

Prostate Health Index in a sample of Iraqi patients with Prostate Cancer and Benign Prostatic Hyperplasia

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Abstract

There is widespread of PSA using as a Prostate Cancer biomarker (threshold of 4ng/ml),but there is no single PSA value that avoids missing serious cancers at a treatable phase, avoids false-positives and unnecessary prostate biopsies. The evaluation of the clinical significant of [-2]proPSA and the Prostate Health Index (PHI) in diagnosis of Prostate Cancer was done in this research to enhance the correct prediction of the prostate cancer. The aim, of this study is to improve the method of testing by using newer PSA biomarkers in the subject sera for evaluating the diagnostic significance of [-2]proPSA and Prostate Health Index (PHI) in the detect of prostate cancer in early stages. A case-control research comprising 54 patients over 50 years old age having Prostate Cancer and Benign Prostatic Hyperplasia recruited from Iraqi urological clinics unit and AL-Amal National Hospital for Cancer Management during the period from July 2018 to March 2019. There was a significantly high difference ($P < 0.001$) of serum PSA, P2PSA and PHI levels among all the study groups. The cut-off values of [-2]proPSA and Prostate Health Index (PHI) based on the ROC curve results in current study were >322 pg/ml and >578 respectively for Prostate cancer patients, while their values range between 322-89 pg/ml, and 578-209 respectively for BPH patients, and <89 pg/ml and <209 for apparently healthy men respectively, the area under curve (AUC) of (P2PSA) and PHI were 0.968, 0.960 for PCa group against noncancerous group respectively, 0.85 and 0.796 for BPH group against control group respectively. Their levels show significant increase in PCa patients in comparison with noncancerous group and in BPH patients when compared with control group.

Keywords: (-2)proPSA; prostate cancer; Prostate Health Index; prostate-specific antigen.

Introduction

Prostate-Specific Antigen (PSA) is well-known prostate cancer (PCa) detection serum biomarker in its early presence⁽¹⁾. According to recent studies, PSA fails to be considered as an accurate PCa predictor biomarker (limited by poor specificity)⁽²⁾.

A considerable effort has been made as a consequence in order to find new biomarkers for the accurate diagnosis of PCa⁽³⁾.

The bound forms of PSA found in serum account 80%–95% and the other minor form found as an unbound (free) state, which involves 3 isoforms: benign PSA (BPSA), proPSA and intact PSA. In addition, a number of truncated proPSA isoforms, involving (-2) proPSA, (-5) proPSA, and (-7) proPSA are present.

Main prostate cancer-specific isoform is [-2]proPSA isoform and it has been concentrated preferentially on immunohistochemical staining in prostate cancer tissue also it has been highly increased in the serum of Prostate Cancer patients⁽⁴⁾.

A test called the Prostatic Health Index (PHI) is a recent equation which joins the PSA, free PSA and [-2]proPSA as one formula which can be applied in order to assist making the correct diagnosis⁽⁵⁾.

In addition, the equation is also effective in discriminating BPH patients from PCa patients in males, especially those with prostate cancer⁽⁶⁾. The score of PHI was validated⁽⁵⁾, then replication of this validity through many multicenter follow-up clinical trials in various countries⁽⁷⁾. The majority of the researches' objectives are

to evaluate the detection significance of PHI in the PSA values between 2-10 ng/ml, as well termed as the detection “gray zone” and little researches have been reported regarding the PHI efficacy even when the patients PSA value exceeds 10 ng/ml. There is a non-negligible rate of males with PSA values higher than 10 ng/ml that possibly who non-cancerous and the rise in PSA values might be a consequence of asymptomatic prostatic inflammation or a result of prostate enlargement⁽³⁾. So we aimed in this study: To improve a method of testing by using newer PSA markers in the subjects sera for evaluate diagnostic significance of [-2]proPSA and PHI in detection of PCa in early stage.

Materials and Method

A case-control research was executed from August 2018 till February 2019. A sample of Iraqi patients >50 years old was diagnosed as Prostate Cancer or Benign Prostate Hyperplasia patient in: AL-Imamain AL-Kadhimain Medical City, Al-Shahid Ghazi Al-Hariri Specialized Surgery Hospital/Urology Consultation Unit, Al-Amal National Hospital for cancer management in Baghdad city. The study includes 84 samples consist of 3 groups: 24 prostate cancer cases, 30 benign prostatic hyperplasia cases and 30 apparently healthy subjects as control.

The current study comprised patients who undergo prostate biopsy for assumed PCa depending on physicians instructions. The patients >50 years old age with prostate cancer and benign prostatic hyperplasia were included in the study; while patients with acute bacterial prostatitis, sexually transmitted infections, patients with chronic renal failure and Patients on finasteride or dutasteride therapy for prostatic disease were excluded. Blood sample were aspirated using disposable syringes in the sitting position. Serum PSA, free PSA and [-2]proPSA estimated by using ELISA technique. PHI was calculated

by applying the equation: $(p2PSA/fPSA) \times \sqrt{PSA}$ ⁽⁵⁾.

Results

There was a significantly high difference ($P < 0.001$) among the all study groups regarding serum PSA and fPSA/PSA% levels. When PSA results were compared between each two groups, a very highly significant increase ($P1 < 0.001$); ($P3 < 0.001$) was found between Prostate Cancer group in comparison with both control group and Benign Prostatic Hyperplasia group respectively, while there was no significant difference ($P2 = 0.859$) between Benign Prostatic Hyperplasia group versus control group.

Regarding fPSA/PSA% results; comparison between each two groups; There was a very significantly high decrease ($P1 < 0.001$) ($P3 < 0.001$) between Prostate Cancer group in comparison with control group and Benign Prostatic Hyperplasia group respectively; in contrast, no significant decrease ($P2 = 0.416$) was found between Benign Prostatic Hyperplasia group against control group (Table 1).

As well as, when the comparison applied for Prostate Specific Antigen PSA derivatives P2PSA and PHI the findings were as listed in table 1: There was a very significantly high increase ($P < 0.001$) among all study groups. When [-2]proPSA and Prostate Health Index PHI results were compared between each two groups, a very highly significant increase ($P1 < 0.001$), ($P3 < 0.001$) was found between Prostate Cancer group in comparison with both control group and Benign Prostatic Hyperplasia group respectively. Also, concerning [-2]proPSA and Prostate Health Index PHI results; a very highly significant increase ($P2 = 0.005$), ($P2 < 0.001$) was found between Benign Prostatic Hyperplasia group versus control group respectively (Table 1).

Table 1: Statistical analysis of Biochemical measurements related to prostatic specific antigen (PSA)

Characteristic	Prostatic carcinoma n=24	BPH n=30	Control n=30	P	P1	P2	P3
	Mean±SEM	Mean±SEM	Mean±SEM				
PSA (ng/ml)	124.12±21.19	5.12 ±0.50	2.57±0.11	<0.001 † HS	<0.001 € HS	0.859 € NS	<0.001 € HS
fPSA/PSA%	11.00 ±1.39	26.71±2.42	24.45±1.90	<0.001 † HS	<0.001 € HS	0.416 € NS	<0.001 € HS

Cont... Table1:Statistical analysis of Biochemical measurements related to prostatic specific antigen(PSA)

P2PSA (pg/ml)	684.75±73.20	236.81±26.40	74.48 ±17.58	<0.001 † HS	<0.001 € HS	0.005 € HS	<0.001 € HS
Prostate health index (P.H.I)	801.39±54.42	440.64±26.86	164.95±17.98	<0.001 † HS	<0.001 € HS	<0.001 € HS	<0.001 € HS

n:number of cases;data were presented as either mean±standard error of mean(SEM);†:One way ANOVA;€: post hoc LSD test;HS:highly significant at P≤ 0.01;NS: not significant at P≤ 0.05; S:significant at P≤ 0.05;P1:P-value for Control vs carcinoma;P2:P-value for Control vs BPH;P3:P-value for Carcinoma vs BPH,PSA: prostate specific antigen,fPSA/PSA%:free prostate specific antigen/prostate specific antigen%;P2PSA:-2pro prostate specific antigen.

The validity indicators such as sensitivity,specificity and AUC for the present diagnostic biomarkers;serum PSA and fPSA/PSA%based on receiver operation characteristic (ROC) curve(Figure1A) were calculated as illustrated in table 2.

Regarding to PCa group versus noncancerous subjects;according toROC curve of serum PSA level,the cut-off value≥9.57ng/ml optimally identified the patients with Prostate Cancer from those who are noncancerous;at this cut-off value the sensitivity was87.5% , specificity

was 100% and the AUC was 0.983.A very highly significant increase (P<0.001) was found between Prostate Cancer versus noncancerous groups .

Regarding serum fPSA/PSA% level; the cut-off value≤11.1optimally identified the patients with Prostate Cancer from those who are noncancerous; at this cut-off value the sensitivity was 75%,specificity was 98.33% and the AUC was0.888.Very high significant decrease(P<0.001)was found between Prostate Cancer group versus noncancerous group(Table 2).

Table 2:Cut-off value, Sensitivity, Specificity and Area Under Curve of Receiver Operation Characteristic(ROC)Curve of Prostate-Specific Antigen(PSA) and its related biomarkers between Prostate Cancer versus group noncancerous group:

Characteristic	PSA(ng/ml)	fPSA/PSA%	P2(pg/ml)	PHI
Cut-off	>9.57	≤11.1	>322	>578
AUC	0.983	0.888	0.968	0.960
Sensitivity	87.5	75	100	91.67
Specificity	100	98.33	91.67	93.33
P-value	<0.001	<0.001	<0.001	<0.001

PSA:Prostate Specific Antigen,fPSA/PSA%:free Prostate Specific Antigen/Prostate Specific Antigen % ,P2PSA:-2Pro Prostate Specific Antigen PHI:Prostate Health Index.P -value:very highly significant at P≤ 0.001;significant atP≤ 0.05.

As shown in table 3; regarding BPH group versus control groupbased on ROC curveof serum PSA level(Figure1B);the cut-off value≥3.17ng/ml ideally established the patients with BPH from those who are apparently healthy men;at this cut-off value the sensitivity was77.78%,specificity was88.1% and the AUC was0.789.A very highly significant increase(P<0.001) was established between BPH category versus control

category.

Regarding,serum fPSA/PSA% level,the cut-off value≤31optimally identified the patients with BPH from those who are apparently healthy men;at this cut-off value the sensitivity was38.89%,specificity was88.1%,and the AUC was0.57.There was no significant difference(P= 0.436)between BPH group

versus control group(Table3).

Thus,in a sample of Iraqi patients;The cut-off values of PSA based on the ROC curve results in current study was ≥ 9.57 ng/ml for Prostate cancer patients,while its value range between 9.57-3.17ng/ml for BPH

patients,and < 3.17 ng/ml for apparently healthy men respectively,and the cut-off value of serum fPSA/PSA% level was $\leq 11.1\%$ for Prostate cancer patients,range between 11.1%-31% for BPH patients and $> 31\%$ for apparently healthy men respectively.

Table 3: Cut off value,Sensitivity,Specificity and Area Under Curve of Receiver Operation Characteristic(ROC)Curve of Prostate-Specific Antigen(PSA)and its related biomarkers between BPH group versus control group:

Characteristic	PSA(ng/ml)	fPSA/PSA%	P2(pg/ml)	PHI
Cut-off	> 3.17	< 31	> 89	> 209
AUC	0.789	0.57	0.85	0.796
Sensitivity	77.78	38.89	100	94.44
Specificity	88.1	88.1	64.29	64.29
P-value	0.001	0.436	< 0.001	< 0.001

PSA: Prostate Specific Antigen fPSA/PSA%: free Prostate Specific Antigen/Prostate Specific Antigen %
 P2PSA: 2-Prostate Specific Antigen PHI: Prostate Health Index P-value: very highly significant at $P \leq 0.001$; significant at $P \leq 0.05$.

The sensitivity,specificity,Area Under Curve and the cut-off thresholds of serum[-2]proPSA and PHI based on ROC curve were obtained to evaluate to what extent the level of possibility of these new chemical biomarkers is contributing and supporting strongly the accurate diagnosis side by side with other chemical biomarkers formerly present (Table2) and (Table3).

The finding of serum The[-2]proPSA level for Prostate Cancer group compared with non-cancerous groups were as following: The cut-off value ≥ 322 pg/ml ideally established the Prostate Cancer patients from those who are noncancerous;at this cut-off value the sensitivity was 100%,specificity was 91.67%and the AUC was 0.968.Regarding these findings;A very highly significant increase($P < 0.001$)was found between these two groups.

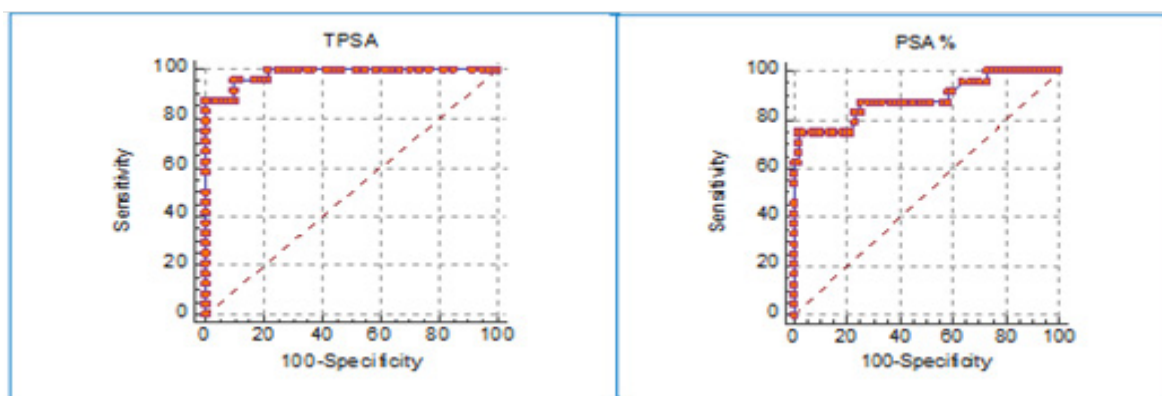


Figure 1: Receiver operation characteristic curve of PSA and fPSA/PSA% between Prostate Cancer versus noncancerous group.

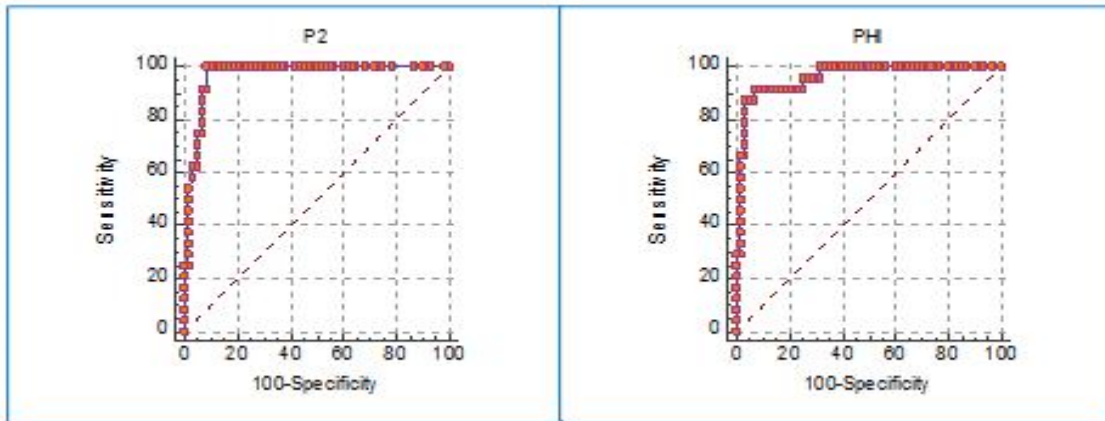
Concerning serum Prostate Health Index(PHI) results for Prostate Cancer group compared with non-cancerous group;the cut-off value ≥ 578 optimally identified the patients with Prostate Cancer from

those who were noncancerous;at this cut-off value the sensitivity was 91.67%,specificity was 93.33%and the AUC was 0.960.A very highly significant increase($P < 0.001$) was found between these two

groups(Table2),(Figure2A).

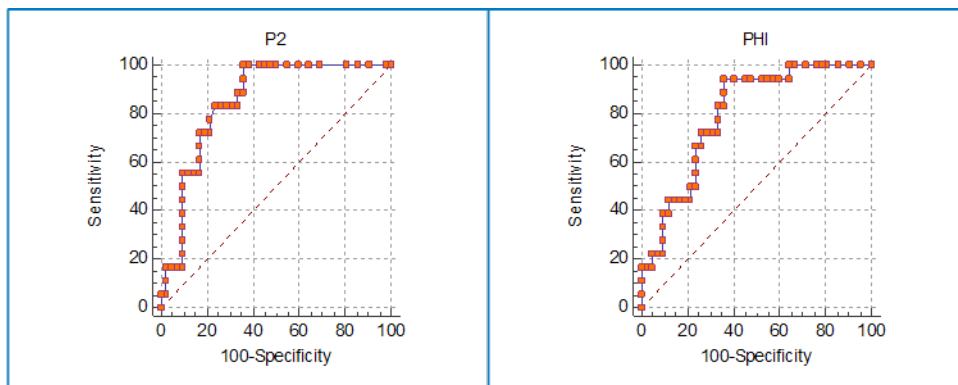
Regarding serum[-2]proPSA level for BPH group versus control group;the cut-off value ≥ 89 pg/ml ideally established the patients with BPH from those who are apparently healthy men;at this cut-off value the sensitivity was100%,specificity was64.29% and the AUC was0.85.

Figure 2:Receiver operation characteristic curve of P2PSA and PHI between Prostate Cancer group and non-cancerous group.



Concerning serum Prostate Health Index(PHI)results for BPH group against control group;the cut-off value ≥ 209 optimally identified the patients with BPH from those whom apparently healthy men;at this cut-off value the sensitivity was 94.44,specificity was 64.29%,and the AUC was0.796.A highly significant increase was found($P<0.001$) between BPH group and control group(Table3)(Figure2).

Figure 3:Receiver operation characteristic curve of P2PSA and PHI between Benign Prostatic Hyperplasia group and control group.



Thus,in a sample of Iraqi patients;this finding means that the cut-off values of(P2PSA) and Prostate Health Index(PHI)based on the ROC curve results in current study were ≥ 322 pg/ml and ≥ 578 respectively for Prostate cancer patients,while their values range between322-89pg/ml,and578-209respectively for BPH patients,and < 89 pg/ml and < 209 for apparently healthy men respectively.

Discussion

In Iraq,Iraqi Cancer Registry in 2016 exhibited that the highest incidence of cancer was among the breast cancer and the lowest was among the Prostate cancer,also the incidence rate(Per100,000Population)of Top Ten Cancer in Males in Iraq in 2016 for Prostate Cancer was 4.13⁽⁸⁾.

The current study findings may be useful for research in future, and our attempt to evaluate new Prostate Cancer diagnostic biomarkers may assist in diagnosis of Prostate Cancer in Iraq. The validity indicators of these new biomarkers have been determined all to be appropriate for that objective.

Prostate specific antigen PSA inaccuracy was established in our study because of false-positive and false-negative indications, whereas Prostate Cancer detection when PSA value 4 ng/ml accepted as a cut-off value; induced in a rate of (15 patients from 39) false positive which accounts 38.46%. It represents that from 39 patients who predictable Prostate Cancer, just 24 cases from them have been proved to be with the disease which account (61.54%). Also, only low percentage (15 patients out of 54) which accounts 27.77% of true negative rate when the value of prostate specific antigen (PSA) levels lower than 4 ng/ml showed no pathological characteristics of Prostate Cancer. A Study for Prostate Cancer (ERSPC) including 162,387 men in European Randomized reported that the PSA test resulted in 75.9% false-positive rate⁽⁹⁾. This false rate was clarified by many factors, such as prostate enlargement like BPH that can elevate PSA value, and without presence of cancer⁽¹⁰⁾ further more, high BMI lowers PSA level⁽¹¹⁾, in addition, the age of males can alter PSA values⁽¹²⁾.

However PSA is regarded as the better prostate cancer diagnostic tumor marker, it is indeed stay a long way from being optimal since there is no ideal value which confirmed Prostate Cancer diagnosis.

In addition, many studies use the fPSA/PSA percent in order to enhance specificity of prostate cancer diagnosis. The lack of absolute data which can demonstrating the ideal fPSA/PSA percent that must be used⁽¹³⁾, in present study; in a sample of Iraqi patients: The cut-off value of fPSA/PSA percent based on ROC curve results finding was $\leq 11.1\%$ for Prostate cancer patients. In 2011, SM Asafudullah et al, concluded that despite various cut-off values for fPSA/PSA percent interval from $<10\%$ to 25% that used via different researchers with difference but satisfactory specificity and sensitivity but the highest rate of prostate cancer cases (approximately 95%) was present to be combined with cut-off value less than 25% in various researches⁽¹⁴⁾, and the findings of our study were well confirmed with them.

Several novel serum biomarkers including [-2] proPSA and Prostate Health Index (PHI) have been developed and significantly increased the prediction potential of detecting Prostate Cancer⁽⁶⁾.

In this work, in order to evaluate these new biomarkers contributing in PCa diagnosis; a sample of Iraqi patients with Prostate Cancer and BPH patients according to Receiver Operation Characteristic (ROC) Curve results of serum (-2) pro Prostate-specific antigen [-2] proPSA and Prostate Health Index (PHI) levels show significant increase in PCa patients comparing with noncancerous group and in BPH group comparing with control group. The results were specific, simple and inexpensive blood tests with additional increase in PCa predictive value that could be used as part of a multivariable approach consisting of PSA and fPSA% biomarkers.

The study results were in harmony with that of Catalona et al. who concluded that results from a separate multi-site study supported the role of p2PSA and PHI as new useful predictors biomarkers of PCa in combination with PSA and fPSA% in reducing unnecessary biopsies⁽⁵⁾, also agreed with Massimo Lazzeri, et al and Heavner, Matt, et al in supporting the diagnostic significance of PHI even when PSA values exceeds 10ng/ml^(3,15) but disagreed with Mariyam Akizhanova et al. who reported that the correlation which found between PHI and the prediction of Prostate cancers poor⁽¹⁰⁾.

Conclusions

Finally, we concluded that: P2PSA and PHI levels have significantly improved validity indicators and diagnostic accuracy in diagnosis and differentiation between men with and without PCa as part of a multivariable approach to PSA and fPSA% tests.

Conflict of Interest – Nil

Source of Funding- Self

Ethical Clearance – Not required

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