International Journal of Medical Science and Health Research

Vol. 2, No. 01; 2018

ISSN: 2581-3366

Performance of the Prostate Health Index for Diagnosis of Prostate Cancer in the Southern African Population

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ABSTRACT

Background: The 'increasing' incidence of prostate cancer (PCa) globally warrants research and introduction of biomarkers which can accurately reflect disease risk and staging, as well as monitor treatment progress. The widely used total prostate specific antigen (PSA test has shown limitations in PCa detection and classification. Prostate Health Index, one such marker has been successfully introduced into clinical practice in many regions especially in the developed countries. Studies in Africa, particularly in under resourced regions like Zimbabwe are limited.

Objectives: The objective of the study was to determine the clinical utility of the PHI in the diagnosis of prostate cancer.

Materials and Methods: A cross sectional study was done on 72 men attending a Urology Clinic at Harare Central Hospital and Parirenyatwa Group of Hospitals, both in Harare, Zimbabwe. Inclusion criteria included a tPSA of >2ng/ml and prostate biopsy request. TPSA, % fPSA and -2 pro PSA were determined and biopsy results were documented. Logistic regression models were used to test PCa predictors.

Results: PHI had a higher area under the Receiver Operating Curve (AUC=0.824) versus TPSA (AUC=0.524) and %fPSA (AUC=0.808). Prediction of prostate cancer, upon the multivariable analyses, using a base model including age, TPSA and %fPSA the AUC at 95% CI was 0.91 at 95% CI 0.85-0.98). Addition of % [-2] form of proPSA (p2PSA) to the base model increased the AUC to 0.92 at 95 % CI (0.86-0.98). Addition of PHI to the base model increased the AUC to 0.95 at 95% CI (0.91-1.00). PHI detected 29 (83%) cancers out of the 35 aggressive cancers at a cut off of 29.76. Out of the 7 nonaggressive cancers (GS < 7), PHI detected 5 (71%) at a cut-off of 29.76 but missed 2 (29%) and classified them as aggressive. There was no significant correlation between PHI and tumour aggressiveness (p=0.237)

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Conclusion: To our knowledge, this is the first study to evaluate the clinical utility of the PHI in the sub region. Our findings are in concordance with reports that the PHI is a good marker for the diagnosis of prostate cancer. The cost effectiveness of PHI makes it an ideal biomarker in under resourced settings like Zimbabwe.

Keywords: prostate-specific antigen, PSA, complexed PSA, free PSA,total PSA, proPSA

Introduction

Prostate cancer (PCa) is ranked as the second commonest diagnosed malignancy and the fifth leading cause of cancer mortality in men, and represents a substantial public health burden [1].In Africa, the highest incidence and mortality rates of 34.3 and 22.1 per 100 000 respectively, were reported in Sub-Saharan Africa compared to 10.6 and 7.0 per 100 000 respectively, for Northern Africa [2]. In addition, the incidence rate of PCa has been reported to be lower in African Americans compared to African men living on the continent[3, 3]. Such variations in incidence rate have been attributed to genetic, socioeconomic and dietary variations among ethnic groups[3, 4]. In Zimbabwe, PCa prevalence increased from 15.4% to 18.1% of all cancer cases in 2012 and further increased to 25.6% in 2013 [2, 5].

Ideally the goal of PCa screening would be to detect asymptomatic disease and improve disease outcomes thus reducing PCa related mortality. The utility of the routinely used serum prostate specific antigen (PSA) as a screening and diagnostic modality for PCa is highly controversial[6]. The test lacks specificity hence has poor discriminatory capacity between PCa and benign prostatic conditions and performs poorly in detecting aggressive cancers[7].Further, a high false positive rate leads to unnecessary biopsies as well as overtreatment of indolent tumours[8]that may not develop into clinically significant PCa in a patient's lifetime[9, 10] Besides the high cost, biopsies carry the risk of infection and discomfort to patient[6].In addition the PSA test performs differently in different racial settings [11-13]

New diagnostic tools are therefore required to improve the specificity of PCa diagnosis and to aid in clinical decision-making. The Prostate Health Index (PHI), approved by the US Food and Drug Administration in 2012, has been reported by some as addressing some of the drawbacks associated with PSA screening. The PHI shows greater specificity and is a combination of three different is forms of PSA: total PSA (tPSA), free PSA (fPSA), and [−2]proPSA (p2PSA),combined in a mathematical formula: PHI = ([−2]proPSA/fPSA) × √tPSA[8].

The PHI has been consistently reported in studies from geographically diverse regions as being more specific for prostate cancer detection than existing standard reference tests of total and free PSA[14, 15]). Increasing PHI scores have also been reported as predictive of greater risk of clinically-significant disease on biopsy and adverse prostatectomy outcomes[16, 17]. However, a limited number of such studies have been conducted in resource limited settings including Zimbabwe where PCa incidence is on the rise.

Materials and methods

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Study Setting and participants

The study was carried out at Harare Central Hospital Harare and Parirenyatwa Group of Hospitals Urology Clinics, Harare, Zimbabwe. Both are teaching hospitals for the University of Zimbabwe's College of Health Sciences.

In this cross-sectional study, eligible subjects were identified among patients suspected of PCa following a serum tPSA>2ng/ml and were scheduled for initial prostate biopsy. Following informed consent, individuals meeting the inclusion criteria were enrolled into the study. A questionnaire was administered to capture participant clinico-demographic information.

Prior to biopsy, 5 ml of whole blood was collected into a plain tube from each participant for measurement of pre-biopsy tPSA, fPSA and -2pro PSA and subsequent PHI computation. The blood sample was placed in an ice box and transported to the Premier Clinical Laboratory, Harare for further processing within 3 hours of collection. Histopathological analysis and Gleason grading were performed by histopathologists who were blinded to the PHI scores. The Gleason grading system according to the updated Gleason grading from the consensus conference was used[18]. Biopsy findings were abstracted from patients' records. Biopsy collection and histopathological analyses were based on current national best practice.

Study population

The study population included 100 consenting male patients aged 50-89 years old attending the Urology Clinic at Harare Hospital and Parirenyatwa Group of Hospitals. These were consenting adult male patients aged 50-89 years,with tPSA> 2ng/ml and had a pending prostate biopsy for histological examination. Patients were excluded if they had a pre-existing diagnosis of PCa, were on 5-alpha reductase inhibitors, hadbacterial prostatitis or acute urinary retention.

Analytical Methods

Total serum PSA and fPSA were measured on the fully automated Snibe Maglumi 2000 Plus analyser(Shenzhen New Industries Biomedical Engineering Co. Ltd, Shenzhen, China)following the manufacturer's protocol and the principles of good clinical laboratory practice. The serump2pro PSA was assayed using a manual ELISA method (Pro-PSA ELISA kit, Human pro-prostate specific antigen(Elabscience Biotechnology Co. Ltd. Houston, Texas, USA) following the manufacturer's instructions.

Statistical Analysis

The Stata version 13.1 statistical package (College Station, Texas, USA) was used for data analysis. Continuous data was summarized using means and standard deviations (sd). Bar graphs were used to summarise categorical data. The Student's t-test was used to compare differences between two means. Logistic regression models were used to test PCa predictors. Multivariate logistic regression modelling was used to assess the performance of the base model with PHI and %p2PSA compared to the performance of the base model. Predictive accuracy of the single markers was measured by area under the ROC curve (AUC).

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Ethical Considerations

The study protocol was approved by the Parirenyatwa Hospital-University of Zimbabwe, College of Health Sciences Joint Research Ethics Committee (JREC58/16).

Results

Clinico-Demographic Characteristics

Of the 100 patients enrolled, 72 (72%) had prostate biopsy results of 42 (58%) had confirmed PCa on biopsy whilst the remainder were classified as 'non PCa'.The participants were further stratified into a dichotomy of tPSA 2-30ng/ml and tPSA>30ng/ml. Table 1 shows a summary of the clinico-demographic parameters and PSA based biomarkers of participants by biopsy outcomes.

Table 1: Clinico-demographic variables by PCa status

Characteristic	Overall (n=72) mean±sd	Non PCa (n=30) mean±sd	PCa (n=42) mean±sd	p-value
Age (years)	76.0±8.2	77.6±6.1	74.9±9.3	0.161
Total PSA(ng/mL) 2-30 (n=32) >30 (n=41)	 12.5±8.0 195.9±112.2	 11.6±8.0 106.9±87.6	 15.2±8.0 214.2±108.9	 0.274 0.019*
Prostate volume (cc)	97.1±63.3	101.9±67.0	91.9±60.0	0.584
%fPSA in tPSA range 2-30 (n=32) >30 (n=41)	 41.9±23.9 16.3±10.2	 48.9±23.1 38.4±39.5	 24.7±9.8 15.1±8.3	 0.008** 0.002**
%pro2PSA in tPSA range 2-30 (n=32) >30 (n=41)	 51.4±27.6 35.7±28.4	 43.1±24.4 28.6±9.4	 76.2±21.4 37.2±30.8	 0.002** 0.471
PHI in tPSA range of 2-30 (n=32) >30 (n=41)	 19.1±14.2 72.2±54.2	 13.9±9.9 25.2±10.9	 34.9±13.8 81.9±54.5	 <0.001*** 0.010**

PCa – Prostate cancer; PHI – Prostate Health Index; tPSA- total prostate specific antigen

There was no significant difference in age between the PCa and non PCa group (p=0.161). The cancer patients had a significantly higher tPSA (214.2±108.9 vs 106.9±87.6) mean± (SD) those with tPSA >30ng/ml range (p=0.019). The PHI valueswere significantly higher in the PCa group (p<0.001 and p= 0.010respectively) in the tPSA 2-30ng/ml and tPSA >30 groups. On the other

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hand, mean serum %fPSA concentrations were significantly lower in the PCa group (p=0.008, p= 0.002 respectively) in the tPSA 2-30ng/ml and tPSA >30ng/ml ranges. The values for %p2PSA were significantly higher only in the PCa group in the tPSA 2-30ng/ml range; p= 0.002.

Characteristics of tPSA, %fPSA and PHI

Total PSA correctly classified 41/42 (98%) of PCa patients and only correctly classified 1/30 (3%) of non-PCa cases. On the other hand, the PHI correctly classified 34/42 (81%) PCa cases and 25/30 (83%) non-PCa cases. Among the 42 cancer patients, 7 (17%) had a nonaggressive cancer defined by a Gleason score (GS) < 7. The PHI correctly classified 29/ 35 (82.3%) PCa cases as aggressive cancers at a cut off of 29.76.Of 7 nonaggressive PCa cases, PHI detected 5/7 (60%) at a PHI cut-off of 29.76. However, there was no significant correlation of PHI with tumour aggressiveness (p=0.237).The diagnostic performance characteristics of tPSA, %fPSA and PHI for the diagnosis of PCa are shown in Table 2 below.

Table 2: Performance Characteristics of tPSA, %fPSA and PHI

Parameter	Cut-Off Point	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
TPSA (ng/ml)	>4	97.6	3.33	58.6	50
%fPSA	22.76	81	80	85	75
PHI	29.26	87.2	83.3	87.2	75.8

PCa – Prostate cancer; PHI – Prostate Health Index; tPSA- total prostate specific antigen

At a cut-off point of >4.0ng/ml, tPSA had a sensitivity of 97.6% and a specificity of 33.3% At cut-off 22.76, %fPSA had sensitivity of 81% and specificity of 80%. At a cut-off 29.26, the sensitivity of PHI was 87.2% and specificity 83.3%. The positive predictive values for tPSA, %fPSA and PHI were 58.6 %, 85 % and 87.2% respectively whilst the negative predictive values were 50 %, 75 % and 75.8 % respectively.

ROC for tPSA, %fPSA and PHI

The receiver operator characteristics of tPSA, %fPSA and PHI to determine their diagnostic performance are presented in figure 1 below.

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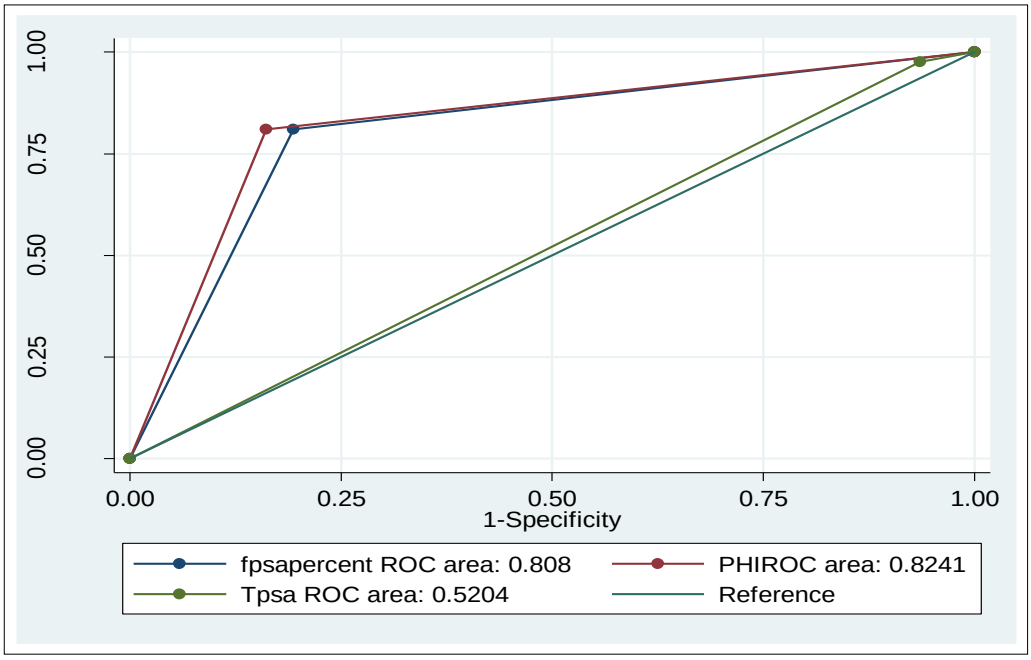

Figure 1: ROC for tPSA, %fPSA and PHI

PHI had the highest area under the Receiver Operating Curve (AUC=0.824) versus tPSA (AUC=0.524) and %fPSA (AUC=0.808).

Positive biopsy rates of PHI

Figure 2 below shows the rates of prostate cancer detection by biopsy for different PHI ranges were 12% for PHI < 20, 10% for PHI 20-<30, 10% for PHI 30-<40, 17% for PHI 40-<50, 12% for PHI 50-<60, 2% for PHI 60-<70 , 2% for PHI 70-<80 and 36% for PHI > 80 .

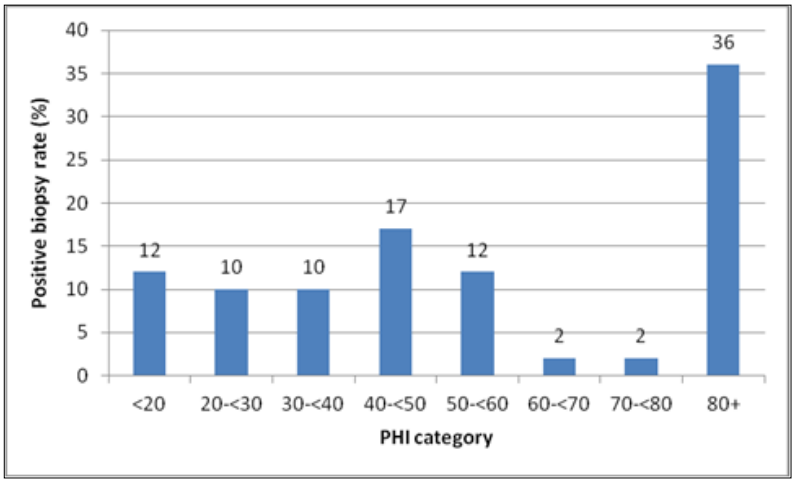

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Figure 2: Positive biopsy rates of PHI

The AUC for the prediction of PCa on biopsy for age, tPSA, %fPSA, %p2PSA and PHI were 0.60, 0.86, 0.85, 0.52 and 0.91 respectively in univariate regression analysis. Multivariate logistic regression model, using a base model that included age, tPSA and %fPSA, the AUC at 95% CI was 0.91 (95% CI 0.85-0.98). Upon adding %p2PSA, the AUC increased to 0.92 (95 % CI 0.86-0.98). Upon adding PHI to the base model, the AUC increased to 0.95 (95% CI (0.91-1.00). However, there was no statistically significant difference between the AUC of the multivariable model with the AUC of the base model (p= 0.435 and p= 0.064) for %p2PSA and PHI respectively.

Discussion and Conclusion

The present study confirms the superiority of the PHI in PCa diagnosis (AUC 0.824). The prediction of PCa detection improved significantly on adding PHI to a base multivariate regression model of age, tPSA and %fPSA. We however failed to demonstrate any significant correlation between PHI and tumour aggressiveness.

As observed by others the PHI in the present studyout-performed its constituent biomarkers showing a high specificity of 83.3% at tPSA>30ng/ml[14, 16]. Na *et al*, 2014,also reported a higher PHI AUC -0.90 for tPSA >20ng/ml versus AUC 0.73 for tPSA 2-10ng/ml and AUC- 0.80 for tPSA 10.1-20 ng/ml [19]. Even at lower tPSA concentrations (4-10ng/ml) De lla Calle et al reported a specificity of 36.6% which is still much higher than the 3.3% reported for tPSA in the present study[14].

Our findings suggest potential clinically accurate utility of PHI in the diagnosis of PCa. The risk of PCa was observed to increase significantly as PHI increases. Routine adoption of the PHI could therefore positively impact physician decision making and selection of the patient population for active surveillance. Furthermore, the use of PHI reduces the number of unnecessary biopsies. In the present study, 24 (83%) biopsies could have been avoided if the PHI was in routine use. Our findings are in concordance with those from other studies[13, 20, 21].

Also noteworthy is the cost of p2PSA which in the present study was more than three times than that of tPSA and fPSA. The cost effectiveness of the PHI would be realised in the long term through global reductions in the cost burden of PCa diagnosis and care. The lower cost of the technologies required for generating the PHI compared to alternative imaging and histopathological devices and personnel also make the PHI a better suited biomarker for PCa diagnosis and monitoring in resource limited settings such as Zimbabwe.

Elsewhere, the PHI has been significantly correlated with PCa tumour aggressiveness[22-24]. Our findings were however at variance and we attribute this to the possible contribution from our smaller sample size although other studies also failed to demonstrate correlation. This smaller sample size also precluded us from suggesting an optimal cut-off point for incorporating the PHI into routine clinical practice. In any event a meta-analysis by Wang *et al*, 2014, reported lack of

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concurrence on the optimal PHI cut-off[22].This calls for more studies in ethnically diverse settings to contribute data that can clarify the uncertainties.

A major strength of the current study is the blinded nature in the interpretation of biopsies by experienced histopathologists. Our study contributes to the literature on the utility of non-traditional PHI technologies on a previously unstudied Southern African population. Racial disparities have been reported in the perfomance of PSA based biomarkers due to polymorphisms in the androgen receptor genes[25, 26].

Our study had the limitation of a small sample size that was largely a result of the limited funding and the inability of potential participants to fund the taking and histopathological examination of prostate biopsies. In addition our data analysis was based on serum tPSA values based outside the critical grey PCa diagnostic window of 4-10ng/ml. However the higher tPSA values used in the present study mirror routine practice in Zimbabwe, where patients present late and most often with much higher tPSA concentrations. Preliminary studies by Na *et al*, 2014 and Chiu *et al*, 2016 (99,107) also reported a higher performance of PHI for PCa detection in higher tPSA values. We also used assay platforms different from those of the National Comprehensive Cancer Network guidelines. Other studies have also however used diverse assay platforms (105, 107). Our approach however mirrors the real life situation in which recommended technologies will not always be readily available. However this use of different assay technologies could potentially also contribute to the differences in findings obtained in different settings even though the superiority of the PHI is clearly demonstrated.

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