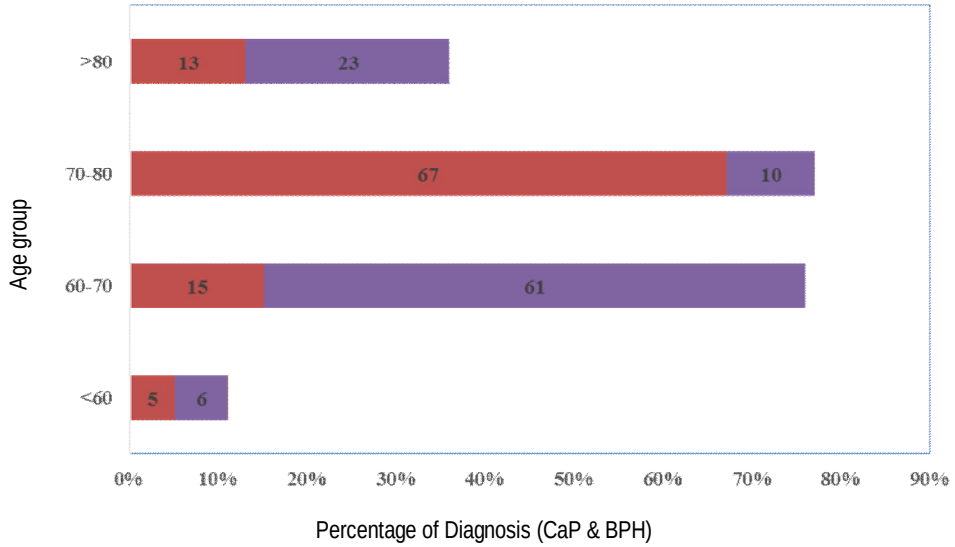

Fig. 1: Age distribution between BPH and CaP (n = 260).

Fig. 1 shows the age distribution of the prostatic carcinoma and BPH patients. The mean ages for carcinoma and BPH were 72±4 and 64±6 years respectively. Patients with prostatic cancer reported 81% former smoker, 14% never smoker and 5% current smoker. In comparison, 17%, 6% and 77% of BPH patients were former, never and current smoker respectively, according to the findings. When comparing prostate cancer and BPH, the findings were not statistically significant (p = 0.365443) (Fig. 2). Figures in the parentheses denote corresponding percentages. Data were analyzed using x^2 test. Cigarette smoking was suggested

affecting various hormone levels and such endocrine disturbances may eventually change PSA levels (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3389568).

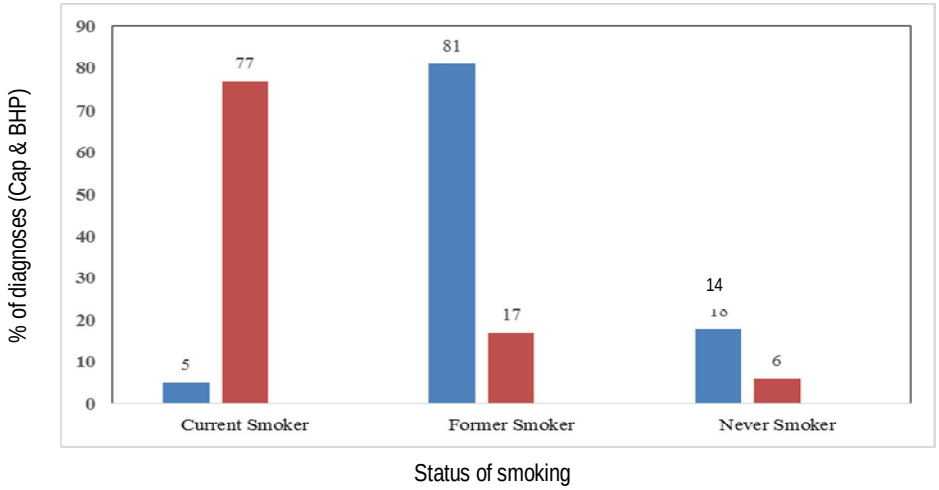

Fig. 2: Comparison of smoking status between BPH and CaP (n = 260).

There was a statistically significant difference in the incidence of low-back pain between the prostate cancer group (18%) and the BPH group (9.0%) (p = 0.00523). Both weight loss and hematuria were shown to be greater in the former group than in the latter group, with a statistical significance (33% vs. 7%, p = 0.04321; 19% vs. 13%, p = 0.02321 respectively). On the other hand, excessive urination, nocturia and urgency was significantly higher in the BPH patients (32%, 23%, 16% respectively) than prostate cancer patients (12%, 8%, 6% respectively), p = 0.00002, 0.00231, 0.00984 respectively (Table 1). Figures in the parentheses denote corresponding percentages. Data were analyzed using x^2-test and were presented as Mean± SD.

Table 1. Comparison of clinical presentation between BPH and CaP (n = 260).

Clinical presentation	Diagnosis		p-value
	Prostate carcinoma (n = 105)	BPH (n = 155)	
Low back pain	18.0%	9.0%	0.00523
Weight loss	33.0%	7.0%	0.04321
Hematuria	19.0%	13.0%	0.02321
Excessive urination	12.0%	32.0%	0.00002
Nocturia	8.0%	23.0%	0.00231
Urgency	6.0%	16.0%	0.00984

Fig. 3 shows the testosterone level of the prostatic carcinoma and BPH patients. In this study, 90% prostate cancer and 70% BPH patients had less than 2.4 ng/ml of testosterone and Mean±SD was lower in PaC than BPH (1.9±0.2 and 2±0.3 respectively) (Fig. 3). Figures in the parentheses denote corresponding percentages. # Student's t-Test and were presented as Mean± SD was employed to analyze the data and level of significance was 0.05.

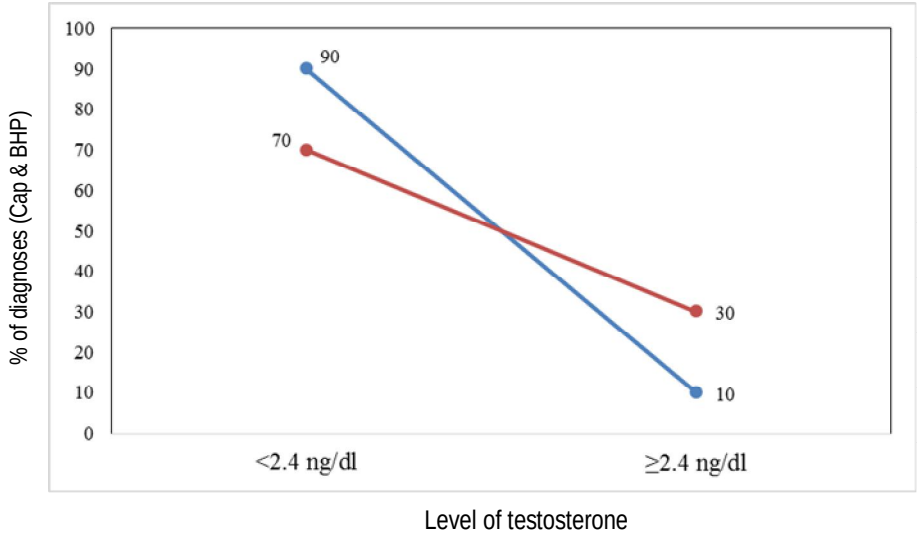

Fig. 3: Testosterone level between BPH and CaP (n = 260).

When comparing TRUS results between BPH and CaP, it was shown that prostatic cancer had a considerably larger percentage of hypoechoic lesions (81%) compared to BPH (19%) (p = 0.00531). Fig. 4 shows the Association of DRE findings between BPH and CaP (n = 260). According to prostate carcinoma (n = 105) the DRE was 81% positive and 19% negative and according to BPH (n =155) the DRE was 3% Positive and 19% negative. And the p-value was 0.00002. Figures in the parentheses denote corresponding percentages. # Data was analysed using x^2-test and the level of significance were 0.05.

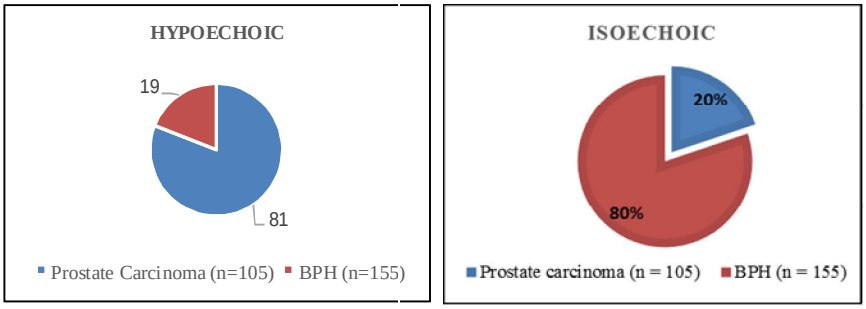

Fig. 4: Association of TRUS findings between BPH and CaP (n = 260).

.

For prostatic cancer, 90% of prostate volumes were below 50 ml and the remaining 10% were 50 or more than 50 ml, but for BPH, 71% had prostate volumes below 50 ml and the remaining 29% were equal to or greater than 50 ml. The mean volume of prostate in prostatic cancer was 35.8±2.1 whereas in BPH (BPH) was 40.3±3.7 ml. The statistical significance of the difference was p = 0.02765 (Fig. 5). Figures in the parentheses denote corresponding percentages. # Student's t-Test was employed to analyze the data and level of significance was 0.05.

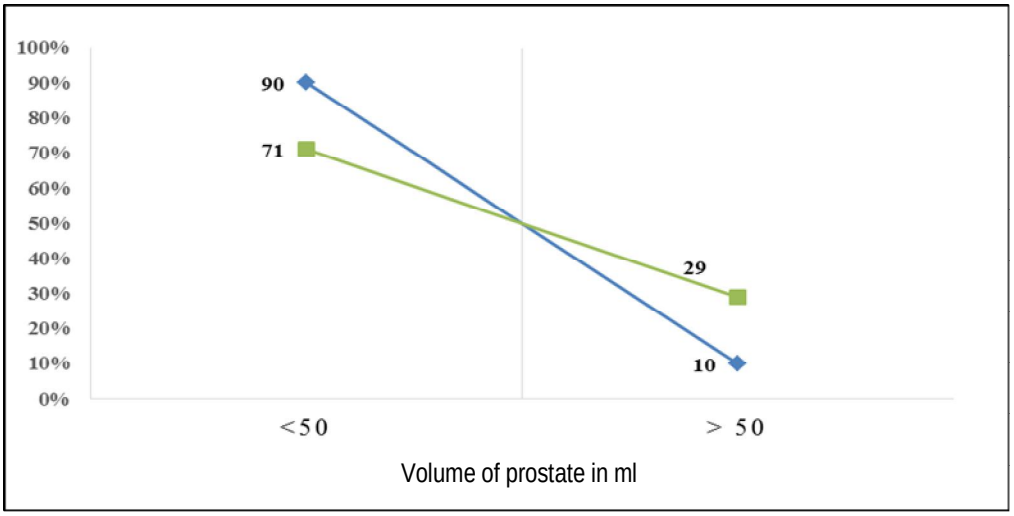

Fig. 5: Association of volume of prostate in diagnosis of BPH and CaP (n = 260).

Table 2 shows the validity or accuracy of serum free PSA Level as a diagnostic testin differentiating prostate cancer from BPH. Using formulae for accuracy or validity it was found that serum free PSA level (at cut off value >0.934 ng/ml) in correctly diagnosing prostatic carcinoma 89, BPH 39 and total 128. On the other hand when serum free PSA level ≤0.936 ng/ml in correctly diagnosing Prostatic carcinoma 16, BPH 116 and total 132.

Table 2. Accuracy of fPSA to detect BPH and CaP (n = 260).

Free serum PSA level (ng/ml)	Diagnosis		Total
	Carcinoma Prostate (n = 105)	BPH (n = 155)	
> 0.934	89	39	128
≤ 0.934	16	116	132
Total	105	155	260

Table 3 shows the accuracy of total serum PSA to detect BPH and CaP. According to prostate carcinoma the total serum PSA (ng/ml) level >4, ≤4 and total were 88, 17 and 105 respectively. Based on BPH the total serum PSA (ng/ml) level >4, ≤4 and total were 80, 74 and 155 respectively. And the total for >4, ≤4 and total were 169, 91 and 260 respectively.

Table 3. Accuracy of total serum PSA to detect BPH and CaP.

Total serum PSA (ng/ml)	Diagnosis		Total (n)
	Carcinoma prostate	BPH	
> 4	88	80	169
≤ 4	17	74	91
Total	105	155	260

Table 4 shows the accuracy of F/T PSA ratio (% fPSA) to detect BPH and CaP. According to prostate carcinoma the F/T PSA ratio for >0.16, ≤ 0.16 and total were 99, 6 and 105 respectively. Based on BPH the F/T PSA ratio were >0.16, ≤ 0.16 and for total were 11, 144 and 155 respectively. And the total for >0.16, ≤0.16 and total were 110, 150 and 260 respectively. The diagnostic accuracy of the test thus determined by the formula, was (99+144)/ (99+11+6+144) ×100 = 93.46%.

Table 4. Accuracy of F/T PSA ratio (% fPSA) to detect BPH and CaP.

F/T PSA ratio	Diagnosis		Total (n)
	Carcinoma prostate	BPH	
>0.16	99	11	110
≤ 0.16	6	144	150
Total	105	155	260

The Table 5 shows the sensitivity of % fPSA (94%) was greater than the sensitivity of tPSA (84%), but the difference was not statistically significant; nevertheless, the specificity of tPSA (48%) was substantially lower than the specificity of free/tPSA (93%) (p = 0.004523). The positive predictive value (PPV) and negative predictive value (NPV) were also significantly lower in the former (tPSA) group (52% and 81%, respectively) than in the latter (% fPSA) group (90% and 96%, respectively) (p = 0.008734 and 0.863272 respectively). The percentage of false positives was significantly higher when tPSA was used to diagnose the disease compared to when % fPSA was used as a diagnostic tool (p = 0.000001). tPSA had substantially lower overall accuracy (62.31%) than % fPSA (93.46%) (p = 0.00528) Table 5 shows accuracies between total and F/T serum PSA ratio. Here, the sensitivity of % fPSA was greater than the sensitivity of tPSA, but the difference was not statistically significant; nevertheless, the specificity of tPSA (48%) was substantially lower than the specificity of free/tPSA (93%) (p = 0.004523). The positive predictive value (PPV) and negative predictive value (NPV) were also significantly lower in the former group (52% and 81%, respectively) than in the latter group (90% and 96%, respectively) (p = 0.008734 and 0.863272 respectively). The percentage of false positives was significantly higher when tPSA was used to diagnose the disease compared to when % fPSA was used as a diagnostic tool (p = 0.000001). tPSA had substantially lower overall accuracy (62.31%) than % fPSA (93.46%) (p = 0.00528).

Table 5. Comparison of accuracies between total and F/T serum PSA ratio.

Variables	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	False +ve	False -ve	Overall accuracy
F/T ratio (% fPSA)	94	93	90	96	10	7	93.46
Total	84	48	52	80	48	19	62.31
P-value	0.576232	0.004523	0.008734	0.863272	0.000001	0.006528	<0.00528

Discussion

Prostate biopsy is the gold standard for diagnosing prostate cancers in men with increased serum tPSA levels or abnormal DRE findings. Earlier, a sextant prostate needle biopsy used to be extensively used for organizing the definitive analysis in patients suspected of having prostate cancer (Levine et al. 1998). However, a 1998 study about published that the false negative rate of prostate most cancers detection with the aid of this technique used to be 30% (Mian et al. 2002). Thereafter, many researchers suggested that the wide variety of core biopsy specimens ought to be extended at some stage in repeat prostate biopsy (Stewart et al. 2001). However, the most appropriate variety of core biopsy specimens nonetheless stays controversial.

In our study, according to prostate carcinoma (n = 105) the free serum PSA level (ng/ml) were >0.934, ≤0.934 and for total were 89, 16 and 105 respectively. Based on BPH (n = 155) the free serum PSA level (ng/ml) for >0.934, ≤0.934 and total were 39, 116 and 155 respectively. And the total of free serum PSA level (ng/ml) for >0.934, ≤0.934 and total were 128, 132 and 260 respectively.

Yang and colleagues carried out a potential blinded find out about of patients with serum tPSA between 4 and 25 ng/ml by way of the usage of f/tPSA for prostate cancers detection (Yang et al. 2005). Optimal cutoff set at 30% should get rid of 30%-36% of unnecessary biopsies and make sure a reasonable sensitivity. However, this cutoff might also no longer be appropriate for patients who have already passed through prostate biopsy. When we set a cutoff of f/t PSA at 30% for our patients, the sensitivity and specificity of the test have been discovered to be 25% and 84%, respectively. This degree of sensitivity used to be no longer acceptable. Therefore, if the most desirable cutoff of f/tPSA was once set at 25%, then the sensitivity and specificity of this variable in the detection of prostate cancers have been 65% and 53%, respectively.

In this present study, according to prostate carcinoma the F/T PSA ratio were >0.16, ≤0.16 and for total were 99, 6 and 105 respectively. Based on BPH the F/T PSA ratio for >0.16, ≤0.16 and for total were 11, 144 and 155 respectively. And the Total for >0.16, ≤0.16 and total were 110, 150 and 260 respectively. The total accuracy of the exam, as determined by the formula, was (99+144)/ (99+11+6+144) × 100 = 93.46%.

Djavan et al. (2000) and colleagues13 recommended a potential learn about of 1051 men with serum tPSA stages of 4-10 ng/ml. The positive costs of prostate cancers detection all through the preliminary prostate biopsy and repeat biopsy had been 22% (231 of 1051) and 10% (83 of 820), respectively (Djavan et al., 2000). In these patients, f/t PSA and transitional-zone Prostate Specific Antign Density (PSAD) had been the most correct predictors of prostate cancer. They recommended that a repeat prostate biopsy of patients with f/t PSA ranges much less than 30% or transitional region Prostate Specific Antign Density (PSAD) of 0.26 ng/ml/cc or larger have to be performed. Vickers and colleagues stated a systematic review of pretreatment PSAV and doubling time as predictors for prostate cancer, showing that there is little proof that the calculation of PSAV and doubling time in untreated patients affords predictive evidence beyond that provided by only tPSA level (Vickers et al. 2009).

Several researches have indicated that reflex tests based totally on PSA isoforms can enhance cancer detection in men with tPSA levels between 2 and 10 ng/ml. In particular, it has been broadly popular that a low %fPSA is a beneficial test to minimize the wide variety of unnecessary biopsies (Roddam et al. 2005). However, it is now acknowledged that fPSA fraction is composed of at least three different types of enzymatically inactive PSA: bound prostate specific antigen (BPSA), intact inactive PSA, and pro-prostate specific antigen (pPSAs), of which BPSA and pPSA are the best characterized. In patients with PCa, pPSAs comprised primarily a truncated structure of pPSA that consists of a proleader peptide consisting of only 2 rather than the regular 7 amino acids (Hori et al. 2013) Thus, serum pPSAs received interest as a probably unique form of fPSA that may additionally assist overcome the current limitation of %fPSA, lowering the best range of useless biopsies.

Conclusion

In men with prostate cancer, PSA is the most reliable blood marker available. This assay, however, has a mediocre selectivity and is particularly unsatisfactory when the PSA concentration is in the range of 4.0-10.00 ng/ml. Precisely calculated % fPSA produces findings without the price or difficulty of transrectal ultrasonography. Aside from that, % fPSA results are a readily available pre-biopsy assessment, and a blood test is more acceptable to patients and less susceptible to variations in procedure than ultrasonography.

References

Aus G, Abbou CC, Bolla M, Heidenreich A, Schmid HP, Van Poppel H, Wolff J and Zattoni F (2005). EAU guidelines on prostate cancer. European Urology 48(4): 546-51.

Bruzzese D, Mazzarella C, Ferro M, Perdonà S, Chiodini P, Perruolo G and Terracciano D (2014). Prostate health index vs percent free prostate-specific antigen for prostate cancer detection in men with “gray” prostate-specific antigen levels at first biopsy: systematic review and meta-analysis. Translational Research 164(6): 444-51.

Cannarella R, Condorelli RA, Barbagallo F, La Vignera S and Calogero AE (2021). Endocrinology of the aging prostate: Current concepts. Frontiers in Endocrinology 12: 554078. doi: 10.3389/fendo.2021.554078.

Carlson GD, Calvanese CB and Partin AW (1998). An algorithm combining age, total prostate-specific antigen (PSA), and percent free PSA to predict prostate cancer: results on 4298 cases. Urology 52(3): 455-61.

Catalona WJ, Richie JP, Ahmann FR, et al. (1994). Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: results of a multicenter clinical trial of 6,630 men. The Journal of Urology 151: 1283-1290.

Catalona WJ, Smith DS, Wolfert RL, Wang TJ, Rittenhouse HG, Ratliff TL and Nadler RB (1995). Evaluation of percentage of free serum prostate-specific antigen to improve specificity of prostate cancer screening. Journal of the American Medical Association 274(15):1214-20.

Djavan BO, Zlotta A, Remzi M, Ghawidel K, Basharkhah AL, Schulman CC and Marberger M (2000). Optimal predictors of prostate cancer on repeat prostate biopsy: a prospective study of 1,051 men. The Journal of Urology 163(4): 1144-9.

Epstein JI, Walsh PC, Carmichael M and Brendler CB (1994). Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1 c) prostate cancer. Journal of the American Medical Association 271(5): 368-74.

Hori S, Blanchet JS and McLoughlin J (2013). From prostate-specific antigen (PSA) to precursor PSA (proPSA) isoforms: a review of the emerging role of proPSAs in the detection and management of early prostate cancer. British Journal of Urology International 112(6): 717-28.

Hugosson J, Roobol MJ, Månsson M, Tammela TL, Zappa M, Nelen V, Kwiatkowski M, Lujan M, Carlsson SV, Talala KM and Lilja HA (2019). 16-yr follow-up of the European randomized study of screening for prostate cancer. European Urology 76(1): 43-51.

Islam MA, Islam SMS and Haque MJ (2022). The role of free prostate-specific antigen in the diagnosis of prostate carcinoma: A cross-sectional study in Rajshahi, Bangladesh. Journal of Bio-Science 30(1): 79-89.

Islam MA, Islam SMS and Haque MJ (2023). Evaluation of serum prostate specific antigen levels to differentiate prostate cancer from benign prostatic hyperplasia. Journal of Teachers Association (TAJ) 36(2).

Keetch DW, Catalona WJ and Smith DS (1994). Serial prostatic biopsies in men with persistently elevated serum prostate specific antigen values. The Journal of Urology 151(6): 1571-4.

Levine MA, Ittman M, Melamed J and Lepor H (1998). Two consecutive sets of transrectal ultrasound guided sextant biopsies of the prostate for the detection of prostate cancer. The Journal of Urology 159(2): 471-6.

Mian BM, Naya Y, Okihara K, Vakar-Lopez F, Troncoso P and Babaian RJ (2002). Predictors of cancer in repeat extended multisite prostate biopsy in men with previous negative extended multisite biopsy. Urology 60(5): 836-40.

Mikolajczyk SD, Marks LS, Partin AW and Rittenhouse HG (2002). Free prostate-specific antigen in serum is becoming more complex. Urology 59(6): 797-802.

National Comprehensive Cancer Network (2012). NCCN Clinical Practice Guidelines in Oncology: Rectal Cancer, http://www.nccn.org/professionals.

Roddam AW, Duffy MJ, Hamdy FC, Ward AM, Patnick J, Price CP, Rimmer J, Sturgeon C, White P and Allen NE (2005). NHS prostate cancer risk management programme. Use of prostate-specific antigen (PSA) isoforms for the detection of prostate cancer in men with a PSA level of 2–10 ng/ml: systematic review and meta-analysis. European Urology 48(3): 386-99.

Stamey TA, Yang N, Hay AR, McNeal JE, Freiha FS and Redwine E (1987). Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. New England Journal of Medicine 317(15): 909-16.

Stewart CS, Leibovich BC, Weaver AL and Lieber MM (2001). Prostate cancer diagnosis using a saturation needle biopsy technique after previous negative sextant biopsies. The Journal of Urology 166(1): 86-92.

Thompson IM, Pauler DK, Goodman PJ, Tangen CM, Lucia MS, Parnes HL, Minasian LM, Ford LG, Lippman SM, Crawford ED and Crowley JJ (2004). Prevalence of prostate cancer among men with a prostate-specific antigen level ≤4.0 ng per milliliter. New England Journal of Medicine 350(22): 2239-46.

Vickers AJ, Savage C, O'Brien MF and Lilja H (2009). Systematic review of pretreatment prostate-specific antigen velocity and doubling time as predictors for prostate cancer. Journal of Clinical Oncology 27(3): 398-403.

Wingo PA, Landis S and Ries LA (1997). An adjustment to the 1997 estimate for new prostate cancer cases. Cancer: Interdisciplinary International Journal of the American Cancer Society 80(9): 1810-3.

Yang CR, Su CK, Chiu KY, Ho HC, Ou YC, Cheng CL and Lee H (2005). Free/total prostate specific antigen ratio for prostate cancer detection: a prospective blind study. Anticancer Research 25(3C): 2439-43.

(Manuscript received on 24th October 2022 and revised on 22nd December 2022)