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ORIGINAL ARTICLE

Significance of prostate health index and its density to predict aggressive prostate cancer at final pathology

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Summary

Purpose: *Prostate Health Index (PHI) and %p2PSA have demonstrated more accurate overall and aggressive prostate cancer (PC) detection at prostate biopsy level, however a significant number of PC patients undergo upgrading and upstaging following definitive surgery. The purpose of our study was to evaluate the ability of p2PSA and its derivatives to predict clinically significant PC at final pathology.*

Methods: *Blood samples from 51 patients, who underwent radical prostatectomy (RP), were collected pre-operatively and tPSA, fPSA, as well as p2PSA values were estimated. %p2PSA, PHI and PHI density (PHID) were calculated according to the relevant formulas. Clinically significant PC was defined as ISUP (International Society of Urological Pathology) grade group ≥2 at final pathology.*

Results: *Mean value of PHID was significantly higher (1.74 vs. 1.24, p = 0.031) in patients with clinically significant PC at final pathology. At ROC analysis, PHI, PHID and %fPSA were the most accurate predictors of clinically significant disease with AUC of 0.69, 0.70 and 0.76, respectively. PHI has demonstrated the best net benefit in predicting clinically significant PC at RP specimens.*

Conclusions: *PHI and PHID demonstrate high predicting value of clinically significant PC at final RP pathology and may define more precisely the preoperative diagnosis of this disease.*

Key words: *clinically significant, diagnostics, prostate cancer, prostate health index, prostate health index density, %p2PSA*

Introduction

Prostate cancer (PC) is the most common type of malignancy among males in Europe accounting for 20% of all newly diagnosed malignancies, that makes about 450.000 of new PC cases a year. Northern and Western European countries belong to a region with the highest PC incidence and estimated age-standardized rate (ASR) of 85.7 and 75.8 per 100 000, respectively. PC is responsible for 10% of all cancer-related deaths in Europe, and is the 3rd most common cancer-related death with the highest ASR of 13.5 per 100.000 in Northern and Central/Eastern Europe [1].

More than 20 years ago after the implementation of widespread and aggressive prostate-specific antigen (PSA; total PSA: tPSA) testing into clinical practice, reduction of PC-related mortality has been observed, though the increment of low-risk PCs with subsequent over-treatment and its negative consequences were inevitable [2,3]. According to literature, over-diagnosis is ranging from 23%

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to 42% of all screen-detected PCs [4,5], aiming an early detection of clinically significant PC as a major concern of biomedical research.

tPSA is produced in the prostatic tissue as a proPSA. One of the proPSA isoforms is [-2]proPSA (p2PSA) which is a truncated form of intact [-7] proPSA. It was determined, that higher levels of p2PSA are detected in PC patients in comparison to healthy males [6]. Subsequently, p2PSA derivatives, such as prostate health index (PHI) and percentage of p2PSA to fPSA (%p2PSA), have been suggested for PC diagnostics with intent to increase the specificity of each single biomarker [7]. The advantages of PHI and %p2PSA for improved overall and aggressive PC detection at prostate biopsy (PB) have been demonstrated in many studies [8-14], while prostate volume-adjusted index, such as PHI density (PHID) has been suggested as a potential diagnostic tool with even higher diagnostic power [15-19]. However, there are still lacking data about %p2PSA and its derivatives prognostic potential to predict adverse pathology at final radical prostatectomy (RP) specimens.

The aim of our study was to evaluate the ability of p2PSA and its derivatives, as well as PHID to predict clinically significant PC at final RP pathology.

Methods

Patients and samples

A prospective study cohort was consisted of 51 males who underwent RP due to organ-confined PC at Vilnius University Hospital Santaros Klinikos (Lithuania) and National Cancer Institute (Lithuania) from January 2015 till December 2016. All males included into the study were older than 50 years with tPSA ranging from 2 to 10 ng/mL and normal findings on digital rectal examination (DRE). In all patients blood samples were collected pre-operatively and tPSA, fPSA, as well as p2PSA were assessed according to the criteria described by Semjonow et al [20]. The samples were processed in a single laboratory using the Beckman Coulter Access® 2 Immunoassay Analyser and Access Hybritech® (Instrumentation Laboratory (Lithuania), B.I) reagents and calibrators for all assays, including tPSA, fPSA, and p2PSA. Hybritech calibration was used for tPSA, and fPSA. %p2PSA was calculated using the formula: (p2PSA/free PSA (fPSA))x100 and PHI as (p2PSA/fPSA)x√tPSA [7]. Transrectal ultrasound was used to measure the volume of the prostate gland. Prostate volume (PV) was calculated using the formula: prostate length x height x width x 0.52. PSA density (PSAD) and PHID were calculated as tPSA and PHI divided by the volume of the prostate, respectively. All histopathologic specimen evaluation was done at the National Centre of Pathology (Lithuania) by dedicated pathologists blinded to the blood serum results. Gleason score was evaluated according to the 2005 Guidelines of International Society of Urological Pathology (ISUP) and ISUP grades were assigned according to ISUP 2014 recommendations [21]. Clinically significant PC was defined as ISUP grade group ≥2 and non-clinically significant PC was defined as ISUP grade group <2.

The current study is an independent arm of the prospective trial investigating the prognostic potential of p2PSA and its indices at PB pathology. The study was approved by the Regional Biomedical Research Ethics Committee (No. 158200-14-759-273) and written informed consent was obtained from all the patients.

Statistics

Frequency tabulation and median with minimum and maximum values were used to describe the distribution of categorical variables and mean with standard deviation was used to describe continues variables. The Shapiro-Wilk test was used to determine the normality of the variables. Student's t-test and Mann-Whitney-U test

Table 1. Clinicopathologic characteristics of the study cohort

Parameter	*All patient (N=51)*
Age, years	
Mean (SD)	62.40 (5.85)
PV, mL	
Mean (SD)	38.71 (16.03)
Biopsy, N (%)	
Primary	42 (82.40)
Repeated	9 (17.60)
cISUP grade, N (%)	
1	28 (54.90)
2	18 (35.30)
3	2 (3.90)
4	3 (5.90)
5	0 (0.00)
Radical prostatectomy, N (%)	
Open	44 (86.30)
Laparoscopic	7 (13.7)
pISUP grade, N (%)	
1	13 (25.50)
2	32 (62.70)
3	4 (7.80)
4	0 (0.00)
5	2 (3.90)
pT stage, N (%)	
pT2	34 (66.70)
pT3a	12 (23.50)
pT3b	5 (9.80)

cISUP: clinical ISUP grading; ISUP: International Society of Urological Pathology; N: number of patients; pISUP: pathological ISUP grading; PV: prostate volume; SD: standard deviation; pT: pathological local tumor staging according to TNM classification

were used for comparisons of normally and non-normally distributed continuous variables, respectively. Receiver operating characteristic (ROC) analysis was performed to evaluate the area under the curve (AUC) for prognostic factors. Decision curve analysis (DCA) [22] was used to determine the net benefit of single biomarkers in guiding clinical decision-making. A two-tailed p value < 0.05 was considered significant. Statistical analyses were performed using statistical analysis system (SAS) package version 9.2 (SAS Institute Inc., Carry, NC, USA).

Results

Overall, 51 patients who underwent RP due to biopsy-confirmed PC were included into the study. Clinicopathologic characteristics of the study cohort are summarised in Table 1. Clinically significant PC was diagnosed in 38 (74.5%) and 23 (45.1%) patients according to RP and PB pathology, respectively. Baseline clinical characteristics, such as age and prostate volume, were well balanced between patients with clinically significant and non-significant disease at RP and PB levels (all p>0.05).

Mean value of tPSA was 4.77 (1.94) ng/mL, fPSA was 0.60 (0.26) ng/mL, %fPSA was 12.71 (5.83) and PSAD was 0.15 (0.08), while mean value of p2PSA was 12.94 (7.14) pg/mL, %p2PSA was 2.38 (0.79), PHI was 50.55 (18.53), and PHID was 1.61 (0.99) for all the patients.

Mean value of PHID was significantly higher (1.74 vs. 1.24, p=0.031) and mean value of %fPSA was significantly lower (11.60 vs. 16.00, p=0.005) in patients with clinically significant PC at final pathology, while a tendency for higher values of PHI (53.31 vs. 42.50, p=0.069) and PSAD (0.16 vs. 0.11, p=0.079) in these patients were observed (Table 2). No statistically significant differences were revealed between investigated biomarkers in patients with clinically significant and non-significant disease at PB.

In univariate ROC analysis, PHI, PHID and %fPSA were the most accurate predictors of clinically significant PC at final pathology with AUC of 0.69, 0.70 and 0.76, respectively (Figure 1A). Comparing single components of PHI, PHI and PHID showed higher predictive power as compared to p2PSA only (AUC: 0.69 vs. 0.51, p=0.006; and AUC: 0.70 vs. 0.51, p=0.092, respectively). Predicting clinically significant PC at PB, the highest AUC was reached for PHI and %p2PSA (both AUC: 0.62), while AUC for PHID was 0.59 (Figure 1B).

We performed DCA to determine the net benefit for each biomarker to predict clinically significant PC at final RP pathology and PB. The best net benefit at final pathology was determined for PHI, when at 45% threshold probability 56% of patients after RP would be diagnosed with clinically significant disease (Figure 2A). PHI also revealed the best net benefit at biopsy level, where at 35% threshold probability 18% of patients undergoing PB would be diagnosed with clinically significant PC (Figure 2B).

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Table 2. Values of estimated serum biomarkers according to clinical and pathological ISUP grading

	Clinical ISUP grading			*Pathological ISUP grading*		
Parameter	*ISUP <2*	*ISUP≥2*	*p value*	*ISUP <2*	*ISUP≥2*	*p value*
Patients, N (%)	28 (54.9)	23 (45.1)	-	13 (25.5)	38 (74.5)	-
tPSA, ng/mL, Mean (SD)	4.64 (1.69)	4.94 (2.24)	0.865	4.09 (1.64)	5.01 (2.00)	0.136
PSAD, Mean (SD)	0.14 (0.08)	0.15 (0.08)	0.683	0.11 (0.07)	0.16 (0.08)	0.079
fPSA, ng/mL, Mean (SD)	0.60 (0.27)	0.60 (0.26)	0.798	0.60 (0.29)	0.60 (0.26)	0.298
%fPSA, Mean (SD)	13.50 (6.30)	11.70 (5.15)	0.372	16.00 (4.49)	11.60 (5.85)	0.005
p2PSA, pg/mL, Mean (SD)	12.62 (6.25)	13.33 (8.22)	0.726	12.83 (7.24)	12.98 (7.20)	0.905
%p2PSA, Mean (SD)	2.27 (0.87)	2.50 (0.68)	0.299	2.09 (0.91)	2.47 (0.74)	0.230
PHI, Mean (SD)	48.44 (20.03)	53.12 (16.59)	0.158	42.50 (22.74)	53.31 (16.30)	0.069
PHID, Mean (SD)	1.54 (1.08)	1.70 (0.87)	0.268	1.24 (1.12)	1.74 (0.92)	0.031

fPSA: free prostate specific antigen; %fPSA: free to tPSA ratio; ISUP: International Society of Urological Pathology; N: number of patients; PV: prostate volume; %p2PSA: p2PSA to fPSA ratio; PHI: Prostate Health Index; PHID: PHI density; PSAD: PSA density; p2PSA: [-2]proPSA; SD: standard deviation; tPSA: total PSA.

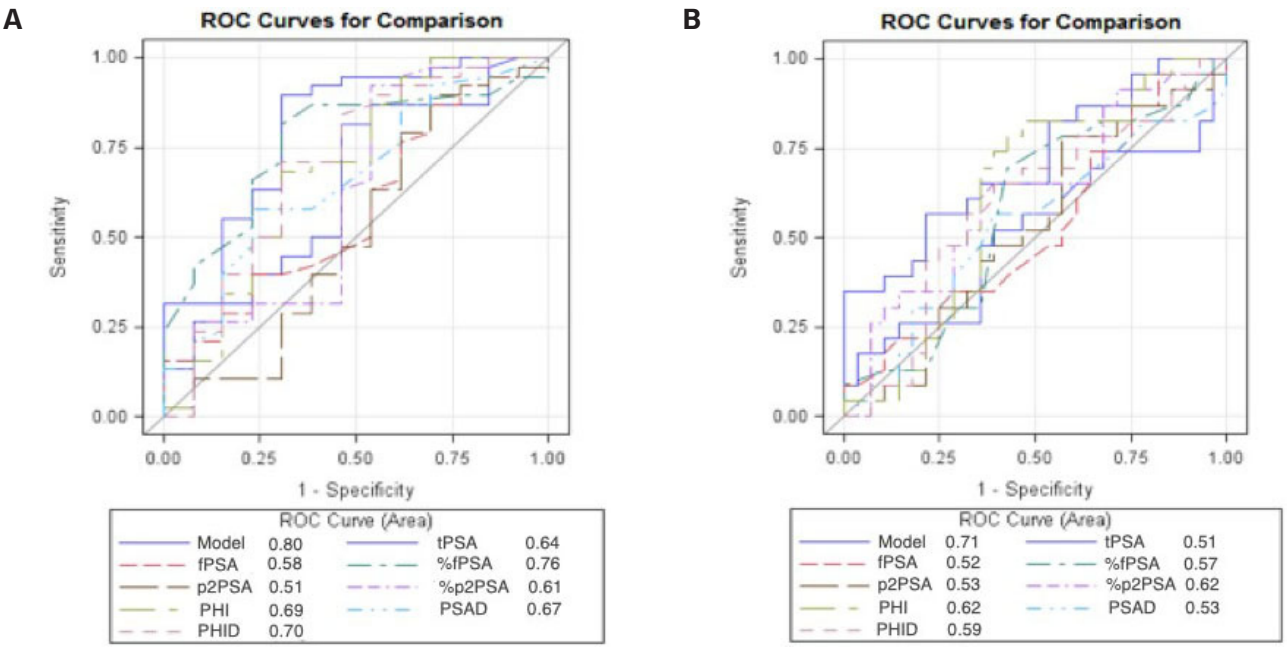

Figure 1. Receiver operating characteristic curves representing diagnostic ability of blood serum biomarkers to predict **(A)** clinically significant prostate cancer at definitive pathology and **(B)** at biopsy.
fPSA: free prostate-specific antigen; %fPSA: free to tPSA ratio; PHI: Prostate Health Index; PHID: PHI density; PSAD: prostate-specific antigen density; p2PSA: [-2]proPSA; %p2PSA: p2PSA to fPSA ratio; ROC: receiver operating characteristic; tPSA: total prostate specific antigen.

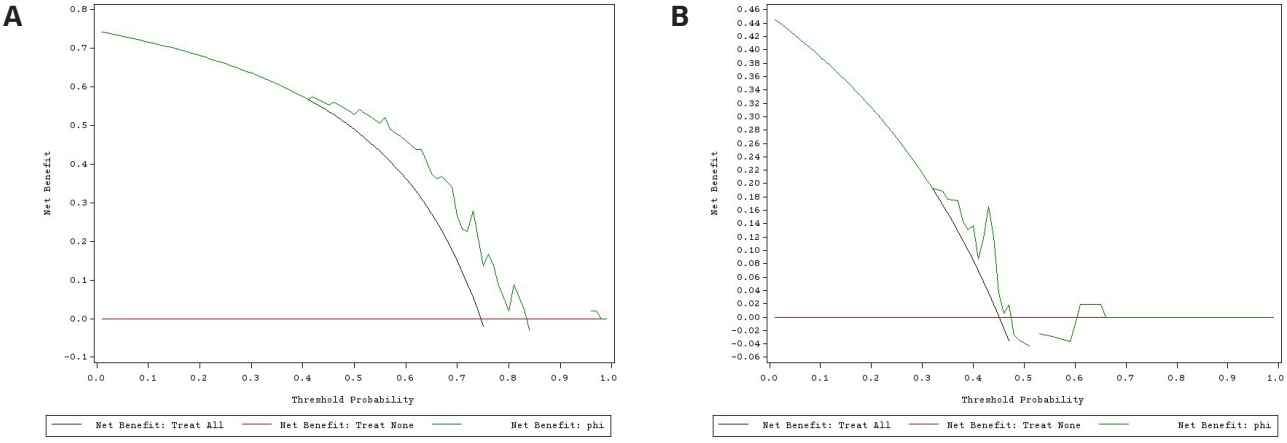

Figure 2. Decision curve analysis for PHI to predict ISUP grade ≥2 prostate cancer **(A)** at final pathology and **(B)** at biopsy. The net benefit is plotted against the threshold probability. The unit of net benefit is true positive.
ISUP: International Society of Urological Pathology; PHI: Prostate Health Index.

Discussion

PC screening programs based on tPSA only still remains a controversial topic in the urological community all over the world and are criticized for its potential harms, such as psychological distress, false-positive results following subsequent PB, as well as over-diagnosis and over-treatment of clinically-insignificant indolent disease, including treatment complications along with negative impact on male's quality of life [23-25].

Therefore, more accurate diagnostic serum markers, such as p2PSA and its derivatives, are urgently needed for clinical practice that could not only identify PC, but also predict clinically significant disease at PB [8-14]. Since considerable number of patients undergoing PB are upgraded and upstaged at final pathology [26], we suggest to estimate preoperative values of p2PSA, %p2PSA, PHI so PHID, and to explore the ability of these markers to predict aggressive PC at final RP pathology.

According to the literature just few studies have investigated the potential of p2PSA and its derivatives to detect clinically significant PC at final pathology. In a cohort of patients undergoing RP, higher values of p2PSA, %p2PSA, as well as PHI and PHID values have been observed pre-operatively in patients with ISUP ≥ 2 PC and locally advanced disease at final pathology [27-33]. It is important to note that higher levels of these biomarkers have been detected even 2-3 years before the diagnosis [28]. Our findings are in line with the literature, where value of PHID (1.74 vs. 1.24, p=0.031) was significantly higher in patients harbouring clinically significant PC at final pathology, while a strong tendency to predict clinically significant disease was observed for PHI (42.50 vs. 53.31, p=0.069).

According to our data, PHID and PHI have demonstrated comparable results to predict clinically significant PC at final RP pathology (AUC: 0.70 and AUC: 0.69, respectively), while the same AUC value for PHI was reported by Fossati et al [30]. However, %fPSA with AUC of 0.76 retained a significant predictor in our ROC curve analysis [2]. At PB level PHI outperformed PHID for detection of clinically significant disease (AUC: 0.62 and AUC: 0.59, respectively), while other studies have reported a bit higher AUC values for PHI ranging from 0.73 to 0.82 [11, 12]. However, %p2PSA, also retained as a strong predictor of clinically significant disease in our cohort (AUC: 0.62), what is in line with other authors, reporting AUC for %p2PSA ranging from 0.64 to 0.68 [9, 12, 34].

Several studies compared diagnostic and prognostic potential of PHI with other molecular biomarkers, such as prostate cancer antigen 3 (PCA3) and transmembrane protease, serine 2 (TMPRSS:2):v-ets erythroblastosis virus E26 onco-gene homolog (avian) (ERG) gene fusion (T2:ERG), but there is no similar data available for PHID. Stephan et al concluded that PHI outperformed the diagnostic accuracy of T2:ERG for PC in PB setting [35). Cantiello et al published their data on the predictive accuracy of PHI and PCA3 to predict adverse pathologic features in males undergoing RP, where only PHI provided significant predictive accuracy in multivariate analysis for clinically significant and locally advanced PC [29].

Only a few studies have explored the combined prognostic power of PHI with other well established PC molecular markers. Joining plasma levels of dysregulated microRNAs with PHI significantly increased the prognosis of metastatic PC [36]. Combination of PHI expression with additional serum biomarkers may increase current PC risk stratification tools and should attract more research.

Our study has several shortcomings. Firstly, the small-size study cohort predisposes a limited statistically significance that precludes strong conclusions. Secondly, it was not possible to make a comparative analysis with other commercially available serum biomarkers, such as PCA3 and 4K test, which could be useful tools in the decision making. Thirdly, multi-parametric magnetic resonance imaging, widely used in modern clinical practice, was not included in our protocol. Finally, several dedicated pathologists have been involved that could make a bias in pathologic analysis of RP specimens. Notwithstanding these limitations, there is a certain strength of our study. It's very important that our statements about diagnostic power of p2PSA and its derivatives are based on final RP pathology. The study revealed the clinical value of PHI and PHID to predict clinically significant PC at final pathology, what is crucial not only in repeat biopsy setting, but also in decision making about definitive PC therapy. To the best of our knowledge, this is one of the first prospective design studies investigating PHID as a PC prognostic biomarker at final pathology.

Conclusions

Higher preoperative PHI and PHID values are associated with clinically significant PC at RP pathology. If the results that we report are reproducible in larger prospective studies, PHI and PHID may be used alone or in combination with other molecular biomarkers in making decisions about individual management strategy for PC patients.

Author contributions

M.B.: collected and analyzed the data and drafted the manuscript. A.U.: collected the data and revised the manuscript. J.J., D.S. and D.V processed the blood samples. A.B. and A.Z. revised the manuscript. F.J. supervised the analysis, revised and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

Conflict of interests

The authors declare no conflict of interests.

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