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Comparison among different p2PSA derivatives on prostate cancer prediction in patients with serum prostate-specific antigen bellow 10 ng/ml

Поређење различитих п2ПСА деривата у предикцији карцинома простате код болесника са серумским нивоом простата специфичног антигена мањим од 10 нг/мл

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SUMMARY

Introduction/Objective The precursor prostate-specific antigen (proPSA) especially its isoform p2PSA is useful in the detection of prostate cancer (PCa). However, the prediction value of different p2PSA derivatives remains unclear. The aim of the study was to compare the performance of the p2PSA, percentage of p2PSA to free PSA (%p2PSA), Prostate health index (Phi), and one prostate dimension-adjusted index, p2PSA density (p2PSAD), with each other for PCa prediction in patients with serum PSA 10 ng/ml or less.

Methods This prospective study included patients who had undergone ultrasound-guided prostate biopsies and p2PSA testing. The data about patients' clinicopathological characteristics were collected and %p2PSA, p2PSAD and Phi were calculated. Different aspect of predictive performance was assessed using the area under the receiver operating characteristic curve (AUC), the specificities at set sensitivities, and clinical utility using decision curve analyses (DCA).

Results Out of 71 patients PCa was diagnosed in 23 (32.4%). Results of multivariate analysis showed that only the Phi and digital rectal examination were independent predictors of PCa. The AUC of p2PSA, %p2PSA, p2PSAD and Phi were 76.2%, 81.5%, 88.7%, 89.6%, respectively. At pre-specified sensitivity of 90% and 95%, Phi demonstrated a greater specificity than the other p2PSA derivatives. Phi and p2PSAD lead to the higher net benefit in DCA.

Conclusion Compared with other p2PSA derivatives Phi is the most useful parameter for selection of the patients that do not need to be undergone to biopsy and thereby avoiding unnecessary procedures.

Keywords: Prostate cancer; p2PSA; Prostate Health Index; early detection of cancer

САЖЕТАК

Увод/циљ Изоформе прекурсора специфичног антигена простате (ПСА) (п2ПСА) и његови деривати показали су вредне резултате у детекцији карцинома простате (КП). Међутим, предиктивна вредност различитих п2ПСА деривата остаје нејасна. Циљ ове студије је да међусобно упореди перформансе п2ПСА, процентуални однос п2ПСА и слободног ПСА (%п2ПСА), Простата Здравствени Индекс (*Phi*) и једног димензији простате прилагођени индекс, густина п2ПСА (п2ПСАД), у предвиђању КП код особа са серумским нивоом ПСА 10 нг/мл или мањим.

МетодеОва проспективна студија укључила је болеснике код којих је учињена ултразвуком вођена биопсија простате и код којих су одређиване серумске вредности п2ПСА. Прикупљани су подаци о клиничко-патолошким карактеристикама болесника и израчунате вредности %п2ПСА, п2ПСАД и *Phi*. Процењени су различити аспекти предиктивних перформанси маркера коришћењем поља испод ROC криве (*AUC*), специфичности при предефинисаним оквирима сензитивности, док је клиничка корисност процењена анализом криве одлучивања (*DCA*).

Резултати КП је утврђен код 32.4% од 71 болесника. У мултиваријантној анализи само су *Phi* и дигиторектални преглед били независни предиктори. *AUC* вредности за п2ПСА, %п2ПСА, п2ПСАД и *Phi* биле су 76,2%, 81,5%, 88,7% и 89,6%, респективно. За предефинисану сензитивност од 90% и 95%, *Phi*је показао већу специфичност у односу на друге п2ПСА деривате. *Phi*и п2ПСАД доводе до веће нето користи у *DCA*.

ЗакључакУ односу на друге п2ПСА деривате, *Phi* се показао најкориснијим у утврђивању код којих мушкараца не треба учинити биопсију, и тиме се избегавају непотребне процедуре.

Кључне речи: Карцином простате; п2ПСА; Простата Здравствени Индекс; рана детекција карцинома

INTRODUCTION

Prostate cancer (PCa) is the most common cancer among European men and the sixth primary cause of cancer-related mortality in men worldwide [1]. Prostate biopsy is the standard procedure for diagnosing PCa in men with elevated serum prostate-specific antigen (PSA) levels or abnormal findings on digital rectal examination (DRE). Testing men for PSA noticeably increases in the number of those undergoing prostate biopsy in the past decades. However, serum total PSA (tPSA) level itself, in the intermediate range, lacks the specificity, and can needlessly provoke avoidable treatment complications with prostate biopsy.

Continuous efforts are being made to discover novel PCa biomarkers or more complex prediction tools to decrease the number of unnecessary biopsies. Multiple PSA derivatives have been introduced as markers of early detection: age-specific PSA reference ranges, percentage of free PSA (%fPSA), PSA density (PSAD) [2]. Early evidence suggests that measurement of the PSA precursor isoform [−2]proPSA (p2PSA), which is predominantly expressed in malignant prostate tissue, and its derivatives (p2PSA/free PSA [%p2PSA] and prostate health index [Phi]), can offer improvement of PCa detection and management [3]. PHI is calculated by mathematical formula using total PSA, free PSA and [-2] proPSA. Large studies from the worldwide have consistently demonstrated that p2PSA derivatives both independently [4–7] and in the models expressed by nomograms [8, 9], artificial neural networks [10], or risk calculators [11] adds to specificity and ensures a greater net benefit for PCa diagnostics than total and %fPSA. Epstein criteria in predicting insignificant PCa cancer have improved prognostic performance by P2PSA derivatives in men capable for active surveillance [12]. Furthermore, p2PSA and its derivatives may correlate with pathologic cancer features after radical prostatectomy [4, 13] or discriminate whether PCa is clinically significant or indolent [5, 9, 14]. However, some studies did not demonstrate benefit for clinical decision-making [13] and these complex prediction tools are

not usually used in daily clinical practice. To overcome this issue, a few other studies have been used prostate dimension-adjusted related indices such as p2PSA density (p2PSAD), %p2PSA density (%p2PSAD) and Phi density (PHID) [14, 15]. In addition, the prediction value of different p2PSA derivatives for detecting PCa when compared to each other remains unclear.

The aim of our study was to compare the performance of the newest p2PSA-based markers including Phi, p2PSA-related indices (p2PSA, %p2PSA) and one prostate dimension-adjusted index (p2PSAD) with each other for PCa prediction in patients with serum PSA level below 10 ng/ml.

METHODS

Patient population

This prospective study involved 71 patients of Clinical Centre Kragujevac between May 2017 and December 2017, who had undergone ultrasound-guided prostate biopsies and p2PSA testing. After obtaining institutional Ethical committee approval (01/17/2608), we collected data about clinicopathological characteristics for each patient as follow: age, DRE, tPSA, %fPSA, transrectal ultrasonography (TRUS) findings, prostate volume (PV), PSAD, p2PSA, %p2PSA, p2PSAD, Phi, total number of cores taken, and Gleason score. All patients signed informed consent prior to examination. Exclusion criteria were: incomplete data, serum PSA level above 10 ng/ml, and conditions that could alter the p2PSA concentration.

DRE were done on all examined patients. DRE was classified as normal, or suspicious/positive. Ultrasound examination as guidance for biopsy was performed using Toshiba (Aplio 300) ultrasound device with 5-10-MHz probe. After obtaining a median of ten core biopsies, it was assessed by local pathologists. TRUS was used to measure the gland in three dimensions, and the prostate ellipse formula was used to calculate PV. PSAD was

calculated by dividing the serum PSA by PV. The primary outcome was the detection of PCa on biopsy.

Specimens and laboratory analysis

At presentation, blood samples were collected before DRE, TRUS or biopsy using standard techniques. Serum samples were obtained from blood and frozen at −70°C within 8 hours for future analysis. All serum samples were thawed at the same time and tested for tPSA, free PSA and [–2]proPSA using UniCel DxI 600 Access Immunoassay System, Beckman Coulter, USA. %p2PSA was calculated using following formula: %p2PSA = p2PSA/(fPSAx1000) x 100; p2PSA density was calculated as ratio of p2PSA level and PV; Phi was calculated using equation (p2PSA/fPSA)*√PSA.

Statistical Analysis

Descriptive statistics was used to characterize patients based on biopsy outcome. In order to identify and quantify potential and independent predictors of PCa, univariate and multivariate logistic regression analysis was performed. The results of regressions were presented in odds ratios (ORs) with 95% confidential interval (CI).

Comparison of different p2PSA-based markers

Cut-off value, area under the receiver operating characteristic curve (AUC) analysis, sensitivity, specificity, positive (PPV), negative predictive value (NPV), accuracy, Hosmer–Lemeshow statistic, and the Brier score were calculated for each marker . The comparisons of AUC were performed using the method proposed by DeLong et al. [16]. We also compared the specificities of PHI at 90% and 95% sensitivities [17]. By using decision curve analyses (DCA), clinical usefulness was assessed [18]. Net benefit graph was calculated and made in

Excel using the recommended formula [18]. All other calculations were performed using SPSS version 23.0 (SPSS Inc., Chicago, IL). Statistical significance was set at $p < 0.05$.

RESULTS

Patients' characteristics

A total of 71 patients were analyzed. The study population included 61 (85.9%) initial biopsies, and 10 (14.1%) repeated biopsies. Prostate cancer was detected in 23 (32.4%) patients. Clinicopathological characteristics of patients with/without PCa included in the study are shown in the Table 1. There were no significant differences in TRUS findings between the positive and the negative biopsy groups. However, age, abnormal DRE, tPSA levels, PSAD, p2PSA, %P2PSA, p2PSAD and Phi were significantly higher in patients with PCa, while PV and %fPSA were significantly higher in the group of patients without PCa.

The logistic regression analysis

Univariate analysis revealed that 6 reference standard tests/factors displayed significant correlation with PCa (Table 2). Also, at univariate analyses, p2PSA, %p2PSA, p2PSAD and Phi were significant predictors of PCa. During multivariable analysis, DRE and Phi have independent prognostic value of PCa (Table 2).

Performance measure of different p2PSA-based markers

Performance measures of different p2PSA-based markers are summarized in Table 3. AUCs of p2PSA, %p2PSA, p2PSAD and Phi were 76.2%, 81.5%, 88.7%, 89.6%, respectively (Table 3and Figure 1). P2PSAD and Phi significantly outperformed p2PSA and %p2PSA as judged by AUC. In pairwise comparison of ROC curves differences between areas Phi and p2PSA and %p2PSA (13.4% and 8.1%, respectively) were significant (p=0.003

and 0.025, respectively). The difference between the AUC of Phi and p2PSAD was not statisticaly significant (p=0.081). The sensitivity of the test, PPV, NPV was the most optimal using Phi, while the predictive accuracy was improved for about 10% (Table 3). All the Hosmer and Lemeshow goodness of fit test statistic did not reach statistical significance, thereby demonstrating a good fit. The Brier's scores ranged from a low of 0.112 for the Phi, the best predictive performance, to a high of 0.179 for the p2PSA.

The specificity of serum markers at set sensitivities of 90% and 95% are shown in Table 4. At pre-specified sensitivity of 90% and 95%, Phi demonstrated a greater specificity than the other p2PSA derivatives. For instance, if sensitivity is set at 95%, the specificity of Phi was 66.7% compared to 35.4% for p2PSAD, 31.2 for %p2PSA and 25% for p2PSA. Furthermore, for example, using a Phi cut-off of 31 (95% sensitivity cut-off), 5% of PCa would have been missed and 47% of men with benign disease would not have been undergone to a biopsy. For comparison, 19-26% would have been spared using other markers. Thus, an additional 21-28% of patients could avoid biopsy using Phi compared to other markers.

Clinical usefulness

Figure 2 shows the results of the DCA. The main assumption of biopsy is that if all patients are undergone to biopsy it saves them from unfavourable outcome. DCA suggested that all p2PSA derivatives are likely to be useful for patients whose decision to pursue further intervention is based on a predicted risk above 6–25%. However, Phi (orange line) and p2PSAD (purpure line) lead to the higher net benefit compared with p2PSA (blue line) and %p2PSA (green line) in various threshold probabilities above approximately 6 and 10%. For example, if a probability threshold is set at 15%, the use of the Phi and p2PSAD decreases the number of unnecessary biopsies by 26 and 9 per 100 patients, respectively, without

missing any of PCa. However, their curves are largely overlapping in different threshold probabilities.

DISCUSSION

In the present study, we compared the performance of the newest p2PSA-based markers (p2PSA, %p2PSA, p2PSAD and Phi) to each other for PCa prediction. Our study findings confirmed that Phi is the strongest discriminative parameter between patients with and without PCa at initial or repeated biopsy in patients with the PSA value bellow 10 ng/ml. Almost all statistical metrics have demonstrated improved diagnostic performance when Phi was compared with other markers.These findings were further confirmed when we compared the specificities at pre-specified sensitivities and an additional 21-28% of biopsies could be avoided. However, the results of the DCA analysis did not confirm the advantage of the Phi compared with the p2PSAD.

Previous studies have determined factors related with higher risk of PCa detection in patients with PSA bellow 10 ng/ml. They included age [6, 8, 9, 13], race [4], DRE [8, 9, 11], tPSA [9, 11, 15], %fPSA [4, 9, 14, 15, 19]), PV[4, 5, 8, 9, 11, 14], PSAD [14, 15], biopsy history [4, 5, 8, 11], family history [4], p2PSA [4, 15], %P2PSA [9, 15], p2PSAD [15], PHI [4, 5, 8, 9, 15] and PHID [14]. A broad variety of different combinations of predictive factors have been identified. Like in previous studies, several of those predicting factors have shown statistical significance in the univariate or multivariate analysis in our study. Nevertheless, some of these parameters did not have value as independent factors. According to the analysis, we found that DRE status and Phi were strong independent predictors of PCa detection. We have included the patients with positive DRE as has been done in other studies [8, 9]. Our prospective study reinforces the evidence that serum isoform p2PSA and its

derivatives, particularly PHI, could be useful for discriminating between patients with or without PCa [5, 6, 11, 14].

Unlike other p2PSA derivatives, Phi is considered a three-component marker. The Phi test is better tool for the identification of clinically significant PCa than its individual components [5]. A systematic review by Pecoraro and colleagues that included 17 studies with 6912 patients on Phi concluded that Phi increases the specificity for PCa detection [20]. For p2PSA the authors reported AUC ranging from 0.51 [19] to 0.62 [21], highlighting a better performance for %p2PSA (AUC from 0.63 to 0.78) [4, 10] and Phi (AUC from 0.67 to 0.78) [19, 22]. For these biomarkers we have found a significantly high accuracy for detecting PCa (AUC 76.2%, 81.5% and 89.7%, respectively) and they are like to be more useful in PCa diagnosis.

For individual risk assessment, the probability of PCa varied considerably depending on Phi values. However, usage of Phi thresholds significantly varied (21.3–29.2) among studies [4–6, 13] and many studies did not report used the cut-offs, making difficult the generalization of the results. The present study has a higher cut-off value for Phi of 31.6 (the 95% sensitivity cutoff). We estimated that 47% of men with benign disease could have been spared a biopsy and 5% of PCa would have been missed. With similar sensitivity selection others found that avoiding unnecessary biopsy was significantly lower (11–30%) with the same percentage of missed cancer [4–6, 13, 21].

There are researches that have compared p2PSA and its derivatives with other new biomarkers. Directly compared Phi outperformed prostate cancer antigen 3 performances when added to the Epstein criteria in order to predict the presence of pathologically insignificant PCa [12]. Additionally, in patients who had been undergone to radical prostatectomy, p2PSA-based parameters turned out to be the most accurate predictors for final pathology results [13, 23]. Baseline and longitudinal p2PSA and Phi determinations are

reported to be significantly related to unfavorable biopsy results in patients that are monitored with active surveillance [9]. Furthermore, if Phi is added to the multivariable risk calculator that increases the predictive accuracy for overall PCa, but differences between risk calculators that include PHI were small [11]. These data suggest that p2PSA-based markers are not only important for PCa diagnosis but also as predictive factors of aggressiveness and possibly of prognosis.

Several studies have demonstrated an inverse relationship between PV and the incidence of PCa. According to the findings of some authors, PV is the most important factor in the interpretation of biomarkers used to detect PCa due to the fact that PV has an influence in PSA values. Accordingly, bigger AUCs were found for Phi, %p2PSA, %fPSA and tPSA in patients with small prostate volume (≤35 ml) then in patients that had large prostate volume (>50 ml) [24]. It is expected that the use of PV in the structure of p2PSAD shows better diagnostic performance compared to one-component biomarker (p2PSA) as demonstrated in our study. However, a comparison with a three-component biomarker showed slightly lower performance while clinical utility cannot be reliably determined due to overlapping the DCA curve. Unlike other studies that show the same specificity at fixed sensitivity of 95% [25], our results suggest less specificity of p2PSAD compared to the specificity of the Phi (35.4% *vs*. 66.7%).

The study's limitation lies in its relatively small patient cohort. Phi testing was recently set up and that is reason for limited sample size. Furthermore, this analysis is restricted by the bias introduced by false negative biopsies. Latest studies have suggested that systematic biopsies are inferior to extended biopsy schemes and magnetic resonance imaging (MRI)-targeted biopsies for the detection of PCa [26]. However, despite the encouraging results of new markers, the main urologist associations continue to recommend the consideration of DRE status, prostate size, ethnicity, age, comorbidity, family history,

previous biopsy results, as well as tPSA values before performing a biopsy, whereas other serum biomarkers require being subject of further investigation to determine their clinical usefulness [27]. However, from a pragmatic viewpoint, all explored p2PSA derivatives are potentially useful in a biopsy decision situation. Cost-effectiveness of PCa detection is improved by using p2PSA derivatives compared to second-line costs caused if PSA-only screening approach is used [28]. Furthermore, in the current MRI era combining p2PSA derivatives and MRI led to even further gains in the detection of PCa that are clinically significant [29]. To our knowledge, this is the first time that comparison among almost all different p2PSA derivatives has been presented. Accordingly, a further study with a large population is needed to evaluate our conclusions. Despite this, the clinical utility of p2PSA derivatives is apparent.

CONCLUSION

This is the first study aimed to determine the diagnostic performance of different p2PSA derivatives in predicting PCa in suspected men. Compared with other markers Phi was the most useful in selection of patients that do not need to be undergo biopsy, thereby avoiding unnecessary procedures.

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Table 1. Baseline patients' clinicopathological characteristics

Characteristics	All (n = 71)	BPH (n = 48)	PCa (n = 23)	P value	LG PCa (n = 13)	HG PCa (n = 10)
Age mean ± SD, years	64.3 ± 5.4	63.4 ± 5.3	66.2 ± 5.3	0.041	64.1 ± 5.7	63.7 ± 5
DRE abnormal n (%)	20 (28.2)	5 (10.4)	15 (65.2)	0.000	8 (61.5)	7 (70)
Total PSA median (IQR) ng/ml	5 (3.7)	4.4 (2.8)	7.1 (3)	0.012	4.8 (3.6)	7.4 (2.5)
%fPSA mean ± SD	19.2 ± 7.6	20.9 ± 7.8	15.7 ± 5.8	0.007	17.1 ± 9.5	12.4 ± 6.4
TRUS findings n (%)	33 (46.5)	19 (39.6)	14 (60.9)	0.128	6 (46.2)	8 (80)
Prostate volume median (IQR), ml	50 (24)	55 (25.2)	45 (19)	0.004	52 (23.2)	39.5 (13.7)
PSAD median (IQR), ng/ml/ml	9.4 (6.5)	8 (4.1)	14.6 (8.4)	<0.001	8.5 (5.7)	16 (5.6)
p2PSA median (IQR), pg/ml	14.3 (11.7)	12.5 (9)	19.6 (13.5)	<0.001	13.7 (10.9)	22.6 (16.2)
%p2PSA median (IQR)	14.6 (7)	13.5 (5.5)	23.8 (13.7)	<0.001	16.9 (16.8)	25.1 (8.2)
p2PSA density median (IQR) pg/ml/ml	0.26 (0.22)	0.23 (0.13)	0.50 (0.37)	<0.001	0.50 (0.46)	0.49 (0.29)
Phi median (IQR)	37.1 (24.9)	29.1 (13.2)	54.2 (31.2)	<0.001	49 (26.4)	65.7 (19.8)
Number of biopsy cores median (IQR)	10 (0)	10 (0)	10 (0)	0.006	10 (1)	10 (0.5)

BPH – benign prostatic hyperplasia; DRE – digital rectal examination; HG – high grade Gleason score ≥ 7; IQR – interquartile range; LG – low grade Gleason score ≤ 6; PCa – prostate cancer; Phi – prostate health index; PSA – prostate-specific antigen; PSAD – prostate-specific antigen density; p2PSA – precursor PSA isoform; SD – standard deviation; TRUS – transrectal ultrasound; %fPSA – percentage of free PSA; %p2PSA – percentage of p2PSA to free PSA.

Table 2. The logistic regression analysis of predictors for prostate cancer

Variables	Univariate analysis OR (95% CI)	P value	Multivariable analysis OR (95% CI)	P value
Age	1.105 (1.001–1.220)	0.048		
DRE	16.125 (4.562–56.990)	< 0.001	9.432 (1.728–51.492)	0.010
tPSA	1.409 (1.084–1.832)	0.010		
%fPSA	0.895 (0.823–0.974)	0.011		
Prostate volume	0.963 (0.934–0.994)	0.018		
PSAD	1.241 (1.106–1.393)	< 0.001		
p2PSA	1.132 (1.052–1.218)	0.001		
%p2PSA	1.002 (1.001–1.004)	< 0.001		
p2PSAD	1.143 (1.068–1.224)	< 0.001		
Phi	1.130 (1.068–1.195)	< 0.001	1.084 (1.010–1.163)	0.024

DRE – digital rectal examination; CI – confidential interval; OR – odds ratio; Phi – prostate health index; PSAD – prostate-specific antigen density; p2PSA – precursor PSA isoform; p2PSAD – p2PSA density ;tPSA – total PSA; %fPSA – percentage of free PSA; %p2PSA – percentage of p2PSA to free PSA.

Table 3. Predictive performance of different p2PSA derivatives

Efficacy measure	p2PSA derivatives			
	p2PSA	%p2PSA	p2PSAD	Phi
Cut-off	> 12.74	> 16.9	> 0.29	> 43.7
AUC (95% CI)	76.2 (64.6–87.8)	81.5 (70.2–92.8)	88.7 (79.6–97.8)	89.6 (81.7–97.4)
Sensitivity (95% CI)	43.5 (23.2–65.5)	52.2 (30.6–73.2)	56.5 (34.5–76.8)	69.6 (47.1–86.8)
Specificity (95% CI)	91.7 (80–97.7)	93.7 (82.8–98.7)	93.7 (82.8–98.7)	93.7 (82.8–98.7)
PPV (95% CI)	71.4 (41.9–91.6)	80 (51.9–95.7)	81.2 (54.4–95.9)	84.2 (60.4–96.6)
NPV (95% CI)	77.2 (64.2–87.3)	80.4 (67.6–89.8)	81.8 (69.1–90.9)	86.5 (74.2–84.4)
Accuracy (95% CI)	76.1 (64.5–85.4)	80.3 (69.1–88.8)	81.7 (70.7–89.9)	85.9 (75.6–93)
HL test, χ^2, P value	7.313, 0.503	11.945, 0.154	10.127, 0.256	6.503, 0.591
Brier score	0.179	0.143	0.119	0.112

AUC – area under the receiver operating characteristic curve; CI – confidential interval; HL – Hosmer-Lemeshow; NPV – negative predictive value; Phi – prostate health index; PPV – positive predictive value; p2PSA – precursor PSA isoform; p2PSAD – p2PSA density; χ^2 – Chi square; %p2PSA – percentage of p2PSA to free PSA.

Table 4. The specificity for p2PSA and its derivatives at prespecified sensitivity of 90%, and 95%.

	p2PSA				%p2PSA				p2PSAD				Phi			
Sensitivity (%)	Specificity (95% CI)[a]	cut off	Biopsy spred (%)	Missed (%)	Specificity (95% CI)[a]	cut off	Biopsy spred (%)	Missed (%)	Specificity (95% CI)[a]	cut off	Biopsy spred (%)	Missed (%)	Specificity (95% CI)[a]	cut off	Biopsy spred (%)	Missed (%)
90	52.1 (18.7–72.9)	> 12.7	38	10	35.4 (16.7–58.3)	>12.7	27	10	47.9 (22.9–93.7)	> 0.22	37	10	66.7 (22.9–81.2)	> 32	48	10
95	25 (8.3–54.2)	> 8.7	19	5	31.2 (14.4–47.9)	>12.5	23	5	35.4 (16.7–87.5)	> 0.16	26	5	66.7 (25–84.4)	> 31.6	47	5

Phi – prostate health index; p2PSA – precursor PSA isoform; p2PSAD – p2PSA density; %p2PSA – percentage of p2PSA to free PSA.

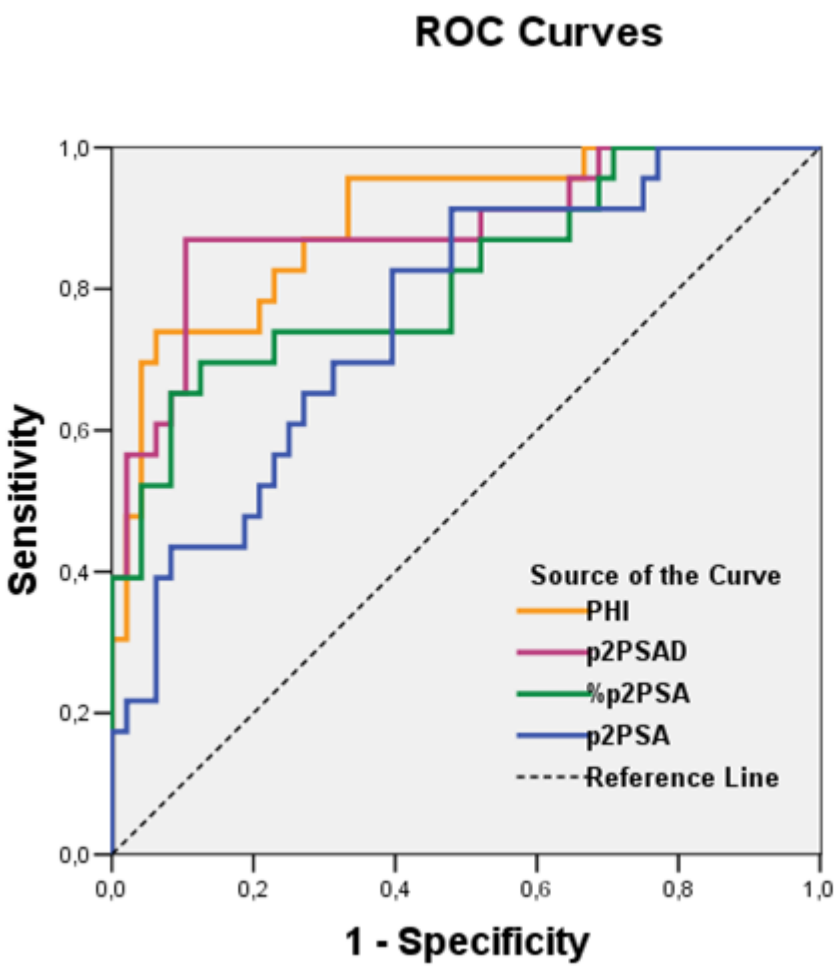

Figure 1. ROC curves analyses
Phi – prostate health index; p2PSA – precursor PSA isoform; p2PSAD – p2PSA density; %P2PSA – percentage of p2PSA to free PSA.

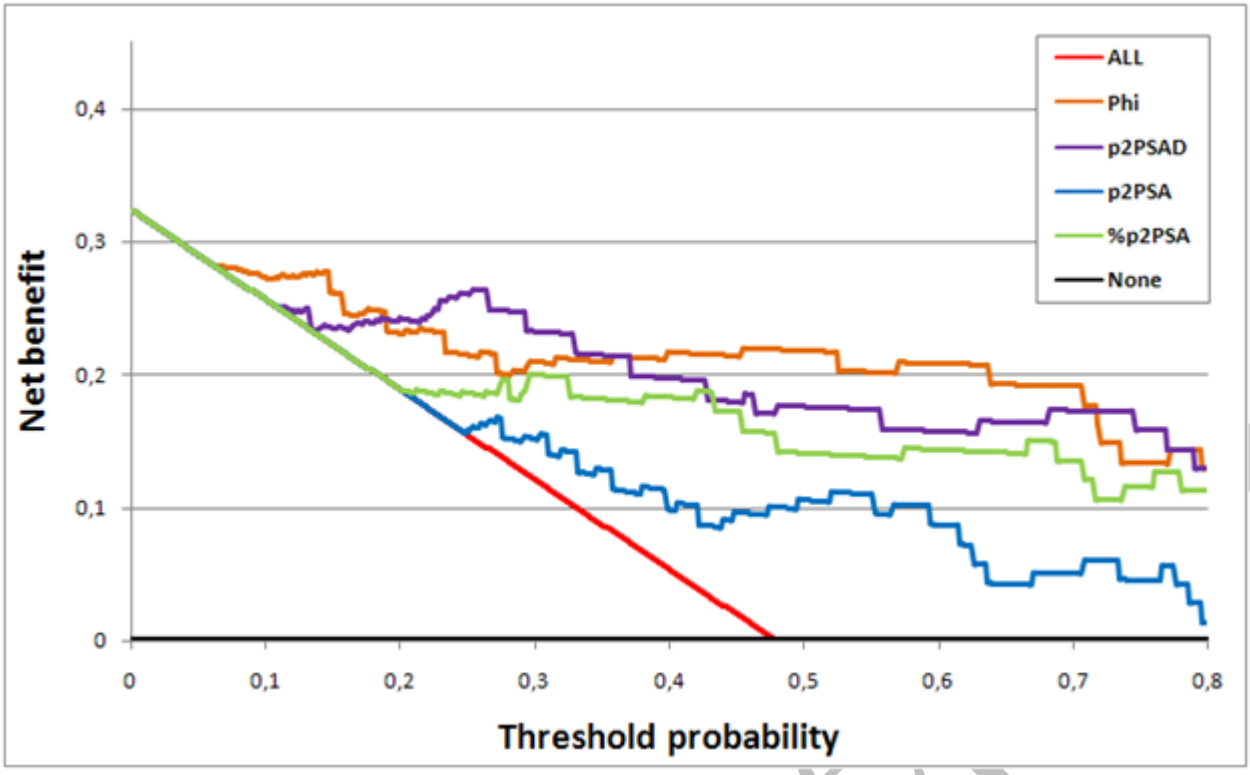

Figure 2. Decision curve analyses
Decision curve analysis of the effect of p2PSA and its derivatives on the detection of prostate cancer. Phi – prostate health index; p2PSA – precursor PSA isoform; p2PSAD – p2PSA density; %p2PSA – percentage of p2PSA to free PSA.

