ORIGINAL ARTICLE

Utility of PSA isoform-[-2] proPSA (p2PSA) and prostate health index in the diagnosis of prostate cancer: A study in Indian population

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Abstract

Background: Measurement of serum total Prostate Specific Antigen (tPSA) for diagnosis of Prostate Cancer (PC) has some limitations since PSA is organ-specific and not disease-specific. Studies across the globe have shown that measuring the isoform of PSA: [-2]-Pro-PSA(p2PSA) and calculating the Prostate Health Index (PHI) increase the specificity, however, very few studies have been done in the Indian population. *Aim and Objectives*: To evaluate tPSA, p2PSA and PHI as diagnostic markers of PC. *Material and Methods:* The pre-biopsy blood samples of 152 subjects were analysed in Beckman-Coulter Access-2 for tPSA, freePSA (fPSA) and p2PSA and %fPSA, %p2PSA and PHI ([p2PSA/fPSA] $\times\sqrt{}$ tPSA) were calculated. Validity indicators were calculated along with Area under the receiver operating Curve (AUC). *Results:* Of 152 subjects, 85 subjects (55.9 %) had PC, and others showed No evidence of Malignancy (NEM). The median tPSA (ng/ml), p2PSA (pg/ml), %p2PSA, fPSA (pg/ml) and PHI values were significantly ($p<0.001$) higher in the PC group than NEM group (148 ng/ml vs. 9.11 ng/ml; 612.3 pg/ml vs. 14.52 pg/ml; 4.98% vs. 1.59 %; 15.7 pg/ml vs. 1.26 pg/ml and 440.19 vs. 32.14 respectively). PSA at cut off value of 10 ng/ml had 91.8% sensitivity, 58.2% specificity, Negative Predictive Value (NPV) 84.8% and Positive Predictive Value (PPV) 73.6%. At a cut-off of 100 pg/ml p2PSA had 81.7% sensitivity, 97.0% specificity, 80.2% NPV, 97.2 % PPV and AUC was 0.930 [95% Confidence Interval(CI): 0.88-0.97]. PHI had 91.8% sensitivity, 55.2% specificity, 84.1% NPV, 72.2% PPV and AUC was 0.919 (95% CI 0.86-0.96). *Conclusion:* Using multiple biomarkers like P2PSA and PHI with better specificity can aid in the diagnosis of PC.

Keywords: Prostate Cancer, P2PSA, Prostate Health Index

Introduction

The Global Cancer Observatory (GCO) 2020 estimates reveal that cancer is a leading cause of morbidity and mortality worldwide with 19.3 million newly diagnosed cases and nearly 10 million deaths around the world [1]. Globally, Prostate Cancer (PC) is the second most common cancer and the fifth leading cause of death among men with approximately 1.4 million new cases and 375,000 deaths [1-2]. The exact mechanism by which PC develops is not clearly known as of today, but it is proposed to be multifactorial with progressive stages depending on many factors including race, ethnicity, lifestyle, environment, viral infections, obesity, and family history [3]. Though the PC burden in most of the Asian countries is lower compared to other parts of the world, an increasing trend in the incidence of PC is being observed in India and the annual percentage

change has been reported to range from 0.14 to 8.6% [4]. This rising trend in PC incidence can be attributed to changes in lifestyle, increased screening, and longer life expectancy, as PC primarily affects males aged 65 and above [4-5].

Population based screening for PC by measuring the levels of serum total Prostate Specific Antigen (tPSA) has led to better management of PC mainly because of diagnosis at early stages [6]. Higher tPSA levels have been associated with higher risk of PC and with increased risk of metastasis [6-7]. However, tPSA test is not specific to PC and tPSA levels are affected by many factors including age, acute prostatitis, ejaculation, catheterisation etc.[5-6]. Few studies have also reported that tPSA levels fail to distinguish between low grade and clinically aggressive PC resulting in unnecessary biopsies for false positive results and overtreatment for indolent tumours [6,8]. According to the National Comprehensive Cancer Network (NCCN) [9], only ~30-35% of men with PSA levels between 4-10 ng/ml have chances of a positive biopsy result. False negative results are also possible with tPSA measurement since it has been reported that nearly 17% of patients with tPSA less than 2 ng/ml and 23.9% of patients with tPSA of 2.1 to 3.0 ng/ml are at risk for PC [10-11]. Even the Melbourne Consensus statement [12] concurs on the need for a multivariable approach for the diagnosis of PC and not to base the decision for prostate biopsy on only elevated tPSA levels. This has led to research on newer minimally-invasive serum based markers for diagnosis of PC or for the decision to go for prostate biopsy. This has been possible in part because of the fact that PSA can exist in multiple forms in blood [12-13].

PSA is a serine protease which belongs to the family of kallikrein-related peptidases. In the blood, most of PSA (70-90%) is complexed with serum protease inhibitors majorly α1-antichymotrypsin and a small portion (10-30%) exists in free or unbound state [14]. Most of the assays measure the total PSA i.e. both the free and complexed PSA. The free PSA (fPSA) in serum, in turn exists in three isoforms – proPSA, intact PSA and benign PSA [6]. Studies have shown that in serum, multiple forms of proPSA also exist-native proPSA form containing a 7-amino-acid pro-peptide leader sequence [(-7) proPSA], or other truncated pro-peptide leader sequences including a 5-amino-acid pro PSA ([-5] proPSA), 4-amino-acid pro PSA ([-4] proPSA), and 2-amino-acid proPSA ([-2] proPSA) [15]. Among these proPSA forms, the predominant isoform found in tumour extracts is [-2] proPSA (p2PSA) [6] which has been reported to play a role in early detection of PC and in the prediction of clinically significant PC [16].

Consequently, the novel blood based markers that have been studied in different parts of the world for their utility in diagnosis of PC [17] include the estimation p2PSA with %p2PSA and fPSA with %fPSA [13]. Patients with PC are more likely to have higher tPSA and p2PSA with a lower fPSA and it inherently makes sense to come up with one single score or index taking into account all the three parameters. Prostate Health Index (PHI) is one such index which is calculated using all the three markers to give one singe score and is calculated using the formula- (p2PSA/free PSA) × $\surd$tPSA) [8]. Prospective international trials [16], have demonstrated that PHI is more useful in the diagnosis of PC than measuring only tPSA or fPSA. Hence, this current study was undertaken to evaluate the role of PSA, fPSA, p2PSA and PHI in the diagnosis of PC in Indian patients who had

undergone prostate biopsy for the first time as a part of their clinical management protocol to rule out or confirm the diagnosis of PC. The objective of the study was to evaluate the markers tPSA, p2PSAand %p2PSA, %fPSA and PHI for their ability to differentiate between patients who were diagnosed to have PC and those who showed No Evidence of Malignancy (NEM) on biopsy as determined by the validity indicators- sensitivity, specificity, negative predictive value, positive predictive value and the Area Under the receiver operating characteristic Curves (AUC) of the markers in a cohort of Indian patients.

Material and Methods

This study was carried out between March 2016 and May 2019 at a hospital in Bangalore which is accredited by the Joint Commission International and is a tertiary care private super speciality hospital and the laboratory services catering to the hospital are accredited by National Accreditation Board for Testing and Calibration Laboratories (NABL).

Patient selection and evaluation

During the study period,152 consecutive patients (n=152) who underwent prostate biopsy for the first time and were ready to be a part of the study were included in the study after obtaining informed written consent. Prostate biopsy was done by qualified clinicians following standard clinical protocols based on other clinical and diagnostic findings. The biopsy specimen was subject to standard histopathological procedure and the presence or absence of evidence of malignancy was reported by a qualified histo-pathologist. The study was approved by the Institutional Ethics Committee for clinical studies of the hospital and we certify that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Sample collection

Blood samples were drawn prior to prostate biopsy using standard aseptic precautions in blood collection evacuated tubes manufactured by Becton Dickenson Company, as specified by the kit manufacturer. All the samples were kept at room temperature for minimum 30 minutes and then centrifuged at 3500 rpm for 10 minutes to obtain the serum. Estimation of tPSA was done immediately and the remaining sera were aliquoted, labelled and stored at -80^{o}C until analysis of the other markers.

Biochemical analysis of markers

All analysis was carried out in Beckman Coulter Access-2 Immunoanalyser using the hybritech kits meant for the respective analyte. The markers tPSA (ng/ml), fPSA and p2PSA (pg/ml) were estimated and%p2PSA [% of (p2PSA/fPSA)], %fPSA [% of (fPSA/tPSA)], and PHI [(p2PSA/fPSA) $\times\surd$ tPSA] [8] were calculated.

Principles of the biochemical assays

The Beckman Coulter Hybritech assay of all the markers are based on the same principle– two site chemiluminescent immunoenzymatic (sandwich) principle. The parameter in the sample binds to the immobilized monoclonal anti parameter on the solid phase while, at the same time, the monoclonal anti-parameter-alkaline phosphatase conjugate reacts with different antigenic sites on the parameter. Materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. When the chemi-luminescent substrate is added, light is generated

which is measured with a luminometer. The intensity of the light produced is directly proportional to the concentration of the respective parameter in the sample. The concentration of the analyte is determined from a stored, multi-point calibration curve [18-19]. Quality assurance of the results was done by using trilevel quality controls from third party control providers for tPSA, and kit controls for p2PSA and fPSA on the day the sample were processed. In-house precision check was done for all the parameters using multilevel controls for 7 days to get a minimum of 21 points for each level and the calculated coefficient of variation was less than 5% for all the parameters.

Statistical analysis

Data were entered into Microsoft excel data sheet and SPSS 22 version (IBM SPSS Statistics, Somers NY, USA) software was used for analysis. Categorical data were represented in the form of frequencies and percentages. Continuous data were represented as mean and standard deviation or as median with interquartile ranges. Mann Whitney U test was used as test of significance to identify the mean difference between two quantitative variables with skewed distribution [20]. A p value of <0.05 was considered to be statistically significant. MedCalc software was used for plotting the Area under the Receiver Operating Curves (AUC) for the markers.

Results

Of the 152 patients, 67(44.1%) patients showed NEM group on biopsy and 85(55.9%) patients were diagnosed to have PC. The age distribution of patients in different age ranges is given in Table 1. The mean age was comparable in the two groups with maximum number (42.3%) of patients diagnosed with PC were in the age range 71 to 80 years and maximum number (41.7%) of patients who did not show any evidence of malignancy were in the age range 61-70 years. Table 2 gives the

Table 1: Distribution of subjects in different age ranges

Age range (in years)	Number of subjects with Prostate Cancer (PC)	Number of subjects with No Evidence of Malignancy (NEM)
<50	00	02
51-60	10	09
61-70	27	28
71-80	36	26
>80	12	02
Total	85	67
Mean age ± SD	71.47 (± 8.46)	68.06 (± 8.56)

Table 2: Comparison of the test parameters in the 2 groups in the study cohort

Parameters	No evidence of malignancy (n=67)					Prostate cancer (n=85)					Mann Whitney U test	*P*
	Mean	Median	SD	Quartiles		Mean	Median	SD	Quartiles			
				Q1	Q3				Q1	Q3		
tPSA(ng/mL)	10.20	9.11	7.40	5.15	12.39	430.5	148.0	920.39	45.90	410.25	403	<0.001*
p2PSA(pg/mL)	24.19	14.52	29.44	8.92	25.69	1600.8	612.3	2001.9	144.62	2962.2	396.50	<0.001*
% p2PSA	1.59	1.15	1.30	0.89	2.06	9.17	4.98	9.75	2.58	15.56	862	<0.001*
fPSA (pg/mL)	1.54	1.26	0.93	0.95	2.03	14.65	15.7	10.58	4.36	26.58	512.50	<0.001*
% fPSA	18.45	16.20	12.25	9.95	23.25	11.11	8.41	8.97	3.68	18.45	1657	<0.001*
PHI	53.91	32.14	73.89	19.75	61.83	2167.3	440.19	3505.04	145.23	2188.1	463	<0.001*

**p-value is significant tPSA= Total Prostate Specific Antigen; p2PSA = [-2] pro PSA; %p2PSA= % of (p2PSA/fPSA) ; fPSA = Free PSA ; %fPSA= % of (fPSA/tPSA); PHI =Prostate Health Index- [(p2PSA/fPSA) ×√tPSA]*

comparison of all the test parameters between the PC and NEM groups. The median tPSA, p2PSA, % p2PSA, fPSA and PHI values in all the quartiles were significantly higher (p<0.001) in the PC group when compared with NEM group. The median %fPSA values in all quartiles was significantly lower (p<0.001) in the PC group. The validity indicators-sensitivity, specificity, Negative Predictive Values (NPV), and Positive Predictive Value (PPV) were calculated (Table 3) for the different markers taking biopsy findings as the gold standard for the results being True Positive (TP), False Positive (FP), True Negative (TN) and False Negative (FN). The details of combined 2×2 contingency tables for the study parameters along with AUC values in our study is given in Table 3.

In routine clinical setting, the criteria for selecting patients for further investigations to rule out PC is tPSA value of more than 4 ng/ml, and when we used this cut off value, the sensitivity was 98.82% and specificity 11.94%, with NPV of 88.88% and PPV of 58.74%. We used a higher cut off of 10 ng/mL based on other studies [21] and got a sensitivity 91.8%, specificity 58.2% with NPV 84.8% and PPV 73.6% (Table 3). A specificity of 58.2% indicates that tPSA could rise even in patients without any evidence of malignancy and may not be very useful when used as the sole test to either rule out PC or for taking the decision for further invasive investigations at a cut off value of 10 ng/ml. The Area under the ROC Curve (AUC) for tPSA is illustrated in Figure 1. The AUC is 0.929(95%CI: 0.876-0.964) with a p value of <0.0001.

According to the kit manufacturer, for p2PSA a median value of 13.41 pg/ml with a range of 3.98 to 90.78 pg/ml was found in patients with cancer [20]. Hence, when we used this cut-off value of 13.41 pg/ml for our study cohort, the sensitivity and specificity were 95.3% and 47.8% respectively. However, on analysis of the AUC for p2PSA, the optimal cut-off value of 100pg/ml was found to give the highest specificity (97%) for PC

Table 3: Validity indicators for the parameters using 2× 2 contingency tables along with their area under the receiver operating curve values

	PC	NEM	Total	Sensitivity %	Specificity %	NPV %	PPV %	AUC (95% CI)
tPSA (ng/mL)								
⩽10	7(FN)	39(TN)	46	91.8	58.2	84.8	73.6	0.929 (0.87-0.96)
>10	78(TP)	28(FP)	106					
Total	85	67	152					
p2PSA(pg/mL)								
⩽100	16(FN)	65(TN)	81	81.7	97.0	80.2	97.2	0.930 (0.88-0.97)
>100	69(TP)	02(FP)	71					
Total	85	67	152					
% p2PSA								
<1.66	14(FN)	48(TN)	62	83.5	71.6	77.4	78.9	0.849 (0.78-0.90)
>=1.66	71(TP)	19(FP)	90					
Total	85	67	152					
%fPSA								
>10	34(FN)	50(TN)	84	60	74.6	59.5	75	0.709 (0.63-0.78)
⩽10	51(TP)	17(FP)	68					
Total	85	67	152					
PHI								
⩽40	07(FN)	37(TN)	44	91.8	55.2	84.1	72.2	0.919 (0.86-0.95)
>40	78(TP)	30(FP)	108					
Total	**85**	**67**	**152**					

PC = Prostate Cancer; NEM – No evidence of Malignancy found on biopsy; tPSA= Total Prostate Specific Antigen; p2PSA = [-2] pro PSA;%p2PSA= % of p2PSA/fPSA;%fPSA= % of (fPSA/tPSA); PHI =Prostate Health Index[(p2PSA/fPSA) ×√ tPSA];FN= False Negative, TN = True Negative, TP = True Positive, FP= False Positive NPV = Negative Predictive Value, PPV = Positive Predictive Value; AUC -Area Under the Receiver Operating Curve

diagnosis with a sensitivity of 81.7% (Table 3). Moreover, with an AUC value of 0.930 (95% CI: 0.878-0.965) with a p value of <0.0001 (Figure 1), p2PSA can be considered to be on par with tPSA measurements.

When we used a cut-off value of 1.66 for %p2PSA based on a previous study [16], in our study it had a sensitivity of 83.5% and a specificity of 71.6% with NPV of 77.4% and PPV of 78.9%. The AUC curve for %p2PSA is shown in Figure 1. The AUC is 0.849(95% CI: 0.782-0.902) with a p value of <0.0001.Our study shows that %p2PSA at a cut off of 1.66, provides an added advantage of being more specific than tPSA.

According to the manufacturer [19], %fPSA below 10% has a greater probability of PC. In the current study, at a cut-off value of <=10%, %fPSA had the sensitivity of 60% and specificity of 74.6% with NPV of 59.5% and PPV of 75%. The AUC for %fPSA (Figure-1) was 0.709 (95% CI: 0.63-0.78; p value <0.0001). In our study, the percentage of fPSA had the least AUC when compared to other markers, however it had better specificity and PPV when compared to tPSA.

According to the manufacturer [19], PHI values more than 40, have high risk for diagnosis of PC. Based on this, in our study when we used a cut off value of 40, we found that PHI has a sensitivity of 91.8% and a specificity of 55.2% with NPV of 84.1% and PPV of 72.2%. The AUC for PHI (Figure1) was 0.919 (95%CI: 0.863-0.957) with a p value of <0.0001. In our study cohort, PHI was comparable to tPSA in terms of the validity indicators and the reason for this could be because percentage of fPSA is used along with p2PSA for calculating PHI. Hence, we can postulate that PHI may have a role as an additional complementary marker along with tPSA.

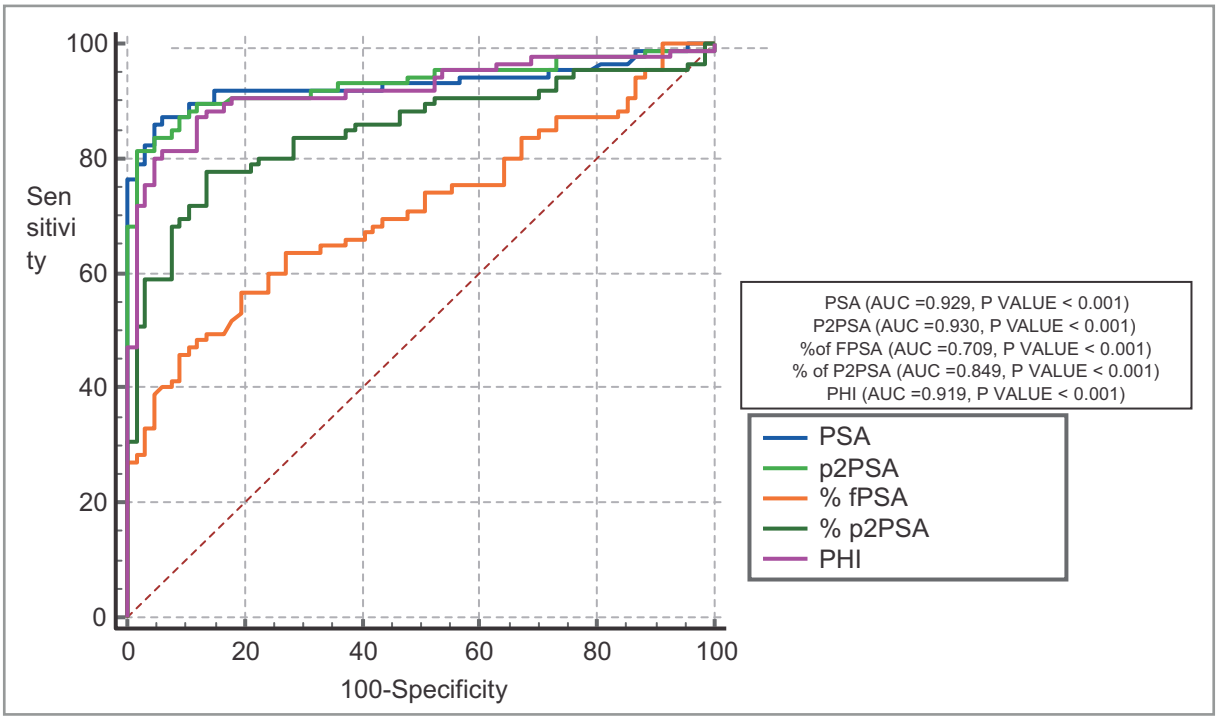

Figure 1: : Area under the receiver operating curves of the markers given in the legend

Discussion

This study was conducted to evaluate the role of the biomarkers, p2PSA and PHI for their ability to aid in the diagnosis of PC in a cohort of Indian population. Our study findings also support previous results [15-17, 21-24] regarding these biomarkers and PHI, p2PSA and %p2PSA were significantly increased in patients who had PC and had better specificity when compared to tPSA. A study in Oman [23] on 136 patients, of which 20.6% had PC and compared with patients with benign prostate conditions, showed a significant stepwise increase in tPSA, p2PSA, % p2PSA, and PHI with median values of 6.7 vs.13.65 ng/ml, 15 vs., 30.6 pg/ml, 1.58 vs. 2.7 and 26.9 vs. 75 respectively. However, this study excluded patients with had tPSA more than 40ng/ml and hence compared to our study, though the median values of all parameters in the group with benign prostate conditions are comparable, they are considerably lower in the group which had PC.

Although tPSA is widely used for PC screening in many countries, the U.S. Preventive Services Task Force [25] recommends that men aged 55 to 69 years make an individual decision whether to be screened or not based on the potential benefits and risks. Moreover, there is no specific cut off value for tPSA to base the decision for further invasive testing like biopsy. Using a routine cut off value of 4 ng/mL might lead to unnecessary biopsies that may lead to complications associated with the procedure. Our study revealed that when we use a cut-off value of 4 ng/mL for tPSA, 38.8% (59 out of 152) of the biopsies could have been avoided and even when we used a higher cut off value of 10 ng/mL, nearly 18% (28 out of 152) of the biopsies could have been avoided.

The PHI developed by Beckman Coulter, Inc combines the values of three biomarkers – p2PSA, fPSA and tPSA to give a number. PHI is an US FDA approved test, which has also been suggested by the European Association of Urology in 2016 to be used as an additional diagnostic marker in men over 50 years with negative digital rectal examination and tPSA in the grey zone between 4 and 10 ng/ml [26-27].Though PHI has regulatory approval in more than 50 countries [27], it has been used sparingly in India. A multicentric study conducted by Chiu *et al*. in 2019 [28], including a total of 1652 subjects with different ethnicities-503 European and 1149 Asian men which showed that by using PHI more biopsies could be avoided in Asian men than European men (56% vs. 40%). In our study, if PHI had been used as one of the decision making parameters, 19.7% (30 out of 152) biopsies could have been avoided.

A study conducted in Malaysia by Othman *et al*. [29] involving 84 subjects, of which 25 subjects had cancer that included patients with tPSA less than 20 ng/ml, the AUC for tPSA, %fPSA, %p2PSA and PHI were 0.558, 0.560, 0.734 and 0.746 respectively. The AUC values obtained in our study for the same parameters are 0.929, 0.709, 0.849 and 0.919 respectively (Table 3) which are considerably higher and the reasons for this could be because of the sample size and the patient demographics of our study cohort including the fact that we included all consecutive patients during the study period who were undergoing prostate biopsy for the first time irrespective of the tPSA values.

This study is one of its kind carried out in an Indian population that adds to existing knowledge on %p2pSA and PHI, which show ethnicity-specific differences. However, this study is relatively small-sized and there are limitations to generalise these findings to the entire population. We also

could not follow up the PC patients to know whether there was any change in the histopathological diagnosis on radical prostatectomy as many patients did not use the services of our hospital for further treatments. Future studies are necessary to further evaluate %p2PSA and PHI for their biological reference ranges in different age groups and the need for using appropriate cut-off values for clinical decision-making with respect to both diagnosis of PC and future treatment. The study does emphasize that there is a need for using more accurate and convenient biomarkers and a multivariable approach can be taken pre biopsy or preoperatively which will assist decision making both for the clinicians as well as the patients.

Conclusion

Screening for PC using a single test and to make the decision to undergo an invasive test like prostate biopsy has its own merits and demerits. In our study, 44.1% of the patients showed no evidence of malignancy on prostate biopsy. In such a scenario, it may be better to use multiple minimally invasive blood based biomarkers like p2PSA and PHI which have better specificity and give value added benefit to both clinicians and patients before taking any invasive testing or treatment decision.

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