

Preoperative Prostate Health Index predicts adverse pathology and Gleason score upgrading after radical prostatectomy for prostate cancer.

Vojtech Novak (✉ vojtech.novak.lf2@gmail.com)

Department of Urology, Charles University 2nd faculty of Medicine University Hospital Motol
<https://orcid.org/0000-0002-5181-2485>

Stepan Vesely

Department of Urology, Charles University 2nd faculty of Medicine University Hospital Motol, Prague, Czech Republic

Hana Luksanova

Department of Medical Chemistry and Clinical Biochemistry, Charles University 2nd faculty of Medicine University Hospital Motol, Prague, Czech Republic

Richard Prusa

Department of Medical Chemistry and Clinical Biochemistry, Charles University 2nd faculty of Medicine University Hospital Motol, Prague, Czech Republic

Otakar Capoun

Department of Urology, General University Hospital and 1st Faculty of Medicine, Charles University, Prague, Czech Republic

Vojtech Fiala

Department of Urology, General University Hospital and 1st Faculty of Medicine, Charles University, Prague, Czech Republic

Olga Dolejsova

Department of Urology, University Hospital and Faculty of Medicine in Pilsen, Pilsen, Czech Republic

Hana Sedlackova

Department of Urology, University Hospital and Faculty of Medicine in Pilsen, Pilsen, Czech Republic

Radek Kucera

Department of Immunochemistry, University Hospital and Faculty of Medicine in Pilsen, Pilsen, Czech Republic

Jiri Stejskal

Thomayer Hospital, Department of Urology and 1st and 3rd Medical Faculty, Charles University, Prague, Czech Republic

Miroslav Zalesky

Thomayer Hospital, Department of Urology and 1st and 3rd Medical Faculty, Charles University, Prague, Czech Republic

Marko Babjuk

Department of Urology, Charles University 2nd Faculty of Medicine University Hospital Motol, Prague, Czech Republic, Medical University of Vienna, Austria

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Abstract

Background: We aimed to explore the utility of prostate specific antigen (PSA) isoform [-2]proPSA and its derivatives for prediction of pathological outcome after radical prostatectomy (RP).

Methods: Preoperative blood samples were prospectively and consecutively analyzed from 472 patients treated with RP for clinically localized prostate cancer at four medical centers. Measured parameters were PSA, free PSA (fPSA), fPSA/PSA ratio, [-2]proPSA (p2PSA), p2PSA/fPSA ratio and Prostate Health Index (PHI) (p2PSA/fPSA)* $\sqrt{\text{PSA}}$. Logistic regression models were fitted to determine the accuracy of markers for prediction of pathological Gleason score (GS) ≥ 7 , Gleason score upgrading, extracapsular extension of the tumor (pT3) and the presence of positive surgical margin (PSM).

Results: Of 472 patients undergoing RP, 339 (72%) were found to have pathologic GS ≥ 7 , out of them 178 (53%) experienced an upgrade from their preoperative GS=6. The findings of pT3 and PSM were present in 132 (28%) and 133 (28%) cases, respectively. At univariable analysis of all the preoperative parameters, PHI was the most accurate predictor of pathological GS ≥ 7 , GS upgrading, pT3 disease and the presence of PSM. Adding of PHI into the base multivariable model increased significantly the accuracy for prediction of pathological GS and GS upgrading by 4.4% (p=0.015) and 5.0% (p=0.025), respectively.

Conclusion: We found that PHI provides the highest accuracy in predicting prostate cancer aggressiveness and expansion of the tumor detected at final pathology. The ability of PHI to predict the risk of Gleason score upgrade may help to identify potentially high-risk patients among men with biopsy proven insignificant prostate cancer.

Background

Prostate cancer (PC) is the second most common cancer to affect men worldwide with rising incidence over the last 15 years [1]. Wide clinical implementation of serum prostate specific antigen (PSA) test has led to improvement of early PC detection and reduction in disease specific mortality [2]. However, the diagnostic accuracy of PSA is limited with frequent overdetection of clinically insignificant cancer. Moreover, up to 30% of patients with low-risk PC at biopsy are found to have features of more aggressive disease at radical prostatectomy (RP)[3]. Multivariable models prior to prostate biopsy or RP lack the accuracy in predicting of cancer aggressiveness at final pathology. In order to classify correctly those patients with clinically significant prostate cancer, the need for novel biomarkers, especially in combination with approved clinical risk factors, is extensively debated.

Several promising blood- and urine- based biomarkers have been suggested for clinical use, with varying results. Among these is [-2]proPSA (p2PSA) derivative, namely the Prostate Health Index (PHI), which has demonstrated improved performance characteristics to PSA [4- 6]. Although many studies have evaluated the relationship between the level of PHI and the result of biopsy Gleason score (GS), little is known about the utility of preoperative PHI for prediction of adverse pathological features in RP specimen. In a single

center study, Guazzoni et al. found that p2PSA and PHI are strong predictors of PC characteristics at final pathology after the surgery [7]. This finding was later confirmed in a multicenter study; however, decision curve analysis did not prove greater clinical net benefit of prediction models incorporating PHI [8]. A recent single center study in 437 patients suggests PHI to be not only good diagnostic tool, but an independent predictor of biochemical recurrence after RP [9].

The aim of this study was to determine the accuracy of p2PSA and its derivatives in predicting pathology outcome within prospectively collected multicenter cohort of patients who underwent RP for clinically localized PC.

Methods

Study population

The study cohort consisted of 472 patients with transrectal biopsy- proven clinically localized PC, who underwent either open or laparoscopic RP at four medical institutions between 2014-2018. The study protocol was approved by the institutional review board at each site before initiation, and the study was performed in compliance with their respective requirements.

Methods

All patients included in our study had complete clinical and pathologic data. Clinical data consisted of age at surgery, PSA, free PSA (fPSA), p2PSA, PHI ($(p2PSA/fPSA) \cdot \sqrt{PSA}$), digital rectal examination (DRE), biopsy GS, number of biopsy cores and number of positive biopsy cores. Pathological data consisted of pathologic stage, pathological GS and surgical margin status. The specimens were processed and evaluated by experienced pathologists who were blind to the blood tests results. Prostate cancer was graded according to the 2005 consensus conference of International Society of Urological Pathology definitions [10]. Clinically significant prostate cancer was defined as Gleason score 7 or greater. Surgical specimens were processed and evaluated according to the Stanford Protocol, and prostate cancer was staged according to the 2002 TNM staging system [11]. A positive surgical margin was defined as the presence of tumour at the inked surface of the resected specimen.

Patients with acute prostatitis, urinary tract infection, prior transurethral resection of the prostate, recent prostatic manipulation or medications that might alter serum PSA concentrations (for example finasteride or dutasteride) were excluded from study. Subjects received no prior treatment for PC at the time of blood draw. A preoperative blood sample was collected before any manipulations that might cause a transient increase in the levels of biomarker. All blood samples were processed with the UniCel Dx1018 Immunoassay System analyser (Beckman Coulter Inc., Brea, CA, USA) and were managed according to the criteria described by Semjonow et al [12]. Blood sample analysis with determination of PSA, fPSA, free to PSA ratio (%fPSA) and PHI was performed using the Hybritech calibration Beckman Coulter in all patients.

Statistical Analysis

The Mann-Whitney test and chi-square test were used to compare continuous variables and proportions in categorical variables between groups, respectively. Univariable and multivariable logistic regression models were fitted to determine the ability of various preoperative variables to predict unfavorable pathological outcome. Receiver operating characteristic (ROC) curve was created for each variable. Predictive accuracy of each variable was quantified as the area under the receiver operating characteristics curve (AUC). A multivariable logistic model assessed their predictive independency. The significance of the difference between AUCs of different predictive models was assessed with the method of DeLong et al. [13]. All statistical analyses were conducted with R - statistical package version 3.5.1. (R Core Team, Vienna, Austria, 2018).

Results

Characteristics of the study population are displayed within Table 1. Patients with significant PC at final pathology had higher preoperative PHI level in the comparison with the rest of patients (65.89 ± 33.26 vs 52.23 ± 25.11 ; $p < 0.0001$). At the biopsy, the proportion of patients with $GS \geq 7$ was 37.3% while at final pathology, the proportion raised to 71.8%. Out of 296 patients with biopsy GS 6, a total of 178 (60%) progressed to significant PC at final histology. Patients with upgrading to significant PC at final histology had higher preoperative PHI level than the patients who had GS 6 both at biopsy and final pathology (62.24 ± 25.71 vs 52.67 ± 25.71 ; $p < 0.0001$). As shown in Figure 1, PHI was significantly stronger predictor of pathological $GS \geq 7$ and GS upgrading in the comparison with conventional PSA (AUC=65.3 vs AUC=59.2; $p = 0.05$ and AUC=64.8 vs AUC=57.4; $p < 0.05$, respectively). On multivariable analyses, PHI proved to be independent predictor of $GS \geq 7$ and GS upgrading (Table 2 and Table 3). Base multivariable model (age, PSA, fPSA and clinical stage) reached the predictive accuracy of AUC = 62.2 for pathological $GS \geq 7$ and AUC=60.9 for GS upgrading. Adding of PHI into the base multivariable model increased significantly the predictive accuracy to AUC=66.6 ($p < 0.01$) for $GS \geq 7$ and to AUC=65.9 ($p < 0.03$) for GS upgrading.

Patients with pT3 and positive surgical margin (PSM) at final pathology had significantly higher preoperative PHI level in the comparison with the rest of patients (70.82 ± 38.58 vs 58.89 ± 28.32 ; $p < 0.001$ and 70.02 ± 39.28 vs 58.89 ± 27.82 ; $p < 0.001$, respectively). Prostate Health Index proved to be independent predictor of pT3 or PSM in multivariable settings (Table 4 and Table 5). Base multivariable model (age, PSA, fPSA, clinical stage and biopsy GS) reached the predictive accuracy of AUC = 58.8 for pT3 disease and AUC=58.3 for PSM. Adding of PHI into the base multivariable model increased the predictive accuracy to AUC=61.2 ($p < 0.182$) for pT3 disease and to AUC=61.2 ($p < 0.187$) for the presence of PSM, however in both cases the increase was not significant.

Discussion

Prostate cancer has been known as the second most common cancer types in current male population, and the one of the leading cause of death for cancer in males [1, 14]. Due to the widespread use of PSA as a primary screening tool for PC, the proportion of low-risk PC has increased considerably, and treatment options for PC are known to differ by risk stratification. Patients with localized PC are advised to undergo not only invasive procedures involving surgery or radiotherapy, but also the modality of active surveillance. Nevertheless, it has been published that up to 30% of patients with low-risk PC at biopsy are found to have features of aggressive disease at RP [3]. In our series of 472 men with PC, the proportion of patients with $GS \geq 7$ at biopsy was 37.3% while at final pathology, the proportion raised to 71.8%. PHI included into multivariable model proved to be the strongest independent predictor of both pathological GS and GS upgrading.

In recent years, the most common strategy for assessing risk of aggressive PC at final pathology was the preoperative prediction tool combining established parameters like PSA, biopsy GS and clinical stage. Many researchers have investigated new predictors of PC aggressiveness including novel biomarkers [15]. Although some new genomic tests have been recently introduced, none of these costly tools is used in a clinical routine setting. Several authors have analyzed the relationship between PSA isoforms and final pathology in patients treated with RP for clinically localized PC [16]. Guazzoni in the analysis of 350 consecutive men found PHI to be significant predictor of $GS \geq 7$ (AUC=74) and/or pT3 disease (AUC=72) [7]. These results were confirmed in a multicenter study performed in 489 patients; however, decision curve analysis did not prove greater clinical net benefit of prediction models incorporating PHI [8]. A recent single center study in 437 patients described lower predictive power of PHI in prediction of $GS \geq 7$ (AUC=65) and/or pT3 disease (AUC=70), however the authors suggests PHI to be independent predictor of biochemical recurrence after radical prostatectomy (AUC=62) [9]. Our results confirm the ability of PHI to predict $GS \geq 7$ (AUC=65) and/or pT3 disease (AUC=60). Moreover, PHI outperformed other preoperative variables in predicting the presence of PSM. Multivariable models showed improvement in the predictive accuracy after inclusion of PHI, although the gain did not reach the level of statistical significance in prediction of pT3 disease and the presence of PSM.

Positive surgical margin is defined as the histological presence of cancer cells at the inked margin on the RP specimen and a number of studies have demonstrated an association between PSM and a risk of disease progression [17-18]. In our study, approximately 28% of patients reported PSM. To our knowledge, there is no published data about the PSA isoforms in the relation to surgical margin status after RP. A tumor marker would be expected to correlate with the grade of differentiation or tumor extent but not necessarily with margin status, which is most likely to be confounded by surgical technique and pathological interpretation. However, in our series of 472 patients after RP, PHI was the strongest predictor of PSM (AUC = 60%) among all the preoperative variables.

Our study has some inherent limitations. The level of accuracy promoted by PHI in our study was noticeably lower in the comparison with previously reported data. The difference may be explained by the multi-institutional nature of the study, when indication criteria for prostatectomy and patients engagement in active surveillance may differ among four institutions involved. In the current study the

proportion of low-risk patients with biopsy GS=6 was considerably higher (63%) in the comparison with above cited papers (36-53%), which supports our explanation [8-9]. Even though all blood samples were managed in the same standardized way at each contributing institution, the data might be influenced by preanalytical and analytical bias. The relatively short follow-up after the RP prevented us from investigating the association of preoperative PHI and the risk of disease progression.

Conclusions

Results from the current study show that PHI could be useful predictor of PC aggressiveness and expansion of the tumor after radical prostatectomy. Moreover, higher value of PHI was associated with the risk of GS upgrading, which may help to identify potentially high-risk patients among men with biopsy proven insignificant PC. Further research is warranted to confirm our findings through the use of multivariable predictive nomograms incorporating PHI.

Declarations

Competing Interests: The authors declare that they have no Competing Interests.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the research committee (Ethics committee of the University Hospital Motol) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to Participate: All participants signed written informed consent.

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Availability of data and material: The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

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Author contributions: All authors have made a significant contribution to the findings and methods in the paper and all authors have read and approved the final draft.

Study concept and design: ŠV

Data collection: VN, ŠV, HL, RP, OČ, VF, OD, HS, JS, MZ, RK

Data analysis and interpretation: VN, ŠV

Drafting of the manuscript: VN, ŠV

Critical revision of the article: OČ, VF, OD, HS, JS, MZ

Abbreviations

area under the receiver operating characteristics curve (AUC), CI (confidence interval), extracapsular extension of the tumor (pT3), free PSA (fPSA), Gleason score (GS), HR (Hazard ratio), Prostate cancer (PC), Prostate Health Index (PHI), Prostate specific antigen (PSA), positive surgical margin (PSM), Radical prostatectomy (RP), Receiver operating characteristic (ROC), R0 (negative surgical margin), R1 (positive surgical margin), [-2]proPSA (p2PSA)

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Tables

Table 1. Clinicopathologic characteristics of 472 patients undergoing radical prostatectomy for clinically localized prostate cancer at four medical centers.

Variable	
Number of patients	472
age (years, median, range)	65.4 (60.28 – 69)
PSA (ng/ml, median, range)	8.04 (5.78 – 11.73)
fPSA (ng/ml, median, range)	0.91 (0.61 – 1.35)
%fPSA (ratio, median, range)	9.29 (4.76 – 13.35)
p2PSA (pg/ml, median, range)	17 (12 - 26)
%p2PSA (ratio, median, range)	19.60 (15.33 – 25.79)
PHI (median, range)	55.68 (42.24 – 72.82)
DRE; n (%)	
negative	329 (69.7)
positive	143 (19.3)
Biopsy Gleason score; n (%)	
6	296 (62.7)
7	141 (29.9)
>7	35 (7.4)
Pathological tumor stage; n (%)	
pT2	340 (72.1)
pT3	132 (27.9)
Pathological Gleason score; n (%)	
6	133 (28.2)
7	274 (58.1)
>7	65 (13.7)
Surgical margin status; n (%)	
R0	339 (71.8)
R1	133 (28.2)

PSA (prostate specific antigen - PSA), fPSA (free PSA), %fPSA (fPSA/PSA), %p2PSA (/fPSA ratio), PHI (Prostate health index), DRE (digital rectal examination), R0 (negative surgical margin), R1 (positive

surgical margin).

Variables	Univariable analysis		Multivariable analysis			
	HR (95% CI)	<i>p</i> value	Base model HR (95% CI)	<i>p</i> value	Base model + PHI HR (95% CI)	<i>p</i> value
Age	0.98 (0.95 – 1.01)	0.1462	0.98 (0.95 – 1.01)	0.1660	0.98 (0.95 – 1.01)	0.1437
DRE	1.62 (1.01 – 2.60)	0.0395	1.71 (1.06 – 2.76)	0.0261	1.63 (1.00 – 2.65)	0.0440
PSA	0.94 (0.89 – 0.98)	0.0025	0.92 (0.88 – 0.97)	0.0013	0.96 (0.91 – 1.00)	0.0531
fPSA	1.02 (0.98 – 1.06)	0.4477	1.09 (0.98 – 1.22)	0.1146	1.04 (0.97 – 1.12)	0.2925
p2PSA	0.99 (0.98 – 1.00)	0.1212				
%p2PSA	0.97 (0.95 – 0.99)	0.0155				
PHI	0.98 (0.97 – 0.99)	<0.0001			0.98 (0.97 – 0.99)	0.0015

Table 2. Univariable and multivariable logistic regression model of preoperative variables predicting pathological Gleason score ≥ 7

DRE (digital rectal examination), PSA (prostate specific antigen), fPSA (free PSA), p2PSA ([-2]proPSA), %p2PSA (2pSA/fPSA ratio), PHI (Prostate Health Index), HR (Hazard ratio), CI (confidence interval).

Table 3. Univariable and multivariable logistic regression model of preoperative variables predicting Gleason sum upgrading .

Variables	Univariable analysis		Multivariable analysis			
	HR (95% CI)	<i>p</i> value	Base model HR (95% CI)	<i>p</i> value	Base model + PHI HR (95% CI)	<i>p</i> value
Age	0.98 (0.95 – 1.02)	0.2943	0.98 (0.95 – 1.02)	0.3404	0.98 (0.95 – 1.02)	0.3068
DRE	1.51 (0.87 – 2.59)	0.1325	1.61 (0.93 – 2.81)	0.0855	1.65 (0.94 – 2.89)	0.0755
PSA	0.95 (0.89 – 0.99)	0.0311	0.93 (0.88 – 0.99)	0.0150	0.96 (0.91 – 1.02)	0.1872
fPSA	1.01 (0.84 – 1.21)	0.9579	1.13 (0.89 – 1.44)	0.2901	1.08 (0.86 – 1.36)	0.4979
p2PSA	1.00 (0.99 – 1.02)	0.7888				
%p2PSA	0.97 (0.94 – 1.00)	0.0666				
PHI	0.98 (0.97 – 0.99)	0.0025			0.99 (0.97 – 0.99)	0.0153

DRE (digital rectal examination), PSA (prostate specific antigen), fPSA (free PSA), p2PSA ([-2]proPSA), %p2PSA (p2PSA/fPSA ratio), PHI (Prostate Health Index), HR (Hazard ratio), CI (confidence interval).

Table 4. Univariable and multivariable logistic regression model of preoperative variables predicting pathological T3 disease.

Variables	Univariable analysis		Multivariable analysis			
	HR (95% CI)	<i>p</i> value	Base model HR (95% CI)	<i>p</i> value	Base model + PHI HR (95% CI)	<i>p</i> value
Age	1.01 (0.98 – 1.04)	0.6902	1.00 (0.97 – 1.04)	0.8237	1.00 (0.97 – 1.04)	0.8436
DRE	1.64 (1.06 – 2.54)	0.0233	1.68 (1.07 – 2.61)	0.0202	1.59 (1.01 – 2.49)	0.0404
Biopsy GS	1.79 (1.07 – 2.98)	0.0043	1.78 (1.08 – 2.85)	0.0135	1.65 (1.02 – 2.38)	0.0324
PSA	0.96 (0.94 – 0.99)	0.0124	0.97 (0.93 – 0.99)	0.0323	0.98 (0.95 – 1.02)	0.3022
fPSA	0.99 (0.95 – 1.03)	0.5891	1.01 (0.95 – 1.07)	0.7388	0.99 (0.95 – 1.05)	0.8705
p2PSA	0.98 (0.97 – 0.99)	0.0001				
%p2PSA	0.98 (0.96 – 0.99)	0.0243				
PHI	0.99 (0.98 – 0.99)	0.0007			0.99 (0.98 – 0.99)	0.0112

DRE (digital rectal examination), Biopsy GS (Biopsy Gleason score), PSA (prostate specific antigen), fPSA (free prostate specific antigen), p2PSA ([-2]proPSA), %p2PSA ([-2]proPSA/fPSA ratio), PHI (Prostate health index), HR (Hazard ratio), CI (confidence interval).

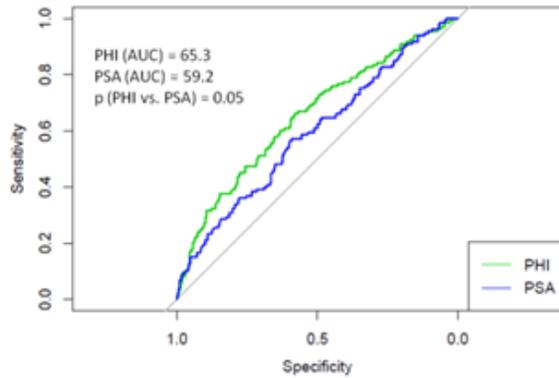
Variables	Univariable analysis		Multivariable analysis			
	HR (95% CI)	<i>p</i> value	Base model HR (95% CI)	<i>p</i> value	Base model + PHI HR (95% CI)	<i>p</i> value
Age	0.99 (0.97 – 1.03)	0.9808	1.00 (0.97 – 1.03)	0.9743	1.00 (0.97 – 1.04)	0.9514
DRE	1.44 (1.06 – 2.86)	0.0067	1.45 (1.07 – 2.65)	0.0066	1.43 (1.02 – 2.58)	0.0121
Biopsy GS	1.52 (1.04 – 2.88)	0.0434	1.51 (1.05 – 2.87)	0.0355	1.48 (1.05 – 2.36)	0.0462
PSA	1.03 (0.99 – 1.06)	0.0970	1.02 (0.98 – 1.06)	0.2120	0.99 (0.96 – 1.04)	0.8618
fPSA	0.98 (0.91 – 1.06)	0.6749	0.97 (0.84 – 1.11)	0.6051	0.98 (0.88 – 1.09)	0.6931
p2PSA	1.02 (1.01 – 1.03)	0.0018				
%p2PSA	1.03 (1.01 – 1.06)	0.0036				
PHI	1.01 (1.00 – 1.02)	0.0014			1.01 (1.00 – 1.02)	0.0066

Table 5. Univariable and multivariable logistic regression model of preoperative variables predicting the presence of positive surgical margin at final pathology.

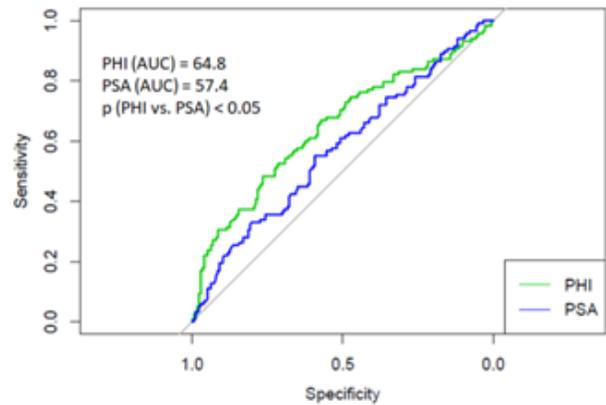
DRE (digital rectal examination), Biopsy GS (Biopsy Gleason score), PSA (prostate specific antigen), fPSA (free prostate specific antigen), p2PSA ([-2]proPSA), %p2PSA ([-2]proPSA/fPSA ratio), PHI (Prostate health index), HR (Hazard ratio), CI (confidence interval).

Figures

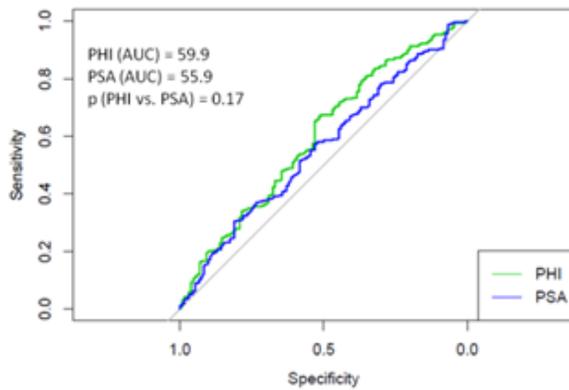
a) pathological Gleason score ≥ 7



b) Gleason score upgrading



c) pathological pT3 disease



d) positive surgical margin

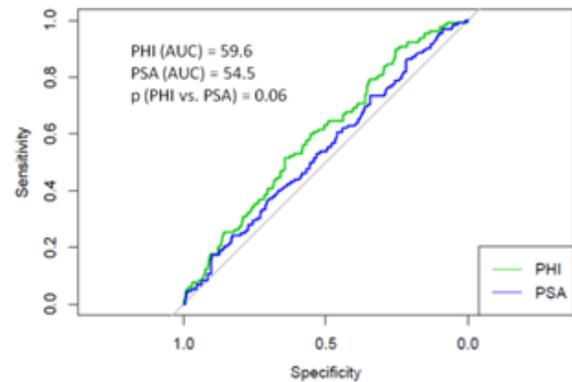


Figure 1

Receiver operating characteristics curves and calculated area under the curve (AUC) values depicting the accuracy of PSA and PHI in prediction of a) pathological Gleason score ≥ 7 , b) Gleason score upgrading, c) pathological pT3 disease and d) the presence of positive surgical margin (PSM) - PHI (Prostate health index), AUC (area under the curve), PSA (Prostate specific antigen), p (PHI vs. PSA) (DeLong test of difference between areas under the curve of PHI and PSA[13]).