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Assessment the Ability of Free/Total Ratio of Serum PSA in Diagnosing Prostate Cancer and Benign Prostatic Hyperplasia

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Abstract

Background: The Prostate gland is the male secondary sexual organ most commonly affectedby benign or malignant neoplasm. Prostate cancer (Ca-P) is one of the most commonly diagnosed cancers in men and is now the third commonest cause of cancer death in western countries.The aim of the study was to evaluate the use of serum prostate-specific antigen levels in differentiating prostate cancer from benign prostatic hyperplasia.

Methods:The present study is a cross-sectional observational study.The study was conducted at the outpatient department and indoor patients at the department of Urology, Rajshahi Medical College Hospital (RMCH), Rajshahi, and different private clinic in Rajshahi City during the period from July 2019 to June 2020.The study population included male patients above 50 years of age, who attended in the department of Urology, Rajshahi Medical College Hospital (RMCH), Rajshahi, and different private clinic in Rajshahi City complaining of irritative or obstructive lower urinary tract symptoms (LUTS) suspected as clinically prostate cancer or benign prostatic hyperplasia (BPHStatistical analysis of the results was obtained by using window-based computer software devised with Statistical Packages for Social Sciences (SPSS-24).

Results: The age distribution of the prostatic carcinoma and BPH patients. Prostatic carcinoma was observed to be significantly higher from 80 years onwards, while BPH was commonbetween 60 - 80 years (p = 0.00001). Table 10shows the validity or accuracy of the free/total ratio of serum PSA as a diagnostic test in differentiating prostatic carcinoma from BPH in patientswith total PSA levels between 4-10ng/ml. The percentage of false positives was significantly higher when total PSA ratio was used to diagnose the disease compared to whenfree to total PSA was used as a diagnostic tool (p<0.000001). The overall accuracy of total PSA was also significantly lower (61.45%) than that of free/total PSA (91.67%) (p< 0.011526).

Conclusion: Free and total prostate specific antigen (PSA) is increased significantly in carcinoma prostate than benign prostatic hyperplasia but free/total ratio of serum prostate-specific antigen level significantly decreases in prostatic carcinoma than benign prostatic hyperplasia.

Keywords: Prostate Specific Antigen (PSA),Benign Prostatic Hyperplasia (BPH),Prostate Cancer (Ca-P).

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Introduction

The male secondary sexual organ most usually afflicted by benign or malignant neoplasia is the prostate gland. Prostate cancer (Ca-P) is one of the most frequent malignancies in males, and it isnow the third leading cause of death from cancer in Western countries [1]. The most prevalent benign tumor in males is benign prostatic hyperplasia (BPH), which has an age-related frequency. In

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postmortem investigations, the prevalence of histological BPH rises from roughly 20% in males aged 41-50 years to 50% in men aged 51-60 years and over 90% in men aged over 80 years [2]. The use of Prostate Specific Antigen (PSA) as a marker for Prostate cancer is based on the fact that only small amounts of PSA leak from the normal prostate into circulation, thus the serum concentrations are normally about 1 million-fold lower than those in seminal fluid. In prostatic disease, the serum concentrations of PSA are often elevated due to loss of barrier afforded by the basal layer of columnar epithelium and basement membrane within the normal gland is likely the site for the egress of PSA into the circulation. These can occur in setting of prostatic disease such as prostatitis, benignprostatic hyperplasia, Prostatic carcinoma and with prostatic manipulation such as prostatic message and prostatic biopsy [3]Despite problems of sensitivity, the serum level of PSA is widely accepted to be the most useful tool for the early detection, evaluation and management of prostate carcinoma [4]. PSA is organ specific rather than cancer specific. Upto 4 ng/ml is considered as normal value. Marginally raised PSA 4-10 ng/ml is doubtful, which means Overlapping of patients with Ca Prostate & BPH [5]. A limitation to the use of PSA testing has been its relative lack of specificity within the 4.0-10 ng/ml range, a diagnostic grey zone in which prostate cancer is present in only 25% of patients [6]. More than 10 ng/ml is suspicious of carcinoma prostate. The concentration of PSA is usuallyhighest in patients with Prostate cancer, intermediate in patients with BPH [7].PSA produced by malignant cells appears to evade proteolytic processing, resulting in a higher fraction of serum PSA complexed to ACT and a lower percentage of Free PSA in men with Prostatic carcinoma compared to men without Prostatic carcinoma [8]. This important observation led to the calculation of the percentage of the ratio of free to total PSA, which has since provided an additional degree of specificity for prostate cancer detection [9]. Recently, better discrimination between Prostate cancer and Benign Prostatic Hyperplasia wasreported using F/T PSA rather than tPSA, within the diagnostic grey zone of PSA levels of 4-10 ng/ml [10]. By using F/T PSA level with TRUS and biopsies confined to patients with a ratio of <0.16, more than 90% of cancer would be detected and >30% of unnecessary biopsies avoided [11].A cross-sectional study was conducted to detect Free PSA (fPSA), Total PSA (tPSA) and Free/ Total ratio of PSA in BPH & Prostate cancer patients in population who came for consultation due to urological symptoms. Those patients having total PSA levels more than 10 ng/ml were selected for biopsy and patients with total PSA levels between 4-10 ng/ml, among whose Free/Total PSA ratio less than 0.16 are also selected for biopsy. Rest of the patients was undergone histopathological examination after operation. Free PSA (fPSA), Total PSA (tPSA) and Free/ Total ratio of PSA level in Prostate cancer and BPH were compared in this study.

OBJECTIVES

General objective

- To assess the ability of free/total ratio of serum PSA in diagnosing prostate cancer andbenign prostatic hyperplasia.

Specific objectives

- To detect the use of serum free PSA in diagnosing prostate cancer and benign prostatichyperplasia.
- To determine the role of serum total PSA in diagnosing prostate cancer and benignprostatic hyperplasia.

To evaluate the use of serum prostate specific antigen levels to differentiate prostate cancer from benign prostatic hyperplasia.

Materials and Methods

The present study is a cross sectional observational study.The study was conducted at the out- patient's department and indoor patients at the department of Urology, Rajshahi Medical CollegeHospital (RMCH), Rajshahi, and different private clinic in Rajshahi City during the period from July 2019 to June 2020.This study was carried out on 288 patients (BPH=192, carcinoma prostate-96) in the department of Urology, Rajshahi Medical College Hospital. Study

population included the male patients above 50 years of age, who attended in the department of Urology, Rajshahi Medical College Hospital (RMCH), Rajshahi, and different private clinic in Rajshahi City complaining irritative or obstructive lower urinary tract symptoms (LUTS) suspected as clinically prostate cancer or benign prostatic hyperplasia (BPH). Inclusion criteria were male patients above 50 years of age with enlarged prostate, Presence of lower urinary tract symptoms such as frequency, urgency, hesitancy, poor flow, incontinence, nocturia etc, Digital rectal examination findings enlarged / nodular / firm /hard prostate and written consent from the patient to carry out examination and relevant investigation.It was aimed to assess the role of free, total and free/total ratio of serum PSA in diagnosis of BPH and carcinoma prostate with reference to histological diagnosis. All the cases were selected as per selection criteria and were evaluated by history, physical examination including digital rectal examination, serum prostate specific antigen level, transrectal ultra-sonogram. From all patients, blood sample were collected before digital rectal examination or any per urethral manipulation. Final diagnosis was obtained by histo-pathological examination, specimen being obtained by per-rectal biopsy with biopsy-gun after operation. This study showed significant difference of free, total and free/total ratio of serum prostate-specific antigen (PSA) in differentiating benign prostatic hyperplasia (BPH) from carcinoma prostate. Statistical analysis of the results was obtained by using window-based computer software devised with Statistical Packages for Social Sciences (SPSS-24).

Results

The age distribution of the prostatic carcinoma and BPH patients. Prostatic carcinoma wasobserved to be significantly higher from 80 years onwards, while BPH was common between <60, 70-80 years ($p = 0.00001$). The mean ages for carcinoma and BPH were 74.3 ± 9.8 and 68.3 ± 6.8 years respectively. [Figure 1]

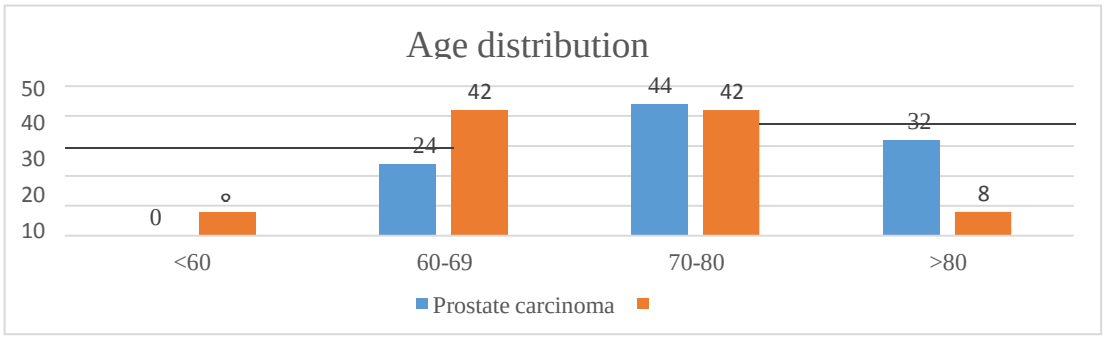

Figure1: Age distribution between BPH and Ca-prostate (n=288)

Demonstrates the comparison of LUTS between prostatic carcinoma and BPH. Sixty eightpercent of the patients of prostatic carcinoma had lower urinary tract symptoms (LUTS) for last 5-10 months, 24% for < 5 months and only 8% for > 10 months. In contrast, 60.0% of the BPH patients had LUTS for 5 - 10 months and the rest 38% for > 10 months. The mean duration of suffering from LUTS was significantly lower in prostate carcinoma (6.28 ± 2.54 months) than that in BPH (9.36 ± 4.36 months) ($p < 0.0001$) [Table 1].

Table 1: Comparison of duration of LUTS between BPH and Ca-prostate (n = 288)

Duration of LUTS (months)	Diagnosis		p-value*
	Prostate carcinoma(n = 96)	BPH (n = 192)	
<5	23 (24%)	4 (2%)	
5-10	65 (68%)	115 (60%)	
> 10	8 (8%)	73 (38%)	
Mean ± SD	6.28 ±2.54	9.36 ±4.36	< 0.0001

Compares the distribution of patients between groups by clinical presentation. The incidence of low-back pain was significantly higher in the prostate carcinoma group (48%) compared to that in the BPH group (8.0%) (p = 0.005077). Weight loss and hematuria were also higher in the former group than those in the latter group, although the differences did not reach the level of significance (32% vs. 26.0%, p = 0.0347 and 4% vs. 0%, p = 0.0455 respectively) [Table 2].

Table 2: Comparison of clinical presentation between BPH and Ca-prostate (n = 288)

Clinical Presentation	**Diagnosis**		**p-value**
	Prostate carcinoma (n = 96)	**BPH(n = 192)**	
Low back pain	46 (48%)	15 (8%)	0.005077
Weight loss	31 (32%)	50 (26%)	0.0347
Hematuria	4 (4%)	0 (0%)	0.0455
No targeted clinical presentation	15 (16%)	127 (66%)	

 # Data were analyzed using χ^2 test and were presented as mean ± SD

Table 3 shows that prostatic carcinoma had a significantly higher proportion of hypoechoeic lesions (80%) compared that found in BPH (6%) on TRUS examination (p < 0.05).

Table 3: Association of TRUS findings between BPH and Ca-prostate (n = 288)

TRUS	**Diagnosis**		**p-value**
	Prostate carcinoma (n = 96)	**BPH (n = 192)**	
Hypoechoeic	77 (80%)	12 (6%)	0.000
Isoechoeic	19 (20%)	180 (94%)	

 # Data were analyzed using χ^2 Test and the level of significance was 0.05.

Demonstrates that positive DRE was significantly higher in prostatic carcinoma (76%) than that in BPH (4.0%) ($p < 0.000$) [Table 4].

Table 4: Association of DRE findings between BPH and Ca-prostate (n = 288).

DRE	Diagnosis		p-value
	Prostate carcinoma (n = 96)	BPH (n = 192)	
Positive	73 (76%)	8 (4%)	0.000
Negative	23 (24%)	184 (96%)	

Table 5 shows that seventy two percent of the volume of the prostate in prostatic carcinoma group was found below 50 ml and the rest 28% was 50 or > 50 ml, while 56% of the BPH group had prostate volume below 50 ml and the rest 50 or above 50 ml. The mean volume of prostate inprostatic carcinoma was 42.5 ± 7.1 ml and that in BPH was 46.6 ± 8.7 ml. The difference was statistically significant ($p = 0.312$).

Table 5: Association of volume of prostate in diagnosis of BPH and Ca-P (n = 288)

Volume of Prostate (ml)	Diagnosis		p-value
	Prostate carcinoma (n = 96)	BPH (n = 192)	
<50	69 (72%)	108 (56%)	
≥ 50	27 (28%)	84 (44%)	
Mean ± SD	42.2 ± 7.1	46.6 ± 8.7	0.312

Table 6 shows the validity or accuracy of free serum PSA level as a diagnostic test in differentiating prostatic carcinoma from BPH. Using formulae for accuracy or validity it is foundthat sensitivity of free serum PSA level (at cut off value of > 0.934 ng/ml) in correctly diagnosing prostatic carcinoma of those who have the disease is (73/96) ×100 = 76.06%, while the specificity of the test in correctly detecting those who do not have the disease is (84/192) × 100 = 43.75%. The positive predictive value (PPV) of the test is (73/181) × 100 = 40.33% andthe negative predictive value of the test is (84/107) × 100 = 78.5%. The test yielded false +veand false -ve (108/181) × 100 = 59.66% and (23/107) ×100 = 21.49% respectively. The diagnostic accuracy of the test thus derived from the formula is (73+84)/(73+108+23+84) × 100

= 54.51%.

Table 6: Accuracy of free PSA to detect BPH and Ca-prostate

Free serum PSA level (ng/ml)	Diagnosis		Total
	Carcinoma Prostate	BPH	
> 0.934	73	108	181
≤ 0.934	23	84	107
Total	96	192	288

Table 8shows the validity or accuracy of total serum PSA in differentiating prostatic carcinoma from BPH. The sensitivity, of total serum PSA (at cut off value of >4 ng/ml) in correctly differentiating prostatic carcinoma of those who have the condition is (81/96) ×100 = 84.37%, while the specificity of the test in correctly detecting those who do not have the disease is (96/192) × 100 = 50%. The positive predictive value (PPV) of the test is (81/177) × 100 = 45.76% and the negative predictive value of the test is (96/111) × 100 = 86.48%. The test yielded false +ve and false -ve (96/177) ×100 = 54.23% and (15/111) ×100 = 13.51% respectively. The overall accuracy of the test thus derived from the formula is (81+96)/(81+96+15+96) × 100 = 61.45%.

Table 7: Accuracy of total serum PSA to detect BPH and Ca-prostate.

Total serum PSA (ng/ml)	**Diagnosis**		**Total**
	Carcinoma Prostate	**BPH**	
> 4	81	96	177
≤ 4	15	96	111
Total	96	192	288

Table 8 shows the validity or accuracy of free/total serum PSA as a diagnostic test in differentiating prostatic carcinoma from BPH. The sensitivity of free/total serum PSA (at cut off value of 0.16 ng/ml) in correctly differentiating prostatic carcinoma from BPH is (84/96) ×100 = 87.5%, while the specificity of the test in correctly detecting those who do not have prostatic carcinoma is (180/192) × 100 = 93.75%. The positive predictive value (PPV) of the test is (84/96) ×100 = 87.5% and the negative predictive value of the test is (180/192) ×100 = 93.75%. The test yielded false +ve and false -ve (12/96) × 100 = 12.5% and (12/192) ×100 = 6.25% respectively. The overall accuracy of the test thus derived from the formula is (84+180)/(84+12+12+180) × 100 = 91.67%.

Table 8:Accuracy of F/T PSA ratio to detect BPH and Ca-prostate.

F/T PSA ratio	**Diagnosis**		**Total**
	Carcinoma Prostate	**BPH**	
>0.16	84	12	96
≤0.16	12	180	192
Total	96	192	288

Table 9shows the validity or accuracy of free/total ratio of serum PSA as a diagnostic test in differentiating prostatic carcinoma from BPH in patients with total PSA level between 4- 10ng/ml. The sensitivity of this test in this Diagnostic gray zone (tPSA level 4-10 ng/ml) in correctly differentiating Prostatic carcinoma from BPH is (34/38)× 100=89.47%, while the specificity of The test in correctly detecting those who do not have prostatic carcinoma is (81/96)

× 100=84.37%. The positive predictive value of the test is (34/49) × 100=69.38% and negative predictive value is (81/85) ×100=95.29%. The test yielded false +ve and false -ve (15/49) × 100=30.61% and (4/85) × 100=4.7%. The overall accuracy derived from formula is (34+81)/ (34+15+4+81) × 100=85.82%.

Table 9: Accuracy of F/T PSA ratio to detect BPH and Ca-prostate.

F/T PSA ratio	Ca-prostate	BPH	Total
≤0.16	34	15	49
>0.16	4	81	85
Total	38	96	134

Table 10shows that the sensitivity of total PSA and free PSA to total PSA ratio was not found to differ, although the specificity was significantly lower in case of total PSA (50%) compared to free/total PSA (93.75%) (p< 0.000226). The PPV was also much lower in the former group (45.76%) than that in the latter group (87.5%) (p< 0.000203), whereas NPV was nearly same in both total PSA and free to total PSA in ratio. The percentage of false positive was significantly higher when total PSA was used to diagnose the disease compared to when free to total PSA was used as a diagnostic tool (p<0.000001). The overall accuracy of total PSA was also significantly lower (61.45%) than that of free/total PSA (91.67%) (p< 0.011526).

Table 10: Comparison of accuracies between total and F/T serum PSA ratio.

Components of validity test (%)	Serum PSA		
	Total	F/T ratio	p-value
Sensitivity	84.37	87.5	0.691568
Specificity	50	93.75	0.000226
PPV	45.76	87.5	0.000203
NPV	86.48	93.75	0.5215186
False +ve	54.23	12.5	0.000001
False -ve	13.51	6.25	0.000001
Overall accuracy	61.45	91.67	< 0.011

Discussion

The use of serum prostate particular antigen tiers in the preoperative staging of individualpatients with clinically localized prostate cancer is controversial. Stamey and associates studied 78 men with prostatic carcinoma and demonstrated that mean serum PSA concentrations had been proportional to medical stage (Al to D2), but they did now not comment on the value of serum PSA determinations to predict the pathological stage in individual patients. [12]Ercole and associates studied serum PSA levels in 209 men with various stages of prostate cancers and suggested that preoperative serum levels may additionally be a beneficial tool to stage

interestingly localized carcinoma of the prostate. [13] They observed that serum PSA levels of larger than 10 ng. / ml. had been greater frequent among patients with extracapsular disease.

In our study, according to age distribution of the prostatic carcinoma and BPH patients. Prostatic carcinoma was observed to be significantly higher from 80 years onwards, while BPH was common between 60 70-80 years (p = 0.00001). The mean ages for carcinoma and BPH were

74.3 ± 9.8 and 68.3 ± 6.8 years respectively. And according to the comparison of LUTS between prostatic carcinoma and BPH. Sixty eightpercent of the patients of prostatic carcinoma had lower urinary tract symptoms (LUTS) for last 5-10 months, 24% for < 5 months and only 8% for > 10 months. In contrast, 60.0% of the BPH patients had LUTS for 5 - 10 months and the rest 38% for

> 10 months.

We additionally studied the impact of a number of variables recognized to have an effect on PSA production: tumor volume, the extent of benign prostatic hyperplasia inside the gland and the degree of histological differentiation. Men with clinically localized prostate cancer frequently have various amounts of benign and malignant tissue inside the prostate. Csapo and associates discovered a direct linear relationship between log of tumor volume of serially transplantable human prostatic most cancers cell lines in nude mice and log of serum PSA values. [14]

Stamey and associates demonstrated a correlation between the log of morphometrically decided tumor volume and the log of serum PSA levels however no correlation between serum PSA and prostate wet weight in grams, or estimated tissue volume of benign prostatic hyperplasia measured from the transverse part of the gland containing the greatest cross-sectional area of hyperplastic tissue. [15] We decided the prostate gland volume, benign prostatic hyperplasia volume and tumor volumes from step-sectioned radical prostatectomy specimens to consider the correlations of serum PSA with these morphometrically decided volumes.

In this present study, according to the accuracy of free serum PSA level as a diagnostic test in differentiating prostatic carcinoma from BPH. Using formulae for accuracy or validity it is foundthat sensitivity of free serum PSA level in correctly diagnosing prostatic carcinoma of those who have the disease is (73/96) ×100 = 76.06%, while the specificity of the test in correctly detecting those who do not have the disease is (84/192) × 100 = 43.75%. The positive predictive value (PPV) of the test is (73/181) × 100 = 40.33% and the negative predictive value of the test is (84/107) × 100 = 78.5%.

Weber and associates confirmed that serum PSA correlated properly with the epithelial volume of benign prostatic hyperplasia. [16] However, due to the fact the epithelial-to-stomal weight ratio can vary 3-fold amongst patients, one can't use benign prostatic hyperplasia volume to granta correct estimation of PSA production. Thus, the variable manufacturing prostatic adenocarcinoma and observed a positive correlation between immunoreactivity for PSA and Gleason histological score. [17]

Serum PSA measurement is the preferred process for diagnostic screening of prostatecancer in men, and a serum PSA level is one of encouraged analytic strategies to decide whether or not a patient have to bear a biopsy of the prostate for detection prostatecancers. [18]Serum tPSA or f/tPSA had an acceptable sensitivity however also had a low specificity since an accelerated levelof PSA should be located in the serum of patients with benign prostatic disease. [19]

In our study, the sensitivity of total PSA and free PSA to total PSA ratio was not found to differ, although the specificity was significantly lower in case of total PSA (50%) compared to free/totalPSA (93.75%) (p< 0.000226). The PPV was also much lower in the former group (45.76%) than that in the latter group (87.5%) (p< 0.000203), whereas NPV was nearly same in both total PSA and free to total PSA in ratio. The percentage of false positive was significantly higher whentotal PSA was used to diagnose the disease compared to when free to total PSA was used as a diagnostic tool (p<0.000001). The overall accuracy of total PSA was also significantly lower (61.45%) than that of free/total PSA (91.67%) (p< 0.011526).

It has been proven that increased levels of nucleic acids had been launched into circulation

which could be isolatedfrom serum or plasma in cancers patients. Thus, cfDNA in serum/plasma has been the center of attention of activity as a novel, potential biomarker for tumor detection. [20] The presence of expanded cfDNA levels has additionally been confirmed in prostate most cancers patients. [21].

Conclusion

In conclusion, it is found that free and total prostate specific antigen (PSA) is increased significantly in carcinoma prostate than benign prostatic hyperplasia but free/total ratio of serum prostate-specific antigen level significantly decreases in prostatic carcinoma than benign prostatic hyperplasia. So, free, total and free/total ratio of PSA can be used uniquely as a screening procedure for early detection of prostate cancer

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