ORIGINAL ARTICLE

Evaluation of prostatic health index (PHI) and -2proPSA in the diagnosis of prostatic cancer.

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ABSTRACT

Background: prostatic specific antigen (Free and total PSA) has been used world- wide for the detection of prostatic carcinoma however it has low specificity especially in PSA range between 4-10 ng/ml, this low specificity leads to unnecessary prostatic biopsy. Prostatic health index (PHI) is a new FDA approved test used to accurately correlate the relationship between prostatic carcinoma and high total PSA of 4-10 ng/ml.
Objective: we assessed the diagnostic performance of -2proPSA and PHI for the finding of prostatic carcinoma in men with total PSA range of 4-10 ng/ml.
Patients and methods: Fifty candidates with PSA between 4-10 ng/ml subjected to blood test for estimation of -2proPSA, free PSA and Subsequently subjected to prostatic biopsy at Azadi teaching hospital/Duhok, during the period of (August 2018 to August 2019) for correlation and prostatic cancer detection using this formula:(-2proPSA/free PSA) x square root (PSA).
Results: fifty patients with range between 50-80 years presented with lower urinary tract symptoms with total PSA of 4-10 ng/ml underwent prostatic biopsy, the mean scores for positive and negative prostatic carcinoma were as follow respectively (median values total PSA: 7 versus 6 ng/ml, -2proPSA: 15 versus 11.5 ng/ml , PHI: 59 versus 33) setting the sensitivity of
90%, PHI had greater specificity for detecting prostatic carcinoma in comparison to free PSA % and total PSA. Area under the curve for PHI and -2proPSA were AUC (0.76 and 0.732) respectively compared to other markers.
Conclusion: In group with PSA between 4-10 ng/ml and normal digital rectal examination, the PHI raised the specificity for the detection of prostatic carcinoma which leads to decrease in number of unnecessary prostatic biopsy.
Keywords: Prostatic health index PHI, Prostate cancer PCa,-2proPSA, free PSA, Area under curve AUC

INTRODUCTION

Prostate specific antigen (PSA) is a cancer biomarker in serum that is commonly found in the very early detection of prostate cancer (PCa). Although, the specificity of PSA is low or limited, biopsy examination is positive in about 25% of patients with PSA in the range (2 ng/ml - 10 ng/ml) [1].Moreover, PCa is found in repeated biopsy testing about 35 % of patients with negative initial test. Hence, based on the guidelines of the “European Association of Urology” (EAU), it is crucial to repeat biopsy in these kinds of patients [2].The evaluation of various fraction of PSA (complex PSA and free PSA) has been suggested to improve the specificity of total PSA.

Interestingly, several papers have highlighted the role of [-2] pro PSA in detection of PCa patients. The introduction of the [-2] pro PSA test by scientist Beckman Coulter have opened a new way for finding PCa [3].At the moment, many studies have shown that male with an overall PSA between (2.5 ng/L to 10 ng/ml), the percent of [-2] pro PSA to free PSA % may recognize between benign and neoplastic prostate illnesses superior to total PSA or %free PSA [4, 5].

It is important to mention that, many finding highlighted the advantages of the Prostate Health Index (PHI), a mathematical combination of total PSA, free PSA and [-2] pro PSA based on the equation =[-2] proPSA/fPSA) × √ tPSA.

As cited earlier, total prostate specific antigen (PSA) has limitation in term of specificity for finding clinically important prostate tumor .Hence, this low specificity cause an excessive number of prostate biopsies [8]. Moreover, PSA examination has also resulted in a rise in the number of patients being tested with potentially clinically-insignificant, low-grade PCa [9].

In this research, we aimed to evaluate the benefit of [-2] pro PSA and PHI in the detection of PCa patients.

PATIENTS AND PROCEDURE

The prospective study was conducted at Azadi Teaching hospital/Duhok to assess the diagnostic performance of PSA and its derivatives namely [-2] pro PSA, and %free PSA and PHI in detection of prostate cancer. In the period from August 2018 to August 2019, serum from 50 patients from Duhok province were collected at Azadi Teaching hospital/Duhok urology Department were examined. The mean age of the candidates was 67.1 (50.0-83.0) years. These patients were expected of having PCa, with total PSA range from 4-10 ng/ml, and go through trans-rectal ultrasound (TRUS) guided prostate biopsies.

All candidate involved in this research were tested for total PSA (tPSA), free PSA (fPSA) and [-2] pro PSA. Based on the prostate biopsy results, the patients were divided into two groups: 25 patients with prostate tumor and 25 patients without prostate tumor.

Hematological samples were obtained from the cubital vein, collected in “VACUETTE®” blood collection tubes (Greiner Bio-One, USA) and done in accordance to Semjonow *et al.* [6]. The separation of sera was done by centrifugation at 1,710 ×g for 10 min and after that the

samples were either tested directly within 3hrs or stored at −20˚C till process carried out.

fPSA ,PSA and PHI and −2proPSA were measured applying a DxI 800 chemiluminescent tool (Beckman Coulter, Brea,California,America) and Hybritech calibration and calculated by applying the equation:%fPSA=(fPSA/tPSA)×100 and PHI=(−2proPSA/fPSA)×√tPSA.

The limits of detection (LOD) were 0.007 ng/ml for PSA, 0.004 ng/ml for free PSA and 0.4 ng/ml for −2proPSA. The limits of quantification (LOQ) were 0.018 ng/ml for PSA, 3.22 ng/ml for −2proPSA.

Statistical Analysis: Statistical analyses were done with MedCalc Version 19.1 (MedCalc Software, 2019). Variation among 2 patients groups was evaluated with the nonparametric Mann– Whitney *U*-test, student t-test were performed.

The sensitivity, specificity, and the area under the receiver operating characteristic (ROC) curve (AUC) were carried out for all serum biomarkers. Spearman rank correlation and Wilcoxon's test were applied for making comparison of the two groups of patients. AUCs were assessed based to DeLong et al.[7]. ROC curves were applied to compare specificities at given sensitivities. In this study, *P* values of less than 0.05 were regarded statistically significant.

RESULTS

Table 1 showcases the highest AUC value recorded for PHI and the lowest for PSA. Table 2 reveals the results variable for both groups of patients, including statistical importance. Table 3 showcases important cut-off point for sensitivity and specificity of the selected biomarker. The Spearmen correlation provide that PHI and -2pro PSA did not varied with age ((r=0.025, p=0.68) which predict the use of the same cut-off apply to all male irrespective to age.

Table 1 Indicates Areas under the curve (AUC) for each biomarker

Variable	AUC
PHI	0.765
%free PSA/PSA	0.638
[−2]pro PSA	0.732
PSA	0.530
Reference PSA	0.55

PHI: prostate health Index; AUC: Area under the curve; PSA: prostate specific antigen; %free PSA: ratio of free PSA / total PSA.

Table2 reveals the Serum levels of tumor markers based on age characteristics and diagnosis

Parameter Median (Min-Max)	PCa N=25	No PCa N=25	*P-value*
Age (years)	67.1 (50.0-83.0)	66.5 (50.0-82.0)	>0.05
PSA (ng/ml)	7 (1.8-19.8)	6(1.7-17	>0.05
%p2PSA	2.48 (2.49–2.57)	1.63 (1.56–1.70)	<0.05
-[2pro] PSA (ng/ml)	20.0 (11.0-133.0)	15.0 (3.0-75.0)	<0.05
%free PSA (%)	11.8 (1-15.7)	15.5 (1.8-12)	<0.05
PHI	59 (18.0-230)	33(13.1-155)	<0.05

PCa, Prostate cancer PHI: Prostate health index; %free PSA: ratio of free PSA/total PSA. PSA: prostate-specific antigen

Table 3.Shows the typical Sensitivity, specificity, of PSA derivatives for detection and prediction of prostate cancer.

Bio Marker	Cut-off value	AUC value	Specificity %	Sensitivity %
PSA (ng/ml)	5	0.53	12	95
PHI	32	0.765	40	95
-2proPSA (ng/ml)	11	0.732	41	95
%free PSA (%)	14%	0.638	16	95

PHI: prostate health Index; AUC: Area under the curve's: prostate specific antigen; %free PSA: ratio of free PSA / total PSA.

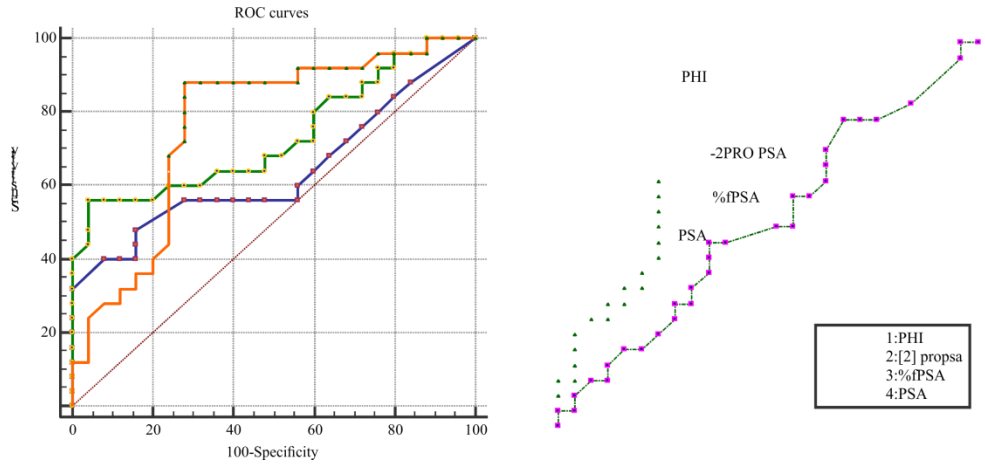

Figure 1. reveals the Receiver operating characteristic curves for the precision of total Prostate specific antigen (PSA), −2proPSA, % free PSA and PHI for expecting prostate tumor at taking the biopsy.

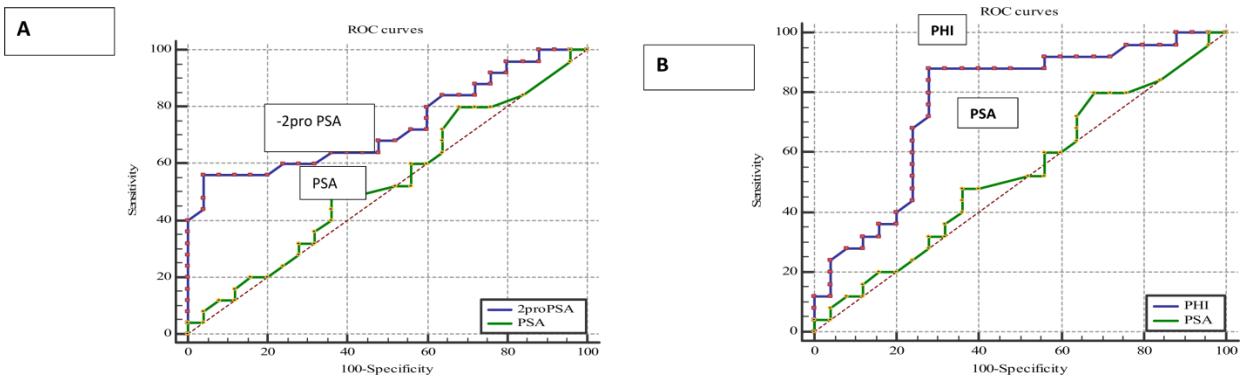

Figure 2. Receiver operating characteristic curves ROC reveals the accuracy of (A) total Prostate specific antigen (PSA) versus [−2] proPSA. (B) Shows Prostate Health Index (PHI) versus PSA for predicting prostate cancer at biopsy.

DISCUSSIONS

Unnecessary prostate biopsy is the main disadvantage of the PSA-based screening test in men. Studies have seen that PSA level can be raised by benign conditions like large benign prostate hyperplasia, manipulation of the prostate and prostatitis. The specificity of a PSA level <10.0 ng/mL to the detection of PCa was only 25% 10. Derivatives of PSA e.g. fPSA, PSA Doubling time, PSA velocity were opted to get Better reliability of discriminating between men who have and who do not have tumor, but none of them has shown to perform high specificity in practice. Interestingly, Pro-PSA concentration is high in cancerous cells, while fPSA is greater in hyperplastic transition zone tissue. There are 4 types of pro-PSA isoform, namely (-2) pro-PSA,

(-4) pro-PSA, (-5) pro-PSA, and (-7) pro-PSA, present in serum, however (-2) pro-PSA is the only form specific to PCa. (-2) pro-PSA has been used to enhance the accuracy of diagnosis of PCa and also evaluating the aggressiveness of the cancer 11. Our prospective current findings confirmed that [-2] pro PSA and PHI as the strongest differentiating parameters between candidate with and without prostate tumor (Table2).This results were in agreement with research conducted by Stephan et al. 201312 and his colleague in regards of [-2] pro PSA and PHI as ideal marker for detection of PCa patients from non PCa . Furthermore, our research showcases the superiority of [-2] pro PSA and PHI as a combination of all three biomarkers in raising the specificity and sensitivity in detection of prostate malignancy.

Our study, reveals that among the different PSA derivatives in expecting the result of prostate biopsy, PHI and p2PSA had the greatest areas under the ROC curves (AUC) of 0.765 and 0.732 (both p value counted < 0.05), respectively, and did better than to PSA, %fPSA were recorded (AUC: 0.53, 0.638,, respectively; p value >0.05, p < 0.05, respectively) (Fig. 1,2 and Table 1,2), which is a nearly, to the results from other paper conducted by Stephan et al. 2013.

ROC comparisons at 95% sensitivity of prostate cancer detection showed that specificities of 40 % for PHI and 41 % for [-2] pro PSA whereas, 12% for PSA and 16% resulted for % fPSA in this research, nearly identical to the results of Fuchsova et al. 13, who found specificities of 30 % for Phi and 16 % for %fPSA, by applying of cut-off of 30 for PHI and 15% for fPSA. This leads to a significant drop in false-negative biopsy.

In order to put into practice the application of new biomarker. Reliable threshold must be set, in our research cut-off of above 32 for PHI and 11 for 2proPSA is highly linked to positive prostate cancer .More than fifty percent of all prostate cancer cases were seen to have PHI within the interval of 31-50 and 11 to 15 2proPSA. It is crucial to mention that this clinical path may lead to a decrease in the cases of negative biopsies on patients 14. Roobol et al. support our study were he found that PHI was better than total, free PSA for the detection of clinically important PCa. Using a PHI cut-off 27.9 can avoid 30% of biopsies with indolent or no PCa15.

CONCULSIONS

Our study demonstrated that both PHI and [-2] pro PSA did well in finding of PCa in Azadi teaching Hospital, Duhok region.

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Conflicts of Interest: All authors have nothing to disclose or declare.

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