

Significance of Serum Prostate Specific Antigen Levels in Evaluating Prostatic Lesions with Histopathological Correlation

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ABSTRACT

Background: Prostate cancer is one of the commonest forms of cancer among men. Serum prostate specific antigen (PSA) used in the diagnosis of prostate cancer is also elevated in other benign and non-malignant diseases of prostate.

Objectives: The objectives of the study were to determine the relationship of serum f(PSA) and t(PSA), its correlation with histopathological findings and to assess the PSA cut off variable in various pathological conditions of prostate with clinical relevance.

Materials and Methods: This study included 141 patients admitted for transurethral resection of prostate and 141 control cases. fPSA was determined on blood samples by sandwich enzyme linked immunosorbent assay and total PSA by Enzyme Linked Fluorescent Assay method. The samples were processed and stained with haematoxylin and eosin.

Results: The mean t(PSA) values for benign, premalignant and malignant lesions were 10.3 ng/ml, 20.36 ng/ml and 75.92 ng/ml respectively. The mean serum fPSA values for benign, premalignant and malignant lesions were 3.2 ng/ml, 9 ng/ml and 13.2 ng/ml respectively. The cut off value for tPSA was 12.25 ng/ml and that of fPSA was 9.4 ng/ml. The p value (<0.0001) was highly significant in determining premalignant and malignant lesions.

Conclusion: Total PSA is raised in premalignant, malignant, inflammatory and benign neoplastic lesions of prostate. In cases where the t(PSA) values are between four - ten ng/ml, f(PSA) is useful marker in cases of malignancies, which were confirmed on histopathology.

Keywords: Benign Prostatic hyperplasia, fPSA, tPSA, Premalignant Lesions, Prostate Cancer.

Introduction

Prostatic carcinoma is one of the most common cancers and the second most common cause of death due to cancers in male. Also the curative treatments are limited to early stages of the disease, making primary and secondary preventions significant.

Prostate specific antigen (PSA) is highly specific for prostate tissue, but not for prostate cancer, as it can be raised in non-malignant conditions like benign prostatic hyperplasia (BPH), inflammation, diagnostic and surgical procedures also. This may lead to confusion in diagnosis especially in prostate cancer detection programs that use PSA as a screening test. However, of the two forms (free and bound), lower levels of free PSA can improve the sensitivity of cancer detection when total PSA is in the normal range (<4 ng/mL) and "gray zone" (4.1 to 10 ng/mL). Still, there is only limited data available on this subject.^[1,2,3] In our study aim was to find the levels of the two biomarkers (total and free PSA) with their correlation in different prostatic pathology; and to assess the prostate specific antigen (PSA) cut off variable in various

pathological conditions of prostate with clinical relevance

Material and Methods

The present study was carried out for two years in pathology department of tertiary care hospital after prior approval from the ethical committee. The study included 141 patients willing to give informed consent ranging from age 30-90 years, and who were admitted to the surgical ward with history of prostatic or urinary complaints. All Prostatic biopsies obtained from surgery department through transurethral resection were included in our study. We excluded patients who had histopathologically proved metastatic carcinomas to prostate, elevated PSA levels in carcinomas other than prostatic pathology and samples with inadequate prostatic biopsies for histopathological reporting.

Control samples (141) were also taken from the normal healthy volunteers of different age groups having no prostatic or urinary complaints.

Blood samples were taken for measurement of fPSA and tPSA before Trans-Urethral Resection Of Prostate (TURP),

and at least a week after digital rectal examination to avoid possible errors caused by the release of PSA from the prostate. The serum samples were stored at -20°C and were tested for fPSA and tPSA. tPSA was estimated by Enzyme Linked Fluorescent Assay (ELFA) method. fPSA was estimated by sandwich Enzyme Linked Immunosorbent Assay (ELISA) method. Clinically, different age wise normal tPSA levels were considered as - 40 to 49 years- 0 to 2.5 ng/mL; 50 to 59 years- 0 to 3.5 ng/mL; 60 to 69 years 0 to 4.5 ng/mL; 70 to 79 years- 0 to 6.5 ng/mL. The serum fPSA value from 0.4 to 1.3 ng/ml were considered as normal.^[4]The tissue samples were collected after biopsy and TURP were fixed in 10%formalin, processed routinely and stained with Hematoxylin-Eosin.

The cases were histopathologically categorized as -

I. Benign prostatic hyperplasia without and with inflammation:

This included BPH, chronic prostatitis, acute prostatitis, chronic active prostatitis and nonspecific granulomatous prostatitis.

II Prostatic intraepithelial neoplasia (PIN): This included Low-grade PIN (LGPIN) and High-grade PIN (HGPN).

III. Prostate Cancer (PCa): This included, Low-grade PCa (LGPCa) and High-grade PCa (HGPCa).

Data analysis was done using Chi-Square test, Fisher exact test, Unpaired t test and ANOVA were ever applicable. The relationship of fPSA with tPSA was determined and its correlation with histopathological findings was established. Receiver Operating Curve (ROC) analysis was done to determine the cut off value for fPSA. P value of <0.05 was considered as statistically significant.[fig.1]

Results

In our study, most of the patients were elderly (>60 years), with average age of 66 years (range 50-82 years). Age-wise distribution showed majority of patients in 60-69 years of age (40%); followed by 70-79 years (38%) and 50-59 years (19%). Three patients were > 80 years of age. Similar distribution was also seen in controls.

On histopathological examination, out of the 141 patients, 99 cases (70.21%) were of BHP, 19 cases (13.48%) of PIN I, 11 cases (7.80%) of PIN II, 5 cases (3.54%) of PIN III and 7 cases(4.97%) of PCa. [fig.2 -6]

The distribution of patients according to normal reference showed that normal tPSA(0-4ng/ml) level present in 43% of patients with BHP; 3% in premalignant lesion and nil in prostatic malignancy. Intermediate tPSA (4-10ng/ml)

level present in 37% of patient with BHP; 26% in pre-malignant lesion and nil in malignancy. High tPSA (>10 ng/ml) level present in 21% of patient with BHP; 71% in pre-malignant lesion and 100 in malignancy. Statistical analysis showed that significantly higher level of tPSA in prostatic malignancy as compared to benign lesion.[table no.1]

Mean tPSA level in patients of BPH were 10.3 ng/ml (ranged from 0.23-78.85 ng/mL); prostatic intraepithelial neoplasia were 20.36 ng/ml (ranged from 2.91-82.0 ng/mL); whereas in prostatic cancer were 75.92 ng/ml (ranged from 12.4-124 ng/mL). Statistical analysis showed that significantly higher level of tPSA in prostatic malignancy as compared to benign lesion ($p<0.001$) and prostatic intraepithelial neoplasia ($p<0.001$). Significantly higher level of tPSA was seen in prostatic intraepithelial neoplasia as compared to benign lesion ($p<0.012$).

Mean fPSA level in patients of BPH were 3.2 ng/ml (ranged from 0.024.3 ng/mL); prostatic intraepithelial neoplasia were 9.0 ng/ml (ranged from 0.90-23.6 ng/mL); whereas in prostatic cancer were 13.5 ng/ml (ranged from 2.5-22.3 ng/mL). Statistical analysis showed that significantly higher level of fPSA in prostatic malignancy as compared to benign lesion ($p<0.001$) and prostatic intraepithelial neoplasia ($p<0.001$). [table no.2]

Significantly higher level of fPSA was seen in prostatic intraepithelial neoplasia as compared to benign lesion ($p<0.01$).The distribution of patients showed that normal fPSA (0-5 ng/ml) level was present in 85% of patient with BHP; 61% in pre-malignant lesion and 14% in prostatic malignancy. Statistical analysis showed that significantly higher level of fPSA in prostatic malignancy as compared to benign lesion ($p<0.001$).

The distribution of patients according to normal reference showed that normal tPSA (0-4 ng/ml) level present in 43% of patient with BHP; 4.5% in LGPIN and nil in HGPN and prostatic malignancy. Intermediate tPSA (4-10 ng/ml) level present in 37%of patient with BHP; 36% in LGPIN; 12.5% in HGPN ; and nil in malignancy. High tPSA (>10 ng/ml) level present in 21% of patient with BHP;59% in LGPIN and 88% in HGPN and 100% in malignancy. Statistical analysis showed that significantly higher level of tPSA in prostatic malignancy as compared to benign lesion ($p<0.001$).

The distribution of patients showed that normal fPSA (0-5 ng/ml) level present in 85% of patient with BHP; 68% in LGPIN; 50% in HGPN, and 14% in prostatic malignancy. Statistical analysis showed that significantly higher level of

fPSA in prostatic malignancy as compared to benign lesion ($p < 0.001$)

Significantly higher levels of tPSA and fPSA were seen in patients with prostatic lesion than normal healthy volunteers ($p < 0.001$), signifying that patient with prostatic lesion have higher levels of tPSA and fPSA as compared to normal healthy population (table no.3).

Discussion

Prostate cancer is common, potentially deadly, and associated with enormous financial health-care costs. PSA is organ-specific, not cancer-specific and serum levels may be elevated in the presence of BPH, prostatitis and other non-malignant conditions. The usefulness of PSA as an early detector of prostate cancer by itself is questionable,

Table 1: Total PSA distribution in patients with prostatic lesions.

Prostatic lesions		PSA Level (ng/mL)					Total
		0-5	5.01-10.0	10.1-15.0	15.1-25	>25	
Benign	N	53	23	5	3	12	96
	%	55.2%	24.0%	5.2%	3.1%	12.5%	100.0%
Pre-malignant lesion	N	1	10	10	8	9	38
	%	2.6%	26.3%	26.3%	21.1%	23.7%	100.0%
Malignancy	N	0	0	1	0	6	7
	%	0%	.0%	14.3%	.0%	85.7%	100.0%
Total	N	54	33	16	11	27	141
	%	38.3%	23.4%	11.3%	7.8%	19.1%	100.0%

Chi-Square test applied. P value 0.001 (Highly significant).

Table 2: Free PSA distribution in patients with prostatic lesions.

Prostatic lesions		Free PSA Level (ng/mL)					Total
		0-5	5.01-10.0	10.1-15.0	15.1-25	>25	
Benign	N	82	7	1	6	96	
	%	85.4%	7.3%	1.0%	6.3%	100.0%	
Pre-malignant lesion	N	23	10	2	3	38	
	%	60.5%	26.3%	5.3%	7.9%	100.0%	
Malignancy	N	1	1	3	2	7	
	%	14.3%	14.3%	42.9%	28.6%	100.0%	
Total	N	106	18	6	11	141	
	%	75.2%	12.8%	4.3%	7.8%	100.0%	

Chi-Square test applied. P value 0.001 (Highly significant).

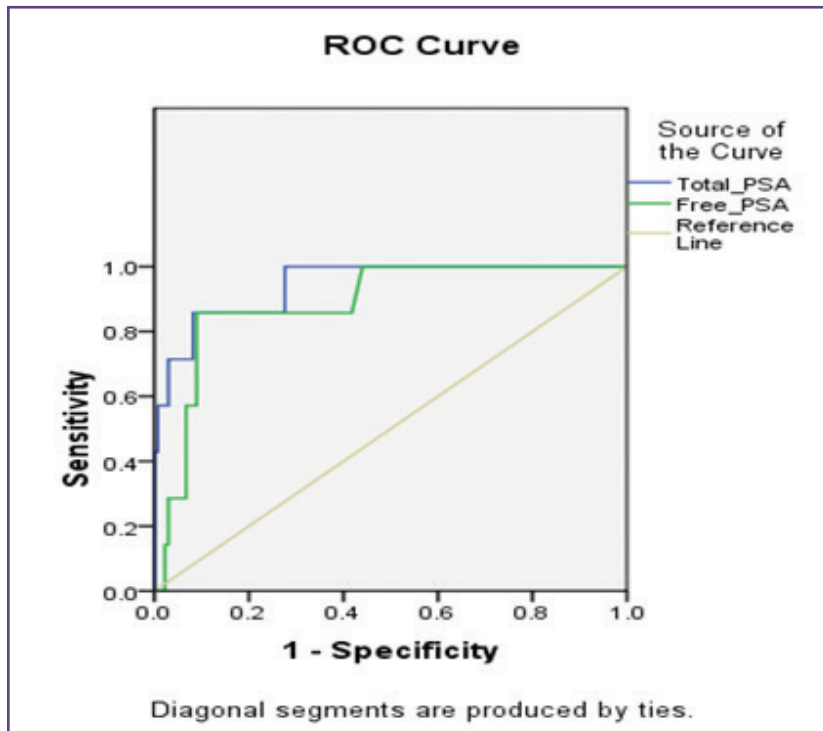
Table 3: Comparison of total PSA and free PSA in patients with prostatic lesions and normal healthy volunteers-

	Total PSA			Free PSA			P value (Significance)
	Mean	SD	Range	Mean	SD	Range	
Patients	16.2783	23.00136	0.23-124.0	4.5243	5.5041	0 - 24.30	0.001(HS)
Control	2.0386	1.25680	0.2-5.2	0.8948	3.253	0.2 - 3.9	

Unpaired t test applied. P value significant if less than 0.05.

Table 4: Sensitivity and specificity of total PSA and Free PSA in detecting prostatic cancer.

Parameter	Cut off	Sensitivity	Specificity	PPV	NPV
Total PSA	>12.25	100 %	72 %	16 %	100%
Free PSA	>9.4	85 %	91 %	33 %	99%



Area under the Curve

Test Result Variable(s)	Area
Total_PSA	.943
Free_PSA	.886

Area under the curve is used for predicting ability of diagnostic test. The higher the value, higher is the predictive ability. Area under curve is interpreted as: 0.50 to 0.75 = fair, 0.75 to 0.92 = good, 0.92 to 0.97 = very good, 0.97 to 1.00 = excellent.

Total PSA has very good predictive value as diagnostic test (AUC 0.943).

Free PSA has good predictive value as diagnostic test (AUC 0.886).

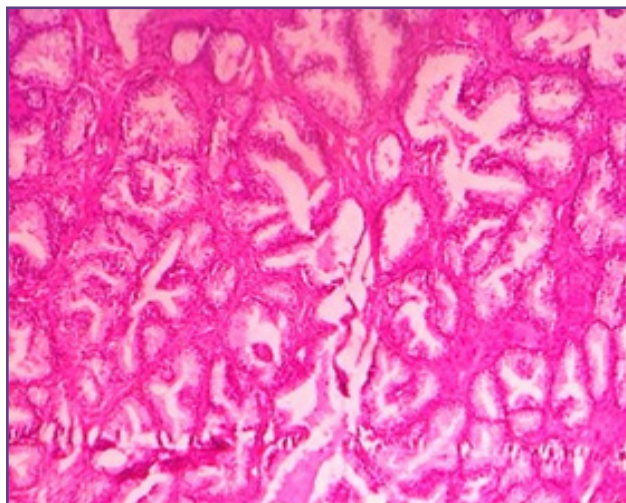


Fig. 2: Benign Prostatic Hyperplasia (H&E Stain-100X) -increased acini and stroma with double layer lining of epithelium.

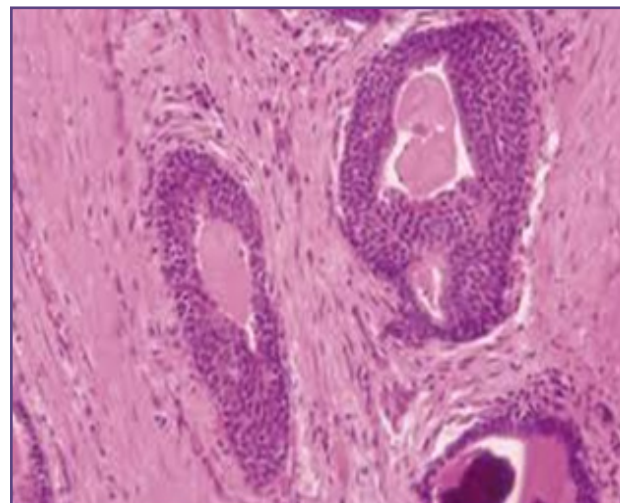


Fig. 3: Low Grade Prostatic Intraepithelial Neoplasia(LGPIN) -multilayering of epithelium with nuclear enlargement (H&E Stain -100X).

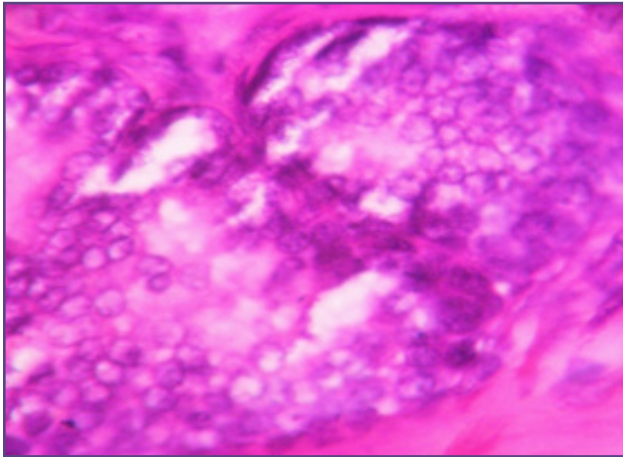


Fig. 4: High Grade Prostatic Intraepithelial Neoplasia (HGPIN) - multilayering of epithelium with hyperchromatic nuclei (H&E Stain-400X).

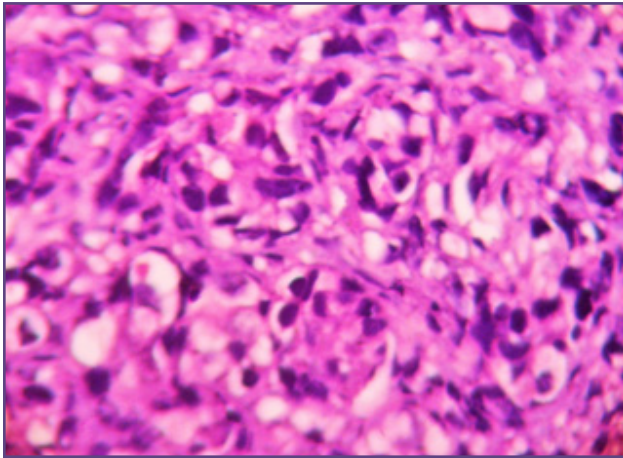


Fig. 5: POORLY DIFFERENTIATED ADENOCARCINOMA OF PROSTATE -GLEASON SCORE 3+4;7/10 (H&E Stain -400X).

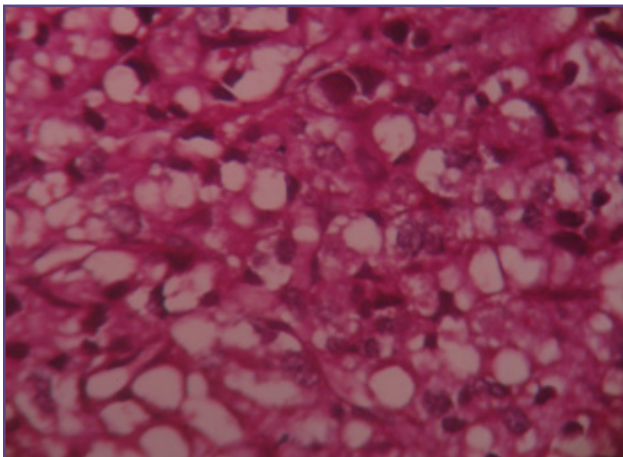


Fig 6 - ADENOCARCINOMA OF PROSTATE-SIGNET RING CELL TYPE; GLEASON SCORE -3+3,6/10 (H&E Stain-400x).

owing to the overlap in PSA values seen in patients with BPH and in those with organ-confined prostate cancer. The need for an accurate marker is driven by the fear of unnecessary biopsies on the one hand, and the risk of missing a treatable cancer on the other.^[5,6,7] Therefore, in our study, we measured two biomarkers (total PSA and free PSA) in 141 patients with prostatic lesion and correlated it with different prostatic lesions; and also attempted to understand an accuracy of PSA cut off variable in various pathological conditions of prostate. Total PSA and free PSA are also measured in equal number of healthy volunteers which were used as a positive control.

Prostate cancer is associated with a lower percentage of free PSA in the serum as compared with benign conditions. fPSA is usually 30% of the total PSA but in malignancy it is reduced <25% of total PSA (tPSA) which is useful to distinguish malignant and benign cases and thus helps in diagnosis of cancer.^[8,9] The free PSA has been used to improve the sensitivity of cancer detection when total PSA is in the normal range (<4 ng/mL) and to increase the specificity of cancer detection when total PSA in the “gray zone” (4.1 to 10 ng/mL). The lower the value of free to total PSA in patient with total PSA in the gray zone, the greater is the likelihood that an elevated PSA represents cancer and not BPH.^[10-14]

Our study showed significantly high levels of tPSA in patients with prostatic lesion than normal healthy volunteers ($p < 0.001$), signifying that patients with prostatic lesions have higher level of tPSA as compared to normal healthy population. Also in our study significantly raised level of fPSA were seen in patients with prostatic lesion and normal healthy volunteers ($p < 0.001$), signifying that patients with prostatic lesion have higher level of fPSA as compared to normal healthy population.

Serum fPSA level ranging from 0.4 to 1.3 ng/mL is used as reference value in most laboratories. In present study, the fPSA level in patients of BPH ranged from 0.04-24.30 ng/mL which was similar to findings by Lakhey et al who reported fPSA range of 0.4-19.82 ng/mL.^[15]

BPH is a heterogenous disease that is characterized histologically by a variable degree of stromal and epithelial hyperplasia. Thus men with a predominance of epithelial hyperplasia are expected to have greater increases in PSA levels than men with predominant stromal hyperplasia.^[16] The variation in PSA levels in BPH can also be explained by the detection of various degrees of inflammatory changes detected histologically in TURP specimens. 35.41% of our BPH patients had histological prostatitis. Lakhey et al reported that 34.6 % of BPH had histological prostatitis.

^[15] Similarly, Kohnen et al reported that 98.1% of BPH had histological prostatitis.^[17] Blumfeld et al also reported that lymphocytic prostatitis was present in 95% of TURP specimens.^[18] Many reports indicate that the serum PSA level is elevated in patients with clinical acute prostatitis.^[19] Lakhey et al show that fPSA of patients with BPH without inflammation and patients with chronic inflammation ranged from normal level to 3.0 ng/mL, while patients with active inflammation had values more than 3.0 ng/mL. Our study showed similar findings.^[15]

In our study, LGPIN and HGPIN were seen in 22 (15.6%) and 16 (11.34%) patients respectively. The corresponding tPSA and fPSA levels in LGPIN were 16.32 ng/ml and 5.12 ng/ml; slightly elevated than normal, while the levels were above 25.92 ng/mL and 7.25 ng/ml in HGPIN. The results of our study are correlating with published literature.^[20,21,22] In a study by Lakhey et al, LGPIN was seen in 7.69% of the 91 patients. Elevated levels of fPSA in HGPIN as compared to LGPIN.^[15] Some studies suggest that PIN causes serum PSA elevation, while other studies dispute this relationship. In our study most of the patients with prostatic carcinoma had serum fPSA levels more than 5.0 ng/mL.^[15,23]

In other study, Alpeshpuri P et al., mean serum PSA values in cases of prostatic hyperplasia with or without dysplasia, prostatitis, well to moderately differentiated adenocarcinoma and poorly differentiated adenocarcinoma were 6.49 ng/ml, 5.35 ng/ml, 18.92 ng/ml and 31.6 ng/ml respectively.^[23]

Statistical analysis of our study showed significantly higher levels of tPSA in prostatic malignancy as compared to benign lesions ($p < 0.001$) and prostatic intraepithelial neoplasia ($p < 0.001$). Significantly higher level of tPSA was seen in prostatic intraepithelial neoplasia as compared to benign lesions ($p < 0.012$). However, tPSA and fPSA in one case of benign lesion was high as 78.8 ng/mL and 24.3 ng/mL whereas tPSA and fPSA in some cases of PIN/PCa are as 2.91 ng/mL and 0.90 ng/mL respectively. Similar overlap has been witnessed in a number of studies using total PSA values, making selection of an optimum cut off value difficult.

The American Cancer Society estimated sensitivity of a PSA at cut-off of 4.0 ng/mL as 21% for detecting any prostate cancer and 51% for detecting high-grade cancers (Gleason ≥ 8). Using a cut-off of 3.0 ng/mL increased these sensitivities to 32 and 68%, respectively. The estimated specificity was 91% for a PSA cut-off of 4.0 ng/mL and 85% for a 3.0 ng/mL cut-off. PSA has poorer discriminating ability in men with symptomatic benign prostatic

hyperplasia. Overall, the positive predictive value for a PSA level > 4.0 ng/mL is approximately 30%, meaning that slightly less than one in three men with an elevated PSA will have prostate cancer detected on biopsy. For PSA levels between 4.0 and 10.0 ng/mL, the positive predictive value is about 25%. However, nearly 75% of cancers detected within the —gray zone of PSA values between 4.0 and 10.0 ng/mL are organ confined and potentially curable.^[24] In our data, though there was overlap of tPSA and fPSA values between BPH and PCa, yet it is significantly higher in case of PIN and PCa. Clinical sensitivity of tPSA to distinguish PCa from BPH is 100% at cut-off value of 12.25 ng/mL. At the cut-off value of the specificity remains low with only 72%. Similarly, clinical sensitivity of fPSA to distinguish PCa from BPH is 85% at cut-off value of 9.4 ng/mL. At the cut-off value of the specificity is higher 91%.

Lakhey et al too reported overlap of fPSA values between BPH and PCa with statistically higher level in PCa. Clinical sensitivity of fPSA to distinguish PCa from BPH is 100% at cut-off value of 1.81 ng/mL.^[15] However, at the cut-off value the specificity remains poor with only 49%. By raising the cut-off value to 12.65 ng/mL, specificity can improve to 94%, limiting sensitivity to only 60%. It was further noticed that use of cut-off value of 5.0 ng/mL will be optimum for clinical use to differentiate PCa with BPH as, sensitivity of 88.8% and specificity of 90.2% can be achieved. (Table no 4)

Considering, the higher sensitivity of tPSA at cut-off value of 12.25 ng/mL, tPSA will be optimum for clinical use to differentiate PCa with BPH as a screening tool and fPSA, owing to its higher specificity at cut-off value of 9.4 ng/mL to be used to confirm the diagnosis.

Our study has few limitations: - First, we excluded the patients with acute retention of urine which are expected to cause elevation in PSA levels that may confound the results. Second, histologic correlation in our study was done on TURP specimens and not prostatectomy specimens. Third, the study was exploratory as it was not powered to detect the pre-determined difference between different groups. Large sample size is recommended to generalize the findings of our study. The cut off value of tPSA was 12.25 ng/ml (not in gray zone) as as the malignant cases were few i.e 7 in 141 in our present study.

Conclusion

Serum tPSA and fPSA are elevated marginally in patients with BPH without inflammation and patients with chronic inflammation. The higher grade lesions (HGPIN and PCa) are associated with tPSA and fPSA values more than 25.92 ng/ml and 7.25 ng/ml. Considering, the higher sensitivity

of tPSA at cut-off value of 12.25ng/mL, tPSA will be optimum for clinical use to differentiate PCa with BPH as a screening tool and fPSA, owing to its higher specificity at cut-off value of 9.4 ng/mL can be used to confirm the diagnosis. The optimal cut-off value of PSA is unclear and depends upon whether optimal sensitivity or specificity. The higher the cut-off value, greater the sensitivity but lesser the specificity. Free PSA may be useful for risk stratification in men with prostate cancer.

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Competing Interest

There is no competing interest.

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