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Does [-2]Pro-Prostate Specific Antigen Meet the Criteria to Justify lts lnclusion in the Clinical Decision-Making Process?

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Abstract

lntroduction: To assess whether [-2]pro-prostate-specific antigen (p2PSA) meets the criteria to justify its inclusion in a predictive model of prostate cancer (PCa) diagnosis and in the clinical decision-making process. ***Materials and Methods:*** A total 172 men with total prostate-specific antigen of 2-10 ng/ml underwent measurement of free PSA and p2PSA before prostate biopsy in an observational and prospective study. From these measurements, the Prostate Health lndex (PHI) was calculated. Clinical and analytical predictive models were created incorporating PHI. ***Results:*** Of 172 men, 72 (42%) were diagnosed with PCa, 33 (46%) of whom were found to be with high-grade disease. PHI score was the most predictive of biopsy outcomes in terms of discriminative ability (area under the curve = 0.79), with an added gain in predictive accuracy of 17%. AII the models that incorporated PHI worked better in terms of calibration close to 45º on the slope. In the decision curve analysis, a threshold probability of 40% we could prevent 82 biopsies, missing only 16 tumors and 5 high-grade tumors. ***Conclusions:*** PHI score is a more discriminant biomarker, has superior calibration and superior net benefit, and provides a higher rate of avoided biopsies; thus, it can be useful for aiding in making a more informed decision for each patient.

Keywords

Prostatic neoplasms; Prostate-specific antigen; [-2]pro-prostate specific antigen; Prostate Health lndex; Clinical decision-making.

Introduction

The use of serum total prostate-specific antigen (tPSA) for prostate cancer (PCa) screening has been the subject of extensive debate; on the one hand, the low specificity leads to a great number of unnecessary biopsies and, on the other hand, the best cut-off leads to distinguishing between cancer and no cancer and to this end we know that PCa and high-grade PCa can be diagnosed in the setting of PSA lower than 4 ng/mL in all races. Studies reporting significant morbidity related to tPSA screening, together with an increase in the incidence of PCa diagnosis and an increase in the treatment of insignificant cancers, have been published. Furthermore, literature offers contradictory results in terms of mortality; the results of the extended follow-up of the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial over a median of 15 years continues to indicate no reduction in PCa mortality in the screening arm, and the results of the European Randomized Study of Screening for PCa confirm a substantial reduction in PCa mortality attributable to tPSA testing, with a substantially increased absolute effect at 13 years [1-4].

A novel biomarker, [-2]pro-prostate specific antigen (p2PSA), a serum isoform of tPSA, has been shown to be preferentially expressed in malignant tissue and to correspond to aggressiveness. Several studies have reported the potential benefit of serum p2PSA measurement in men investigated far PCa [5-8]. Improvements in the prediction of PCa in the prostate biopsy related to p2PSA testing have been widely reported, and more recently, some studies describe the clinical utility of p2PSA arising from nomograms and decision-curve analyses [9, 10].

The Prostate Health Index (PHI) is a formula that combines all 3 forms (tPSA, free PSA [fFSA] and p2PSA) into a single score that can be used in clinical decision-making processes [11]. PHI is calculated using the following formula: (p2PSA/fFSA) x $\sqrt{}$tPSA. Intuitively, this formula makes sense in that men with a higher tPSA and p2PSA, and with a lower

fPSA, are more likely to have clinically significant PCa.

Not many validations of PHI have been published [9, 10]; thus, our purpose is to investigate whether p2PSA meets criteria to justify its inclusion in a predictive model of PCa diagnosis and in the clinical decision-making process.

Materials and Methods

Study Design

This study was an observational, prospective cohort study, performed between January 2015 and December 2016, of patients at a University Hospital in Madrid, Spain. The study was designed to test the clinical utility of p2PSA and its derivatives, percentage of p2PSA (%p2PSA) and PHI, in the real setting of our patients. PHI was calculated using the following formula ([p2PSA/fPSA] x √tPSA), developed at Beckman Coulter. In addition, the percentage of fPSA (%fPSA) was calculated as ([fPSA/tPSA] x 100) and %p2PSA as ([p2PSA pg/mL/fPSA ng/mL] x 100).

Study Population

The present study cohort consisted of 172 men older than 45 years with tPSA of 2-10 ng/mL with or without a suspicious digital rectal examination (DRE) who underwent PH1 testing at our institution as part of a diagnostic evaluation for PCa in the setting of a first or successive biopsy. Ali the patients provided consent prior to blood draw and the study was approved by the Ethics Committee. Exclusion criteria were the following: patients with acute prostatitis, patients with previous endoscopic manipulation of the lower urinary tract 3 months before biopsy, or patients being treated with dutasteride or finasteride for the last 6 months.

Methods

Prior to the prostate biopsy, blood was drawn to measure pre- biopsy tPSA, fPSA, and p2PSA levels. The samples were centrifuged within 2 h, according to the recommendations

of Semjonow et al. [12], and the sera were stored in aliquots at -80 ºC until the analysis. The sera were analyzed using the Access Hybritech p2PSA and PHI Inmunoassay System, an automated random-access analyzer that performs immunoassays (Beckman Coulter). The authors were blinded to the identity of each serum sample.

Patients then underwent transrectal ultrasound-guided prostate biopsies, and at least 12 cores were taken with a standard template (apex, mid and base); extra sampling of echogenic lesions were performed if identified. Prostate biopsy specimens were analyzed histologically and graded according to the 2005 International Society of Urological Pathology Consensus Conference 2005 [13]. Low-grade PCa was defined as Gleason 6 and high-grade PCa as Gleason 7 and higher. Demographic characteristics and the medica! history of each patient were recorded in regard to age, DRE, previous biopsy and prostate volume. Four models including biomarkers were defined (Model 1: tPSA + fPSA + %fPSA; Model 2: tPSA + fPSA + %fPSA + p2PSA; Model 3: tPSA + fPSA + %fPSA + %p2PSA; and Model 4: tPSA + fPSA + %fPSA + PHI), and 2 additional models including laboratory and clinical items were defined: the PSA model (age, DRE, prostate volume and tPSA) and the PHI model (age, DRE, prostate volume and PHI).

Study End Points

The primary end point was to evaluate whether p2PSA and its derivatives met criteria to justify its inclusion in a predictive model of PCa diagnosis and in the clinical decision-making process. The secondary end point was to determine the relationship between p2PSA and its derivatives and the pathologic characteristics at biopsy.

Statistical Analysis

The Kolmogorow-Smirnov test was used to assess the normal distribution of variables. Patients were stratified according to the presence or absence of PCa at biopsy. The Pearson *x2*- test was used for comparison of categorical variables and the unpaired student *t* test and

Mann-Whitney U test were used, respectively, for comparison of normally and not normally distributed continuous variables.

Reliability diagnosis indexes-sensitivity, specificity, positive predictive value, negative predictive value (NPV), positive likelihood ratio (PLH) and negative likelihood ratio (NLH) - were calculated at several biomarker cut-off points. Predictive accuracies, discrimination of variables, combination of variables, and models to predict PCa were assessed by quantifying the area under the receiver operating characteristic curve (AUC); curves were com- pared with the DeLong test [14-15]. The internal validation was assessed by calibration, using the Hosmer-Lemeshow goodness- of-fit test, and calibration graphics was obtained. A scatter plot was used to assess the relationship between the predicted probabilities of the PHI model and the PSA model and to assess the impact of the PHI model compared with the PSA model.

Multivariable logistic regression models were also performed to assess the prediction of PCa at biopsy. ORs with 95% Cis were also calculated.

Finally, we used decision curve analysis (DCA) to determine whether the novel biomarker (p2PSA and PHI) increases the net benefit over a realistic range of threshold probabilities compared with the models without the novel biomarker. As described by Vickers and Elkin [16], if the decision curves for the alternative models cross at any point within the plausible range of threshold probabilities, then the marker is not useful for decision making. If the decision curve of the model with the new marker dominates that of the model without being over the plausible range, then the marker can inform clinical practice. The net benefit and the number of interventions prevented were calculated [17].

Results

At the end of the study, 72 (42%) of the 172 men had been diagnosed with PCa, of whom 33 (46%) were diagnosed with high-grade disease. Table 1 shows the clinical characteristics

of the study cohort. Analysis of the avail- able biomarkers showed that PHI score was the most predictive of biopsy outcomes (cancer vs. no cancer) in terms of discriminative ability (AUC = 0.79), as described in Table 2. In the complex sample univariate logistic regression models, %fPSA *(p* = 0.04), p2PSA *(p* = 0.001), %p2PSA *(p* = 0.0009) and PHI *(p* = 0.0008) were significantly associated with the presence of cancer at biopsy; in the multivariate analysis, PHI added to the base model a gain in predictive accuracy of 17% (Table 3). Table 4 shows sensitivity, specificity, positive predictive value, NPV, PLH and NLH at 3 levels of predictive variables: best combination (S4a), high sensitivity (S4b) and high specificity (S4c). PHI shows the best balance between sensitivity and specificity (77 and 77%, respectively) and in the best combination, PHI also has the best NPV; thus, a positive result in this setting increases the chance of PHI being a true positive. At the best balance of sensitivity and specificity (Table 5), a PHI :2:59.87 can prevent 77 biopsies, missing 16 cancers and only 7 Gleason biopsies ≥7. Calibration of the tPSA + fFSA + %fFSA model, the tPSA + fFSA + %fFSA + PHI model, and calibration of the PSA model and PHI model are shown in Figure la-d respectively. None of the diagonals of the calibration curves is perfect, but calibration curves that include PHI in the models appear to work better.

Logistic regression coefficients were used to develop a nomogram based on the independent predictors of PCa at biopsy: age, prostate volume, DRE, and PHI. Figure 2 PSA model (S1 [b]). There is an appreciable scatter from the 45º line, indicating that the models with PHI are potentially useful for patient counseling, because its risk probabilities can be seen to vary markedly from those of the other models.

Finally, we calculated the DCA far the various models that are plotted in Figure 4 to estimate the results in a clinical context. The net benefit of Model 4 (tPSA + fPSA + %fPSA + PHI) is clearly greater than that of other models compared with "treating all" far any probability threshold starting from 20%. The net benefit is obvious at a 45% threshold

probability. Table 6 shows the number of biopsies prevented, the number of missed cancers and the number of Gleason ≥7 using a model that includes PHI (Model 4). At a threshold probability of 40% we could prevent 82 biopsies, missing only 16 tumors and 5 high-grade tumors (Table 6).

Discussion

Although tPSA, fPSA, and %fPSA have been associated with the diagnosis of both PCa and more biologically aggressive disease at biopsy, more accurate biomarkers are needed to reduce the number of unnecessary biopsies and unnecessary treatments. The PCa intervention versus observation trial indicated the need for better PCa screening methods and understanding of the disease, and provided evidence far watchful waiting as an appropriate farm of management for some, and perhaps many, patients [18].

In the present cohort, PHI was significantly more accu- rate than tPSA, fPSA, and %fPSA in determining the presence of PCa at initial or repeat extended biopsy; these results are in concordance with several single and multi-institutional studies [7, 9, 19, 20]. First, PHI achieves better balance between sensitivity and specificity and better indexes of PLH and NLH; in our study, for example, a man with a PHI score >59 has a probability of PCa >70% and a 3.8-fold increase in his relative risk for a positive biopsy; something that has been previously reported [11]. Risk stratification using this strategy, however, is a crude method to inform a biopsy decision. PHI also discriminates better because the AUC is higher and the addition of PHI to a logistic regression model increases the prediction of PCa in terms of AUC and OR, as previously reported [7]. If we are provided with 2 models that discriminate in a similar way, we should choose the one that has the best relationship be- tween predicted and actual outcomes, resulting in the close slope of 45º in the calibration plot. In this particular case, PHI calibrates better in the internal validation than in other models published [9]. As other authors have done, we incorporated PHI into a clinical model with age, DRE, and

prostate volume and created a well-calibrated nomogram, which were useful to evaluate the effectiveness of PHI [21]. Although discrimination and calibration are essential aspects of a prediction model, they do not evaluate clinical usefulness, such as the ability to make better decisions with a model that incorporates a new variable than without a model. DCA is a method for assessing the benefits of a model through a range of patient preferences in accepting the risk of overtreatment or overdiagnosis and undertreatment or underdiagnosis to facilitate decision making [16, 17]. The hypothesis in our study was that we could make better decision for prostate biopsy and prostate diagnosis if we integrated PHI with standard bio- markers (tPA, fPSA, and %fPSA). It is necessary to define a threshold cut-off that balances the risks and benefits. In this study, we applied the DCA to evaluate the cost and benefit of various models with or without PHI. For the midrange threshold probabilities between 20 and 45%, the model that incorporates PHI is superior to other models with the best benefit in applying the model with PHI between 30 and 45% threshold probabilities. In this setting, the net benefit for the marker is higher than that for performing universal biopsies. The use of PHI could not only prevent unnecessary biopsies but also minimize the risk of missing significant or high-grade cancers.

PHI score is a more discriminant biomarker, has superior calibration, has a superior net benefit, and provides a higher rate of prevented biopsies; therefore, it can be useful for making a more informed decision for each patient in a representative western European community.

The main focus areas that we should take into account are the cost-benefit analysis and the availability of all these new biomarkers. tPSA is not expensive and it is available in all public healthcare centers, and covered by all private insurance companies; in the same setting, we can consider some other simple biomarkers such as the neutrophil to lymphocyte ratio, which can predict PCa [22]. At the other end of the scale is the prostate MRI; it improves

diagnostic performance and can be cost effective, since it results in fewer unnecessary biopsies and is generally accepted as the most accurate and promising imaging modality for assessing the local staging of PCa, but nevertheless, it is not widely available and the cost is not always covered in both cases, public and private health [23, 24].

We acknowledge several limitations to this study. The sample size is relatively small because support for the study was obtained from a research grant. As such, the observed ORs included some broad Cis. Nonetheless, statistical significance was consistently achieved. Because recruitment was based on patients' consent to participate, it is impossible to exclude a selection bias. This study is focused on transrectal ultrasound biopsy, which is known to carry an inherent false-negative rate [25]. The study population included only those men who underwent biopsy based on clinical evaluation of standard variables (high tPSA and DRE). And finally, our cohort of patients is not yet externally validated.

Disclosure Statement

We declare that we do not have any financial or commercial interests that represent a conflict of interest in connection with the work submitted.

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Table 1. Study cohort characteristics.

	Ali, *n* = 172	**No Pea, *n* = 100 (58%)**	**Pea, *n* = 72 (42%)**	***p* value**
Age, years	66.7±7.0	65±6.8	68±6.6	0.001*
DRE				0.001†
Normal	118 (69)	79 (79)	39 (54)	
Abnormal	54 (31)	21 (21)	33 (46)	
Previous biopsy				0.9†
No	151 (88)	88 (88)	63 (87.5)	
Yes	21 (12)	12 (12)	9 (12.5)	
Prostate volume, mL	42.5±20.3	45.7±23.3	38.1±14.3	0.009**
Gleason score				
≤6	N/A	N/A	39 (54)	
7	N/A	N/A	19 (26)	
≥8	N/A	N/A	14 (20)	
tPSA, ng/mL	5.4 (4.2-7.0)	5.3 (4.0-6.8)	5.4 (4.5-7.2)	0.20**
fPSA, ng/mL	0.62 (0.43-0.89)	0.63 (0.4-0.94)	0.59 (0.44-0.59)	0.81**
%fPSA	0.12 (0.08-0.16)	0.13 (0.09-0.18)	0.11 (0.07-0.13)	0.0008**
p2PSA, pg/mL	14.5 (10.0-23.9)	13.3 (9.1-21.2)	18.8 (13.0-30.0)	0.0007**
%p2PSA	0.26 (0.18-0.40)	0.21 (0.16-0.33)	0.33 (0.23-0.45)	0.0009**
PHI	56 (36.2-85.3)	41.3 (32.9-57.2)	78.2 (62.1-100)	0.0001**

PCa, prostate cancer; DRE, digital rectal examination; tPSA, total PSA; fPSA, free PSA; PHI, prostate health index. Values expressed in median and interquartile range for quantitative variables, and absolute and percentage for qualitative variables. * Student paired test; ** Mann-Whitney U test; † Chi^2 de Pearson.

Table 2. Discriminative ability of biomarkers for predicting PCa.

	AUC of individual predictor variables (95% CI)
tPSA	0.554 (0.468-0.640)
fPSA	0.501 (0.427-0.590)
%fPSA	0.616 (0.523-0.694)
p2PSA	0.679 (0.602-0.759)
%p2PSA	0.682 (0.601-0.764)
PHI	0.797 (0.727-0.867)

AUC, area under the curve; tPSA, total PSA; fPSA, free PSA; %fPSA, percentage free PSA; p2PSA, [-2]pro-prostate specific antigen; %p2PSA, percentage [-2]pro-prostate specific antigen; PHI, prostate health index.

Table 3. Univariate and multivariate base models analysis predicting PCa.

	Univariate analysis		Multivariate analysis base model		Multivariate analysis base model plus p2PSA		Multivariate analysis base model plus %p2PSA		Multivariate analysis base model plus PHI	
	OR(95%CI)	*p* value	OR (95% CI)	*p* value	OR(95% CI)	*p* value	OR(95%CI)	*p* value	OR(95% CI)	*p* value
tPSA	1.12 (0.97-1.32)	0.10	1.06 (0.77-1.46)	0.7	1.01 (0.79-1.41)	0.75	1.09 (0.85-1.44)	0.47	0.93 (0.68-1.26)	0.60
fPSA	0.88 (0.59-1.30)	0.55	1.2 (0.18-5.3)	0.80	0.37 (0.04-3.03)	0.35	0.44 (0.06-4.10)	0.31	0.59 (0.05-4.5)	0.65
%fPSA	0.07 (0.02-0.90)	0.04	0.05 (0.03-3.47)	0.31	0.06 (0.02-4.89)	0.37	0.07 (0.03-4.79)	0.19	0.07 (0.02-4.59)	0.30
p2PSA	1.05 (1.02-1.08)	0.001			1.08 (1.03-1.12)	0.0008				
%p2PSA	1.03 (1.01-1.05)	0.0009					1.04 (1.02-1.06)	0.0009		
PHI	1.03 (1.01-1.04)	0.0008							1.02 (1.01-1.04)	0.0008
AUC of multivariate models (95% CI)			0.612 (0.598-0.697)		0.749 (0.672-0.826)		0.719 (0.641-0.798)		0.797 (0.727-0.867)	
Gain in predictive accuracy (95% CI)			0.612 (0.598-0.697)		0.137 (0.074-0.229)**		0.107 (0.043-0.112)**		0.175 (0.139-0.190)**	

tPSA, total PSA; fPSA, free PSA; %fPSA, percentage free PSA; p2PSA, [-2]pro-prostate specific antigen; %p2PSA, percentage [-2]pro-prostate specific antigen; PHI, Prostate Health Index; AUC, area under the curve.** $p < 0.001$; DeLong test.

Table 4. Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio for prediction of PCa: best combination, high sensitivity and high specificity.

	S	SP	PPV	NPV	PLH	NLH
Best combination						
tPSA, ng/mL ≥5.34	52	51	42	60	1.06	0.94
fPSA, ng/mL ≤0.70	61	60	51	69	1.53	0.65
%fPSA ≤0.ll	44	42	34	52	0.76	1.33
p2PSA, pg/mL ≥14.86	62	61	52	69	1.59	0.62
%p2PSA ≥0.27	68	69	60	75	2.19	0.46
PHI ≥59.87	77	77	70	82	3.35	0.30
High sensitivity						
tPSA, ng/mL ≥3.48	90	18	43	72	1.10	0.56
fPSA, ng/mL ≤1.08	91	14	44	75	1.05	0.69
%fPSA≤0.21	91	13	42	67	1.05	0.65
p2PSA, pg/mL ≥8.36	95	20	45	85	1.19	0.25
%p2PSA ≥0.14	93	18	44	79	1.13	0.39
PHI ≥28.69	95	20	45	85	1.19	0.25
High specificity						
tPSA, ng/mL ≥9.7	10	89	40	58	1.1	0.90
fPSA, ng/mL ≤0.30	8	86	29	57	1.07	0.57
%fPSA ≤0.07	22	90	60	62	2.2	0.67
p2PSA, pg/mL ≥32.1	31	90	68	65	3.10	0.57
%p2PSA ≥0.47	20	89	56	61	1.86	0.80
PHI ≥93.1	40	89	71	68	3.64	0.67

S, sensitivity; SP, specificity; PPV, positive predictive value; NPV, negative predictive value; PLH, positive likelihood ratio; NLH, negative likelihood ratio; tPSA, total PSA; fPSA, free PSA; %fPSA, percentage free PSA; p2PSA, [-2]pro-prostate specific antigen; %p2PSA, percentage [-2]pro-prostate specific antigen; PHI, prostate health index.

Table 5. Analysis set at best combination of sensitivity and specificity.

	Unnecessary biopsy avoided *n* (%)	Missed cancer, *n* (%)	Missed Gleason biopsy 7 *n* (%)
%fPSA 0.11	60 (35)	39 (54)	15 (50)
p2PSA 14.8	61 (35)	27 (37)	12(38)
%p2PSA 0.27	67 (39)	23 (32)	13 (39)
PHI 59.87	77 (45)	16 (22)	7 (21)

%fPSA, percentage free PSA; p2PSA, [-2]pro-prostate specific antigen; %p2PSA, percentage [-2]pro-prostate specific antigen; PHI, Prostate Health Index.

Table 6. Net benefit, interventions avoided, missed cancers, and missed Gleason ≥7 in Model 4.

TP, %	Net benefit		Difference	Reduction	Missed	Missed Gleason
	Treat all	Model 4	Net benefit	in biopsies, n	cancers, n	≥7, n
20	0.27	0.30	0.03	28	2	0
25	0.22	0.25	0.03	40	4	1
30	0.17	0.26	0.09	47	6	2
35	0.11	0.26	0.15	68	12	2
40	0.03	0.24	0.20	82	16	5
45	-0.06	0.21	0.25	84	21	7

TP, threshold probability; Model 4 = tPSA + fPSA + %fPSA + PHI.

Figure legends

Fig. 1. Calibration plot of models. **a** Model 1 (tPSA, fPSA, %fPSA). **b** Model 4 (tPSA, fPSA, %PSA, PHI). **e** PSA model (age, DRE, prostate volume, tPSA). **d** PHI model (age, DRE, prostate volume, PHI). X-axis represents the predicted probability and the y-axis represents the observed fraction of prostate cancer in the cohort. Instructions: the 45º dashed line represents ideal predictions, the circle represents patient groups, and the statistics at the upper left shows the model performance. In the case of the PHI model, the plot visualizes the proportion of patients falling within various predicted ranges when the nomogram is applied.

Fig. 2. Nomogram predicting the probability of PCa based on age, DRE, prostate volume, and PHI. Instructions: to obtain the nomogram-predicted probability, locate patient values on each axis. Draw a vertical line to the point axis to determine how many points are attributed for each variable value. Sum up the points for all variables. Locate the sum on the total point line to assess the individual probability of prostate cancer at biopsy. PHI, Prostate Health Index; DRE, digital rectal exam; Prostate vol, prostate volume; PCa, prostate cancer.

Fig. 3. Scatterplot demonstrating the relationship between the predicted probabilities of **(a)** the tPSA + fPSA + %fPSA + PHI and tPSA + fPSA + %fPSA and **(b)** the predicted probabilities of PHI shows the nomogram developed using these variables, and Figure 3 shows the probabilities of the models with or without PHI model and PSA model to predict PCa. tPSA, total PSA; fPSA, free PSA; %fPSA, percentage of fPSA; PHI, Prostate Health Index; PCa, prostate cancer.

Fig. 4. Decision curve analysis **(a)** for prediction of net benefit and **(b)** for prediction of interventions avoided. Decision curve analysis of the effect of prediction models on the detection of prostate cancer. The net benefit is plotted against various threshold probabilities. Model 1 is a basic model that includes total prostate-specific antigen (tPSA), free

prostate-specific antigen (fPSA), and percentage of fPSA to tPSA. Model 2 is a basic model that includes all the factors in Model 1 plus [-2]proPSA (p2PSA). Model 3 is a basic model that includes all the factors in Model 1 plus the percentage of p2PSA to fPSA. Model 4 is a basic model that includes all the factors in Model 1 plus Prostate Health Index.

Figure 1.

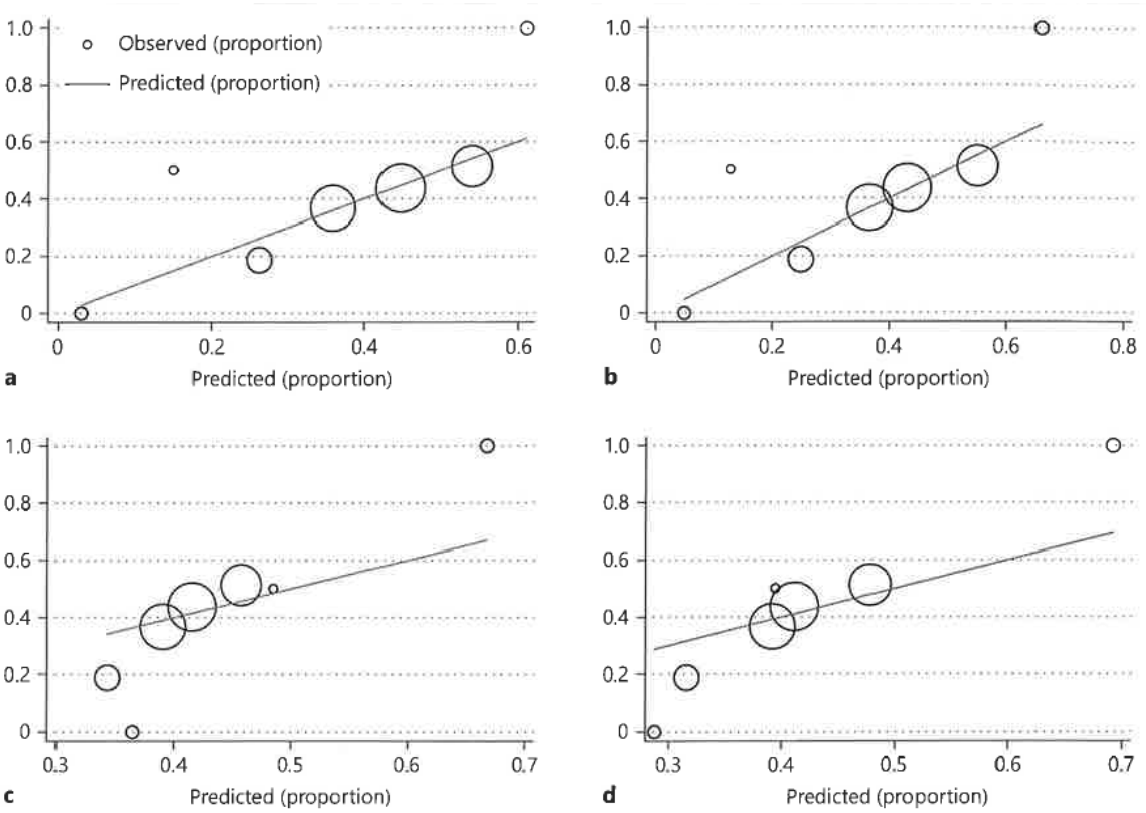

Observed (proportion)
Predicted (proportion)
1.0
0.8
0.6
0.4
0.2
0
0.2
0.4
0.6
Predicted (proportion)
a
0.8
b
0.3
0.5
0.7
c
d

Figure 2.

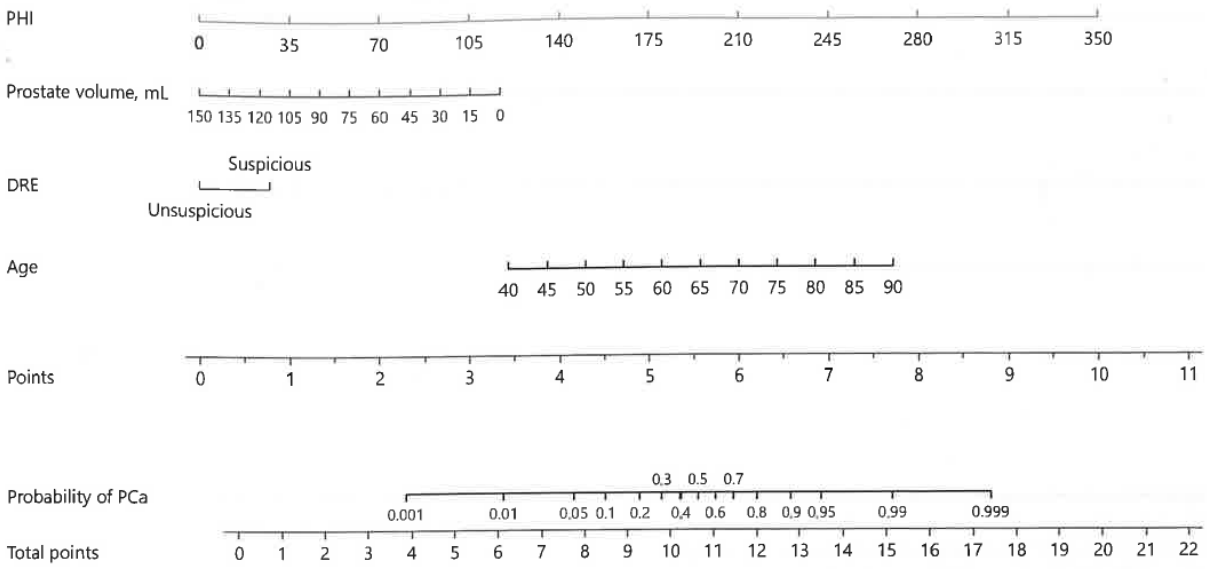

PHI
0 35 70 105 140 175 210 245 280 315 350
Prostate volume, mL
150 135 120 105 90 75 60 45 30 15 0
DRE
Suspicious
Unsuspicious
Age
40 45 50 55 60 65 70 75 80 85 90
Points
0 1 2 3 4 5 6 7 8 9 10 11
Probability of PCa
0.3 0.5 0.7
0.001 0.01 0.05 0.1 0.2 0.4 0.6 0.8 0.9 0.95 0.99 0.999
Total points
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22

Figure 3.

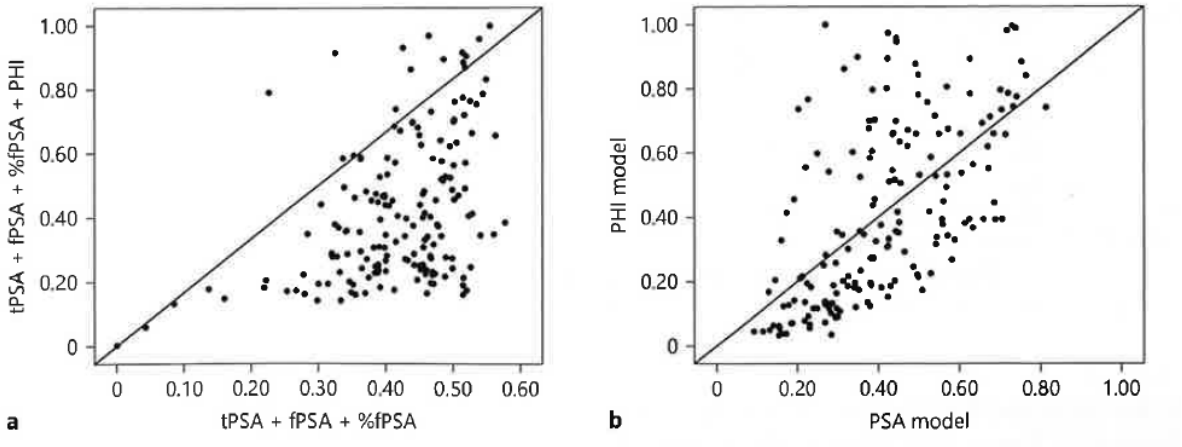
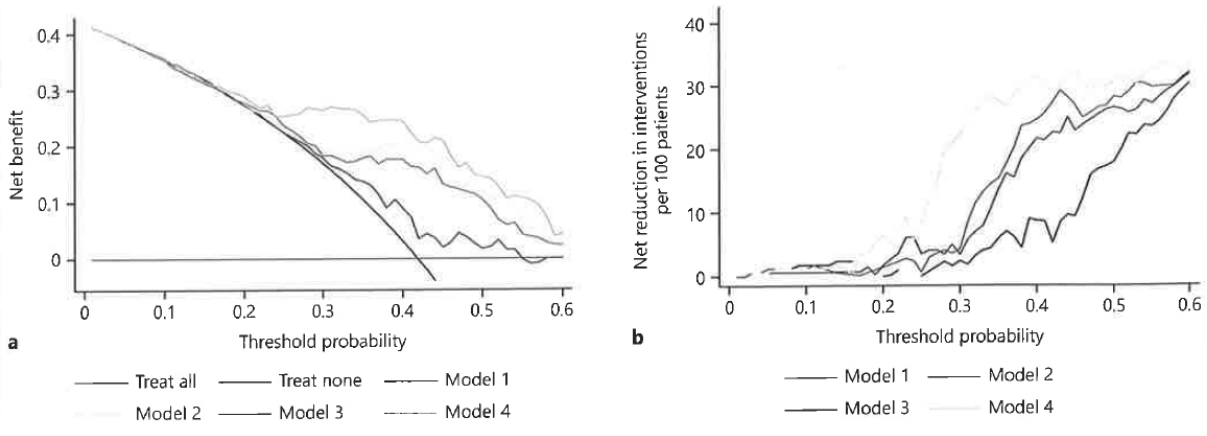

1.00
0.80
0.60
0.40
0.20
0
tPSA + fPSA + %fPSA + PHI
0
0.10
0.20
0.30
0.40
0.50
0.60
tPSA + fPSA + %fPSA
a
1.00
0.80
0.60
0.40
0.20
0
PHI model
0
0.20
0.40
0.60
0.80
1.00
PSA model
b

Figure 4


Net benefit
0.4
0.3
0.2
0.1
0
0
0.1
0.2
0.3
0.4
0.5
0.6
Threshold probability
a
Treat all
Treat none
Model 1
Model 2
Model 3
Model 4
Net reduction in interventions per 100 patients
40
30
20
10
0
0
0.1
0.2
0.3
0.4
0.5
0.6
Threshold probability
b
Model 1
Model 2
Model 3
Model 4