Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol. 5 No. 12 (2024): December 2024 Issue
https://doi.org/10.51168/sjhrafrica.v5i12.1478
Original Article

UNVEILING THE ROLE OF PROSTATE HEALTH INDEX IN PROSTATE CANCER DIAGNOSIS: INSIGHTS FROM AN INDIAN POPULATION PROSPECTIVE STUDY.

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ABSTRACT

Introduction
The Prostate Health Index (PHI) is based on various Prostate-specific Antigen (PSA) derivatives and has been approved in Europe, Australia, and the United States. PHI outperforms its components for the prediction of overall and high-grade prostate cancer on biopsy. This study aimed to evaluate the usefulness of the Prostate Health Index (PHI) in the Indian context and its role in guiding biopsy decisions when prostate-specific antigen (PSA) levels fall within the borderline or inconclusive range.

Patients and Methods
A total of seventy-five patients with PSA in the range of 4-20ng/ml were enrolled in the study. For each patient, PSA parameters including total PSA, free PSA, and p2PSA were determined from blood samples. PHI was determined using the formula (Beckman Coulter) PHI= (p2PSA/free PSA) x √ PSA. All the patients underwent Trans-rectal ultrasound (TRUS)-guided prostate biopsy. The diagnostic performances of these PSA derivatives were compared to predict carcinoma prostate.

Results
About 53.33% were found to be of benign etiology and 46.67% were of malignant etiology based on the histopathology report of the prostate biopsy. PHI had the highest Area UnderThe Curve (AUC) value of 0.9686, followed by p2PSA (0.9236). At the cut-off value of 35.7 PHI has a sensitivity of 94.28% and a specificity of 90% to detect high-grade malignancy. Using the cut-off value of PHI=35, 46.67% of the prostate biopsies could be prevented.

Conclusion
PHI outperformed PSA in detecting Prostate cancer (PC). Higher value of PHI was connected to high-grade PC. The authors strongly feel that PHI should be widely available in India.

Recommendation
Biopsy is recommended for patients receiving an intermediate to high-risk *PHI* score as opposed to biopsy patients receiving a low PHI score.

Keywords: *Prostate cancer, Prostate health index, Prostate cancer screening, free PSA, PSA prognosis*
Submitted: 2024-11-10 **Accepted:** 2024-12-23 **Published:** 2024-12-30

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INTRODUCTION

Prostate cancer (PC) is the fifth most prevalent cancer overall and the second most common cancer in men diagnosed globally [1]. Additionally, it ranks as the sixth most common cancer-related death among men worldwide. [2]. Though its incidence is lower among Asian countries as compared to Caucasians, the incidence-to-mortality ratio is much higher in many Asian countries [3, 4].

Since cancer is not a reportable disease in India, information on the true incidence of prostate cancer is scarce. For prostate cancer, the average annual cancer

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incidence rate in India ranged from 5.0 to 9.1 per 100,000/year [6]. There has been a consistent rise in the incidence as well as mortality rates of chronic diseases such as cancers in Asian countries in recent years [5]. The prevalence of prostate cancer has increased as a result of longer life expectancies, changing lifestyles, and greater access to medical facilities. In developing nations, however, there are presently few ways to identify the disease at an early stage.

Prostatic specific antigen (PSA) and digital rectal examination (DRE) have been used as screening tools in the diagnosis of prostate cancer. Prostate cancer mortality has undoubtedly decreased as a result of PSA-based screening. Additionally, it has caused overdiagnosis and overtreatment. The limited specificity of PSA results in numerous unnecessary biopsies, each of which has its problems. A prostate biopsy is usually associated with anxiety, discomfort, and also a monetary burden on the patient. Other complications include hematuria, urinary tract infection, rectal bleeding, severe sepsis, etc. [7, 8]. PSA can be elevated in various other non-malignant conditions such as prostatitis, urethral instrumentation, and prostate manipulation. PSA remains within a normal range even in some malignant patients. Therefore, there has been an urgent requirement to validate other indicators for the detection of carcinoma prostate.

To increase the specificity, PSA velocity, Free PSA (f PSA), and PSA density (PSAD) have been utilized. Prostatic Health Index (PHI), prostatic Cancer Antigen 3 (PCA3), and 4- kallikrein score have been shown to improve early cancer detection [9]. Among all these, PHI has been proven to be the most cost-effective and it was approved by the FDA in 2012. Various studies have been published about the validation of PHI in Asian countries but as far as we are aware, no such study has been conducted on Indian men.

This study aimed to evaluate the utility of the Prostate Health Index (PHI) in the Indian context, specifically its role in guiding biopsy decisions when prostate-specific antigen (PSA) levels are inconclusive. Additionally, the study aimed to determine appropriate PHI cut-off values for assessing disease severity and guiding subsequent prostate biopsy decisions. By incorporating PHI into clinical practice, the study sought to explore its potential to reduce the cost of prostate cancer diagnosis and risk assessment in India.

METHODS AND MATERIALS

Study Design

This study was an observational prospective study.

Study Setting and Participants

It was conducted in the Urology Department, Ruby Hall Clinic, Pune, India on 75 patients.

Inclusion and Exclusion criteria

Patients aged 50-75 years and serum PSA levels between 4 to 20.0 ng/ml were included in the study. Exclusion criteria were - 1. Patients having prostatitis, urinary tract infection documented on urine culture, 2. History of catheterization or other urinary tract instrumentation within the previous month preceding presentation, 3. Patients who have already undergone transurethral prostate excision (less than 3 months duration) 4. Patient with a history of prostate biopsy or carcinoma prostate.

Methodology

To assess the size of the prostate gland, upper tracts, urinary bladder, and post-void residual urine, a trans-abdominal ultrasound examination was performed.

Patients who gave their consent allowed blood samples to be taken, which were then immediately stored at 4°C.Samples were centrifuged and refrigerated within two hours of collection. For further analysis, the serum was frozen at 70°C. Blood samples were used to calculate the PSA values total PSA, fPSA, and p2PSA for each patient. Using the equation PHI= (p2PSA/free PSA) x √PSA, PHI was calculated using Beckman Coulter's instructions. By dividing the blood tPSA level by the prostate volume (PV), as determined by TRUS, PSAD was estimated. The %fPSA was determined.

Before the prostate biopsy, written authorization was acquired. Transrectal ultrasound biopsy was performed on all the participants in the study with at least 12 prostate cores under local/spinal anesthesia under adequate antibiotic cover. Biopsy specimens were evaluated in our hospital Pathology laboratory and were reported by the senior pathologists in the department. We compared the diagnostic performances of these PSA derivatives to predict carcinoma prostate. We also compare these parameters to the Gleason score (GS) of the cancer-positive patients.

Statistical analysis

Data was collected in a predesigned proforma and later tabulated in a Microsoft Excel sheet. Results on categorical data were shown as n (% of cases) and the data on continuous measurement are presented on Mean ± Standard Deviation. To do the statistical analysis, SAS 9.4 was used. The statistical significance of the difference in mean values of measurable variables was evaluated using the Student's t-test. Using the chi-square test and Fisher exact test, categorical data were examined. For PHI and PSA, sensitivity and specificity were computed. A P-value

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of less than 0.05 was considered significant. If necessary, additional suitable statistical tests were run on the data. Multivariable logistic regression models were employed in SAS to ascertain the capacity of numerous preoperative variables to forecast poor pathological outcomes.

Ethical Consideration

After getting approval from our institute's ethics and scientific committee (Ref. No: P/RHC/Academics/ 1820 /2021), we conducted this study from September 2019 to September 2021.

RESULTS

In this study, the data of 75 patients was analyzed. Of which 53.33% were found to be of benign etiology and 46.67% were of malignant etiology based on the histopathology report of the prostate biopsy. The majority of the patients in our study were between the ages of 61 and 70 years. It was also shown that the majority of cancer patients were also of age group 61-70 years. Based on their ultrasonography grading, 46.67 percent of patients had a prostate size in the range of 30-50cc. In this range, 21.33 percent of patients had benign disease and 25.33 percent had malignant disease. The mean PSA value calculated was 7.7ng/ml in the benign group compared to 10.7ng/ml in the malignant group (Table 1-3).

Table 1- Comparing the data between benign and malignant groups

	Variable	Benign (n=40)	Malignant (n=35)	P-Value
1	Age(years) (mean±sd)	69.3±8.47	69.0± 7.89	0.883
2	Prostate size(cc) (mean±sd)	59.4±27.12	40.0± 15.76	0.0013
3	PSA(ng/ml) (mean±sd)	7.7 ±3.29	10.7± 4.74	0.003
4	Free PSA (mean±sd)	1.7 ±0.89	1.7± 1.09	0.71
5	% f PSA(F/T) (mean±sd)	23.6 ±12.58	16.5± 7.94	0.012
6.	P2PSA (mean±sd)	12.2±7.00	32.3±16.02	0.001
7	PHI (mean±sd)	22.40±12.46	66.70±25.91	0.001

Table 2-Comparing the data in significant and insignificant cancer patients

	Variable	Insignificant (n=7)	Significant (n=28)	P-value
1	Age(years) (mean±sd)	70.0±6.56	68.7 8.28	0.586
2	Prostate size(cc (mean±sd))	35.90 ±12.56	41.1± 16.41	0.869
3	PSA(ng/ml) (mean±sd)	9.0 ±5.0	11.1± 4.67	0.274
4	Free PSA (mean±sd)	1.8 ±0.89	1.6± 1.14	0.825
5	% f PSA(F/T) (mean±sd)	21.7 ±5.40	15.2 ±8.01	0.014
6.	P2PSA (mean±sd)	38.5± 22.37	30.8 ±14.12	0.457
7.	PHI (mean±sd)	61.5± 34.96	68.0 ±23.77	0.274

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Table 3- Comparing the data in two groups based on PSA values of 4-10ng/ml and 10-20ng/ml

	Variable	Benign	Malignant	P value	Benign	Malignant	P Value
		PSA 4-10ng/ml			PSA 10-20ng/ml		
1	Age (years) (mean±sd)	70.9± 8.06	68.6± 7.11	0.584	63.4±7.55	69.4±8.95	0.1072
2	Prostate size(CC) (mean±sd)	55.1±25.48	40.4 ±18.29	0.105	74.5±28.68	39.6±12.70	0.057
3	PSA(ng/ml) (mean±sd)	6.3±1.73	7.0±1.88	0.013	12.6±2.57	15.1±2.89	0.1054
4.	Free PSA (mean±sd)	1.6±0.85	1.0±0.25	0.0009	2.1±0.97	2.5±1.15	0.0139
5	% fPSA(F/T) (mean±sd)	25.2±12.93	15.8±6.80	0.0001	17.8±9.84	17.3±9.27	0.0009
6.	P2PSA (mean±sd)	11.6±7.49	23.9±7.39	0.001	14.3±4.73	42.2±17.95	0.0001
7.	PHI (mean±sd)	20.5±10.93	62.1±18.94	0.001	28.8±15.77	72.2±32.13	0.001

The mean PHI value in the benign group was 22. It was 66 in the malignant group. If the PHI threshold value had remained at 25, 34.67% of unnecessary prostate biopsies might have been prevented. In addition, only two individuals with adenocarcinoma were detected in the PHI range of 25-34.9 in this analysis. Both patients had a 3+3 Gleason score.

PHI had the highest AUC value of 0.9686, with a 95 percent confidence limit, according to a univariable accuracy analysis. PSA had an AUC of 0.6986, while percent of PSA had an AUC of 0.6679. At the cut-off value of 35.7, PHI has a 94.28% sensitivity and a 90% specificity (Table 4 and 5).

TABLE 4-Senstivity and Specificity of PHI, PSA, free PSA%, P2PSA in detecting significant PC.

Test	AUC	Sensitivity	Specificity	Reference value
PSA	0.6986	62.85 %	70 %	8.50
PHI	0.9686	94.28 %	90 %	35.7
F/T	0.6679	65.71%	70 %	11.49
P2 PSA	0.9236	82.85 %	95 %	21.05
PIRADS _MRI	0.9664	97.14 %	85.7 %	3

TABLE 5- Sensitivity, specificity, PPV, NPV OF PHI at various cut-off values

	SENSITIVITY	SPECIFICITY	PPV	NPV	% BIOPSY AVOIDED	PC MISSED
PHI >25	100%	65%	71.42%	100%	34.6	0
PHI >35	94.8%	87.5%	86.84%	94.59%	46.67%	5.71%
PHI >55	65.71%	97.5%	95.83%	76.4%	52%	34.28%

DISCUSSION

PSA in combination with DRE is being used as a screening tool in the detection of prostate cancer. PSA-based screening has reduced mortality risk by 21%, but it has also resulted in overdiagnosis and overtreatment [10.]. The primary drawback of PSA-based screening is that more men are subjected to prostate biopsies. The specificity of serum PSA to diagnose prostate cancer is only 25% below 10ng/ml. [11, 12,13].

Many PSA derivatives like that of PSA velocity, free PSA, %f PSA, and PSA doubling time have been

employed to increase the differentiating ability between men with cancer and those without cancer. However, none of them has been able to increase the specificity in the clinical practice. Malignant cells have a greater concentration of pro PSA as compared to hyperplastic transitional zone tissue which has higher free PSA. Four types of proPSA exist in serum -2proPSA, 4proPSA, 5proPSA and 7proPSA. Out of which only the 2proPSA form has been specific to prostate cancer [10, 16].
PHI assay is calculated as a mathematical algorithm by incorporating total PSA, free PSA, and pro-2 PSA[x]. Comparing PHI to total PSA in the 2.5–10ng/ml range, a positive prediction was substantially more accurate [14]. PHI increases specificity for prostate cancer while maintaining high sensitivity. PHI could prevent unneeded biopsies by 39% [15,16,17,18]. Numerous such studies have been carried out in various populations and have consistently produced comparable outcomes with various PSA values. PHI is used in the diagnosis of prostate cancer in the range of 4-10 ng/ml at the first biopsy or extended biopsy. US FDA approved the PHI assay in 2012 and it has been adopted into the US NCCN guideline. According to the 2016 European Association of Urology guidelines, PHI can be used as an additional diagnostic method for men with PSA levels between 2 and 10 ng/ml and a negative DRE. [19].

In a multi-institutional prospective trial in 2011, Catalona et al [20] included 892 men with PSA levels between 2 and 10 ng/ml and normal DRE. In comparison to total PSA or free to total PSA (% fPSA), PHI demonstrated improved specificity for identifying cancer prostate on biopsy, with a sensitivity of 80–95%. PHI had an AUC of 0.70 compared to a total PSA of 0.53 and %fPSA of 0.65. Additionally, a prostate biopsy revealed a 1.61-fold increased risk of prostate cancer that was significant (Gleason score greater than or equal to 7).
In their study, Guazzoni et al. [21] evaluated the predictive efficacy of fPSA, tPSA, %fPSA, p2PSA, and PHI for pathological Gleason and pT3 illness. By using univariate analysis, both%p2PSA and PHI were reliable indicators of pathological Gleason 7 and pT3 disease (p-value 0.0001).

A multicentric investigation by Lazzeri et al. 22 involved 646 participants with PSA levels between 2 and 10 ng/ml. 264 people (40.1%) had PC. Men with and without prostate cancer had significantly different median fPSA,% fPSA, p2PSA, and PHI values. PHI, p2PSA, and p2PSA significantly improved the accuracy in the multivariable logistic regression model by 6.4%, 5.6%, and 6.4%, respectively (all p 0.001). At the PHI cut-off of 27.6, 15.5% of the total biopsies might have been avoided.
In 2013 **Sanda et al** [23] conducted a multicentric study to show that PHI not only outperformed total and free PSA but also was superior in predicting clinically – significant prostate cancer. The probability of cancer was 9.8- 50.1 % in the PHI range of 27 to 55 and that of clinically significant cancer was 3.9 to 28.9 %. Only a single patient was GS 4+3 at PHI < 27.

Tan et al studied 157 Asian males with a PSA value of 4–10 ng/mL and underlined the importance of PHI in the early identification of prostatic cancer. 19.1% of cases of prostate cancer were detected. Considering the cut-off level of PHI at 26.75, 49% of prostate biopsies could be avoided. At PHI 26.75, 3 prostate cancer patients were missed (two had GS of 3+3 and one had 4+3). All patients had significant cancer at the PHI cut-off of 55. The PHI was three times more effective at predicting prostate cancer in the initial biopsy while maintaining 90% sensitivity. [15].

Another retrospective study was performed in the Asian population by **Ng et al** [20] with PSA 4-10 ng/mL with normal DRE. PHI fared better than other markers in terms of cancer detection since 9% of people had prostate cancer (AUC of tPSA was 0.547 and AUC of PHI was 0.781).
Po-fan et al [24]found the effect of combining PHI and mpMRI in 102 subjects in the Asian population. 38.2% were diagnosed to have prostate cancer with significant disease (GS=>7) in 23.5%. At the cut-off of PHI=30, the specificity, sensitivity, NPV, and PPV to predict prostate cancer were 43.6%,91.7%, 94.4%, and 33.3% respectively. The AUC of PHI was 0.735. If the biopsy was limited to patients with PIRADS 3 and PHI 30, 50% of cases could be averted.

Juan et al prospective .'s study [25] involved 101 patients with PSA levels ranging from 3 to 10 ng/ml. The patients were 63.7 years old on average. The size of a prostate was 46cc on average. Univariate analysis of the data showed a significant association between % fPSA and PHI. In multivariate analysis, the best AUC curve was shown for PHI (0.749) followed by %fPSA (0.708) and p2PSA (0.671).

The PHI was also helpful in avoiding unnecessary biopsies in patients with PSA 10 to 20 ng/mL. [26]. **Chiu et al** [16] investigated 312 Chinese men from 2008 to 2015 with PSA 10-20ng/ml and normal DRE. 17% of the 312 men who participated in the trial had prostate cancer discovered by biopsy. Both PHI and PSA fared well in their study in terms of predicting prostate cancer and high-grade prostate cancer. The PHI cut-off value of 35 allowed for the avoidance of 57.1% of biopsies while only 6.7% of low-grade and 2.2% of high-grade prostate cancer were missed.

A prospective cohort of 261 males who had prostate biopsies and had negative DRE and TRUS was investigated by Na et al. [17]. Regarding age, tPSA,%fPSA, PSAD, p2PSA,%p2PSA, and PHI, the AUC scores for the total cohort were 0.598, 0.751, 0.646, 0.789, 0.814, 0.808, and 0.853, respectively. PHI was found to be the strongest

indicator of prostate biopsy outcomes, particularly when the tPSA was between 10.1 and 20 ng/ml. For the total cohort, the AUC scores difference between PHI and tPSA was 0.102 (P = 0.001), 0.233 (P = 0.003) in patients with tPSA (10.1-20 ng/ml), and 0.119 (P = 0.013) in patients with tPSA >20 ng/ml. Of all the available markers, PHI has proven to be the most effective at predicting when unneeded biopsies would be performed.

The majority of individuals with prostate cancer in India are detected with either a locally advanced stage or metastases since PSA screening is not frequently performed. More precise diagnostics are required to identify prostate cancer patients to diagnose cancer at an earlier stage and to reduce unnecessary biopsies. Despite these encouraging outcomes, PHI has not received much attention in India. As far as we are aware, no such research has been done in India regarding the usefulness of PHI in the Indian population for detecting prostate cancer.
In our study, we included 75 patients with PSA 4-20 ng/ml. Our cohort had a positive biopsy rate of46.67%, which is comparable with the positive biopsy rate of Marija et al, Juan et al, Tan et al, Lazzeri et, Po-fan, et al, Chiu et al 53.3%, 43.6%, 19.1%, 40.1%, 38.23%,16.9% respectively[30,25,15,22,24,16].

According to information found in the literature, we found that PHI was the most reliable indicator of prostate cancer at biopsy and would prevent the need for numerous needless biopsies. As per Table No. 4, using the value of PSA as 8.5, we could have avoided 37.3 %of prostatic biopsies(in 28 patients). PHI and p2PSA with cut-off values of 34 and 39 could prevent 45.3% and 52% of unnecessary biopsies. Tan et al [15] resulted in 49% avoidance of prostate biopsies using a PHI cut-off of 27. Lazzeri et al [22] showed 15.5 % of biopsies could have been prevented using a PHI cut-off value of 27.6. Po-fan et al also stated, that if a biopsy was limited to patients with PIRADS ≥ and PHI ≥30, it could be avoided in 50% of the cases. Chiu et al proved that by using a PHI cut-off value of 35, 57.1 % of biopsies could be avoided.

The NCCN recommended PHI > 35 for estimating high-grade malignancy in PC early detection [27]. The PHI cutoff, however, was set anywhere between 24.9 to 32 in certain Eastern Asian studies with a sensitivity of 90% [15,17,28]. A recent multicenter study found that PHI > 30 predicted high-grade (GS 7) cancer in Asian men, but PHI > 40 predicted the disease in European men [29]. Table 5 compares the diagnostic effectiveness of various PHI cutoffs. 5.71% PC would have been overlooked even though PHI of 35 might have stopped up to 46.67 percent of biopsies. For balancing the proportion of biopsy avoided with the percentage of PC missed, PHI 25 was a superior cutoff. Therefore, this study's results suggest that using a low threshold value for PHI is preferable. Males who have a negative PHI test, or one that is below the threshold value, can therefore safely forego a prostate biopsy.

Despite the good diagnostic precision, PHI is still not widely accessible in India. In a developing country like India, the cost-effectiveness of PHI in the detection of prostate cancer is an important question. This can be supported by the PHI's level of specificity and the amount of needless biopsies that can be reduced as a result of its application. If we add the financial burden that occurs in the management of prostate biopsy-related complications, especially urosepsis, the use of PHI in our Indian scenario can offer larger savings. Thus, PHI seems to be a cost-effective option for deferring further testing in some men, given the extent of overdiagnosis and overtreatment.

CONCLUSION

With PHI, the diagnostic "gap" between PSA screening and a prostate biopsy will be filled. The PHI can be utilized to make the finest, most personalized patient management decisions for patients with prostate cancer when combined with family and patient history. As a result, it is possible to significantly reduce the number of prostate biopsies that are now ordered and reported to be cancer-free.
For the detection of clinically relevant prostate cancer, PHI performs better than other individual components. An increased risk of high-risk pathology is predicted by rising PHI scores. We strongly feel that PHI should be widely available in India.

LIMITATION

The study is limited by its short duration and small sample size.

RECOMMENDATION

Biopsy is recommended for patients receiving an intermediate to high-risk *PHI* score as opposed to biopsy patients receiving a low PHI score.

ACKNOWLEDGMENT

To all the participants for their cooperation and patience.

LIST OF ABBREVIATIONS

PHI- Prostate Health Index
PSA- Prostate-specific Antigen
TRUS- Trans-rectal ultrasound
AUC- Area UnderThe Curve
PC- Prostate cancer
DRE- digital rectal examination
fPSA- Free PSA
PSAD- PSA density

PCA3- prostatic Cancer Antigen 3
PV- prostate volume
GS- Gleason score

CONFLICTS OF INTEREST

There are no potential conflicts of interest among the authors to mention.

SOURCE OF FUNDING

This research did not receive any funding.

AUTHOR'S CONTRIBUTION

All authors contributed to the study design, data collection, analysis, and manuscript preparation.

DATA AVAILABILITY

The datasets generated and analyzed during the study are available from the corresponding author upon reasonable request.

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PUBLISHER DETAILS

Student's Journal of Health Research (SJHR)

(ISSN 2709-9997) Online

(ISSN 3006-1059) Print

Category: Non-Governmental & Non-profit Organization

Email: studentsjournal2020@gmail.com

WhatsApp: +256 775 434 261

Location: Scholar's Summit Nakigalala, P. O. Box 701432, Entebbe Uganda, East Africa