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DIAGNOSTIC PERFORMANCE OF PROSTATE HEALTH INDEX (PHI) IN PREDICTING PROSTATE CANCER ON PROSTATE BIOPSY; A SINGLE CENTER STUDY

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Abstract

The Prostate Health Index (PHI) is a new test combining total, free and (-2)proPSA into a single score. It was recently approved by the FDA and is now commercially available in the U.S., Europe and Australia. Our aim is to investigate whether PHI improves specificity for detecting clinically significant prostate cancer and can help to reduce prostate cancer biopsies.

We examined 100 men age 50 years or older with prostate specific antigen 4 to 10 ng/ml („gray zone„) and normal digital rectal examination with suspected prostate cancer who had undergone biopsies and were divided into a benign and malignant group. In this population we compared the performance of prostate specific antigen, % free prostate specific antigen, (-2)proPSA and PHI to predict biopsy results and, specifically, the presence of clinically significant prostate cancer using multiple criteria.

We found statistically significantly increased levels of −2proPSA, PHI and PSA and decreased levels of %freePSA in patients diagnosed with prostate cancer by prostate biopsy vs. patients with benign prostatic conditions (median values: −2proPSA: 28.3 vs. 20.11 ng/l, PHI: 73.04 vs. 30.5, total PSA: 7.3 vs. 6.48 ng/ml and %free PSA: 17.06 vs. 25.62%). On receiver operating characteristic analysis PHI had the highest AUC for overall prostate cancer (AUCs PHI 0.954, percent free prostate specific antigen 0.345, (-2)proPSA 0.753 and prostate specific antigen 0.656). The optimal cut-off for PHI in the study population was 42.8 with sensitivity of 85.7% (95% CI: 54.8-90.6) and specificity of 86.1% (CI 95%, 0.913-0.995). Whereas, in the tPSA for cut-off 6.54 sensitivity is 61.9 and specificity 59.5, respectively. The Prostate Health Index was significantly higher in men with Gleason 7 or greater. In our study for the PHI levels (36-54.99) only 23.08% of patients had Gleason score ≥ 7.In patients with PHI levels >55, 76.92% of patients had Gleason score ≥ 7.

The new PHI test outperforms its individual components of total, free and (-2)proPSA for the identification of clinically significant prostate cancer. PHI may be useful as part of a multivariable approach to reduce prostate biopsies and overdiagnosis.

Keywords: PHI; prostate cancer, early detection, prostate biopsy.

Introduction

Prostate cancer (PCa) is the second most common cancer in men worldwide [1]. According to the latest WHO data published in 2020 Prostate Cancer Deaths in North Macedonia reached 259 or 1.13% of total deaths.

The age adjusted Death Rate is 17.47 per 100.000 of population and ranks North Macedonia on the 77th place in the world [2]. Prostate-specific antigen (PSA) is the most widely-known prostate specific biomarker. The total level of prostate-specific antigen (tPSA) has long been used as a tumor marker for prostate cancer (PCa). T

otal PSA has a limited sensitivity and specificity for PC detection. Its low specificity led to an excessive number of prostate biopsies and unnecessarily high levels of treatment (overtreatment), while its low sensitivity meant a decrease in detection of low-grade PCa. [3, 4].

However, it has limited sensitivity and specificity in diagnosing PCa. In addition to PCa, a large number of cases with elevated total PSA (tPSA) is due to benign prostate conditions such as benign prostate hyperplasia and chronic prostatitis. Other factors that also affect tPSA levels include biological variation, urinary tract infection, prostatic manipulation or ejaculation [5].

Because of these limiting factors, it is almost impossible to find a universal appropriate tPSA cut-off for the diagnosis of prostate cancer. Prostate biopsy is still the gold standard for confirmation of PCa. However, only about 25- 30% of men who have had biopsies for elevated tPSA levels were found to have cancer, while the majority had false-positive tests and underwent unnecessary biopsies. Furthermore, 15% of biopsies in men with lower levels of tPSA had detected cancer [6].

In last decades, several PSA isoforms have been identified that may increase the specificity for prostate cancer[7].

In particular, the (-2) form of proPSA ('p2PSA') has become commercially available, with improved performance over either total or free PSA for prostate cancer detection on biopsy [8].

The Prostate Health Index (PHI) combines all three forms (total PSA, free PSA and p2PSA) into a single score that can be used to aid in clinical decision-making [9].

PHI is calculated using the following formula: ([-2]proPSA/free PSA) × √PSA.

PHI, developed by Beckman Coulter, Inc., was introduced as a new marker for improving the clinical sensitivity and specificity in prostate cancer diagnosis particularly for men with borderline raised tPSA levels and DRE not suspicious of the cancerous state.

The categories of PHI suggested by the manufacturer and supported by many investigators include: very low risk (0-26.99), low risk (27-35.99), moderate risk (36-54.99), and high risk (55+) categories. In most studies, the diagnostic performance of PHI was evaluated at limited tPSA range of 4-10ng/ml.

A non-negligible proportion of patients with tPSA beyond this range may not have PCa. In view of this, our study aimed to further evaluate the diagnostic performance of PHI in Macedonian men with a wider concentration range of tPSA levels.

Material and methods

Study design and population

This is a prospective observational non-randomized study from 2018 to 2019 conducted at General City Hospital 8 th September in Skopje, R.of North Macedonia. The study included consecutive men above 50 y/o, with negative DRE, undergoing transrectal ultrasound-guided (TRUS) prostate biopsy for suspected PCa with tPSA level of 4-10ng/ml. Men receiving 5-α-reductase inhibitors, evidence of acute prostatitis, urinary tract infection and those with previous history of prostatic surgery for any prostatic condition were excluded from this study.

Blood samples were drawn prior to TRUS biopsy. Patients then underwent TRUS biopsy according to standardized protocol; with a minimum of 12 biopsy cores taken. PCa was identified and graded according to the 2005 consensus conference of the International Society of Urological Pathology.

The primary endpoint of this study was to directly compare the diagnostic accuracy of %p2PSA and PHI (index tests) in the detection of prostate cancer in comparison to the tPSA and %fPSA (standard tests). The number of potentially avoidable biopsies if these tests were used as a guide for prostate biopsy decision was calculated.

Patients were stratified into two groups: with prostate cancer and no cancer group.

Biochemical analysis

Serum samples for TPSA, fPSA and p2PSA were collected and centrifuged within two hours of collection, aliquoted and stored at -70ºC until analysis. Testing was performed on Access2 automated immunoassay analyser (Beckman Coulter, CA, USA), using Hybritech calibrators, controls, and reagents..

%fPSA (fPSA/ tPSAx100), %p2PSA (p2PSA/fPSAx100) and PHI ([p2PSA/fPSA]x√tPSA) were then obtained via calculation.

Statistical analysis

Statistical analyses were performed using SPSS v.24 software. Continuous and categorical variables were summarised by the median and interquartile range (IQR) for skewed data and frequency measures, respectively. Mann-Whitney U test was used for comparisons of continuous variables and Chi-Square test was used for comparisons of categorical variables. Medcalc v.17.0.4 software was used to plot receiver operating characteristic (ROC). Predictive accuracy was quantified as the area under the receiver operating characteristic curve (AUC). The AUC between variables were compared using Delong's method. A two-sided p-value <0.05 was considered statistically significant in all analyses.

Ethics

This study was approved by the research ethics committee of faculty of Medicine, University of Ss. Cyril and Methodius Skopje, Republic of North Macedonia.

Results

100 patients consented to the study. 21% had prostate cancer, 79% are without cancer. The median age was 69.2 ± 6.8 years. No statistically significant difference was noted in the age between patients with or without PCa (69.8 ± 7.2 vs 70.8 ± 4.8 y/o, p=0.24). (Table 1).

Table 1. Correlation between age and PSA

	Age (y/o)		**p value**
	mean ± SD	min- max	
PCa	70.8 ± 4.8	61 – 77	t=1.18
no PCa	69.8 ± 7.2	51 – 85	p=0.24

no PCa (benign prostatic conditions); t(Student t-test)
PCa (prostate cancer)

Table 2. Basic clinical characteristics of the study population

	Descriptive Statistics		
	mean ± SD	min- max	median (IQR)
PSA	6.66 ± 1.7	4.02 – 10	
PHI	42.01 ± 26.1	8.8 – 133	34.93 (27.51 – 45.8)
fpsa	1.82 ± 1.1	0.36 – 6.81	1.47 (1.17 – 2.36)
%fpsa	26.75 ± 13.8	0.81 – 78.89	24.02 (16.34 – 34.34)
pro2psa	27.03 ± 20.9	5.41 – 156.97	22.25 (14.03 – 31.41)
%pro2psa	1.65 ± 0.9	0.4 – 5	1.4 (1.045 – 1.88)

The PSA in both groups was 6.66 ± 1.7. PSA was 7.33 ± 1.6ng/ml in the group with PCa, and 6.48 ± 1.6ng/ml in the group with no PCa. The difference between them was 0.85ng/ml and it is slightly statistically significant, p=0.039. %p2PSA and PHI values were significantly higher in patients with PCa. Conversely, no statistically significant difference was noted in %fPSA and fPSA values between patients with and without PCa.

PHI levels in patients with PCa and patients without PCa are statistically more significant then tPSA (p<0.0001). PHI was significantly higher in patients with PCa. PHI had mean values 79.01 ± 33.4 and 32.18 ± 10.4, for the groups with PCa and without PCa respectively, and median values of 73.04 and 30.5 respectivly.

Table 3. Comparison of PSA, fPSA, %fPSA, %p2PSA, p2PSA and PHI between the two groups of patients

	PSA (ng/ml)			**p value**
	mean ± SD	min- max		
PCa	7.33 ± 1.6	4.71 – 9.97		t=2.1
no PCa	6.48 ± 1.6	4.02 – 10		*p=0.039
	Fpsa			**p value**
	mean ± SD	min- max	median (IQR)	
PCa	1.56 ± 0.9	0.54 – 3.5	1.24 (0.95 – 1.7)	Z=1.5
no PCa	1.89 ± 1.13	0.36 – 6.81	1.56 (1.2 – 2.37)	p=0.12
	%fpsa			**p value**
	mean ± SD	min- max	median (IQR)	
PCa	21.92 ± 12.5	7.8 – 44.85	17.06 (12.93 – 28.7)	Z=2.17
no PCa	28.04 ± 13.9	0.81 – 78.89	25.62 (18.4 – 34.39)	*p=0.03
	%p2psa			**p value**
	mean ± SD	min- max	median (IQR)	
PCa	2.95 ± 1.1	1.5 – 5	2.59 (2.21 – 3.9)	Z=6.3
no PCa	1.30 ± 04	0.4 – 2.57	1.23 (0.95 – 1.6)	***p=0.00000
	p2psa (ng/ml)			**p value**
	mean ± SD	min- max	median (IQR)	
PCa	44.95 ± 34.8	13.04 – 156.97	28.3 (25.72 – 60.7)	Z=3.55
no PCa	22.27 ± 11.5	5.41 – 52.21	20.11 (13.47 – 28.49)	***p=0.000385
	PHI			**p value**
	mean ± SD	min- max	median (IQR)	
PCa	79.01 ± 33.4	36.8 – 133.3	73.04 (48.31 – 103.1)	Z=6.4
no PCa	32.18 ± 10.4	8.8 – 58.82	30.5 (25.4 – 38.71)	***p=0.00000

no PCa (no prostatae cancer) Z(Mann-Whitney U Test);
***p<0.0001
PCa (prostate cancer)

Graph 1. Whisker plots of PSA and PHI in the two groups

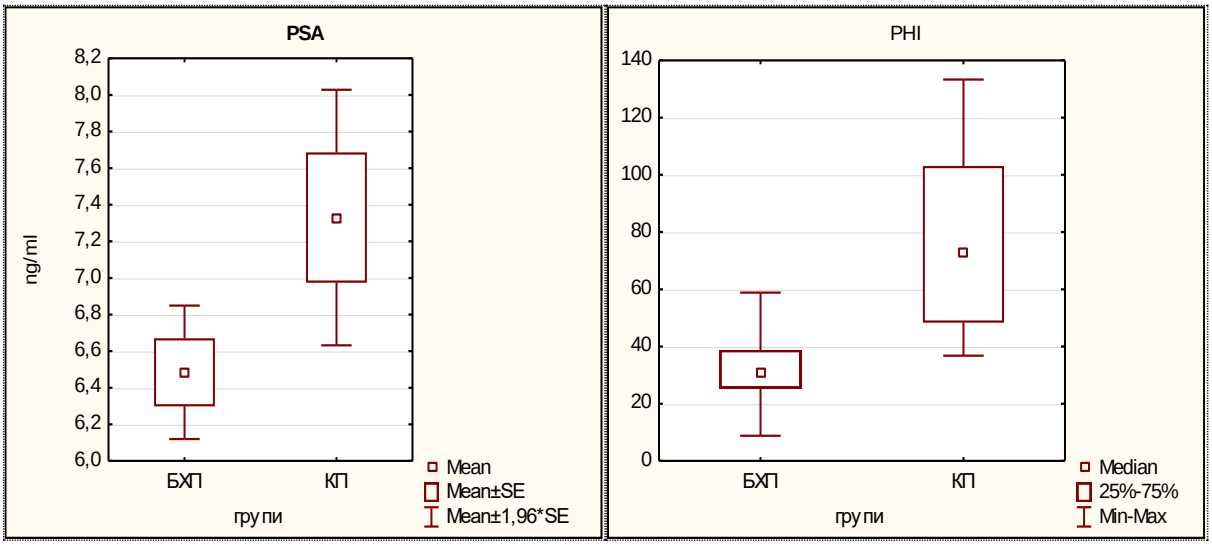


Table 4. Different levels of PHI divided in 4 groups: 0-26.99, 27-35.99, 36-54.99 and 55+ was analyzed in the patients with and without PCa.

PHI	n	**PCa** n (%)	**no PCa** n (%)	**p value**	**difference between two proportions**
0 – 26.99	23	0 (0.00)	23 (29.11)	X^2=52.8 ***p=0.000	**p=0.0048
27 – 35.99	30	0 (0.00)	30 (37.97)		***p=0.0007
36 – 54.99	30	7 (33.33)	23 (29.11)		p=0.7
55>	17	14 (66.67)	3 (3.8)		***p=0.0000

no PCa (no prostatae cancer) X^2 (Pearson Chi-square);**p<0.01,***p<0.0001
PCa (prostatae cancer)

In the group with very low risk 0-26.99 only 23 patients (29.11%) were with no evidence of PCa. And 30 patients (37.97%) without PCa were in the group with low risk. In the group with moderate level of PHI values 36-54.99 only 7 (33.33%) were with PCa and 23 (29.11%) without PCa. Finally, in the PHI group with the highest level (55+), 14 (66.67) patients were with PCa compared to only 3 (3.8%) with no evidence of PCa. There was a statistically significant difference between two groups with and without PCa, p<0.0001.

Table 5. Univariate and multivariate logistic regression analysis including all the prostate markers and age

Controls vs Prostate cancer				
	Univariate		Multivariate	
	p value	OR (95% IP)	p value	OR (95% IP)
age	0.239	1.046(0.971-1.126)		
PSA	*0.043	1.344(1.0099-1.791)		
PHI	***0.000	1.164(1.082-1.253)	***0.000	1.162(1.079-1.232)
fpsa	0.235	0.723(0.424-1.235)		
%fpsa	0.074	0.961(0.92-1.004)		
p2psa	**0.001	1.027(1.027-1.102)		
%p2psa	***0.000	2.25(1.79-8.81)	***0.000	2.13(1.56-7.60)

*p<0.05, ***p<0.0001

Univariate and multivariate logistic regression analysis were used to accurate the predictive value of PSA and its various parameters. Univariate analysis of the various parameters (PSA, PHI, p2PSA, %p2PSA) showed that PHI and % p2PSA were the most accurate predictors of PCa in the study population. (p=0.043, p<0.0001, p=0.001 and p<0.0001, respectively).

Table 6. AUC including all the prostate markers (PSA, fPSA,%fPSA, p2PSA, %p2PSA and PHI)

	AUC	Std. Error[a]	Asymptotic Sig.[b]	95% Confidence Interval	
				Lower Bound	Upper Bound
PSA	0.656	0.063	0.029	0.532	0.780
fpsa	0.390	0.071	0.121	0.250	0.529
%fpsa	0.345	0.075	0.029	0.197	0.493
p2psa	0.753	0.057	0.000	0.642	0.865
%p2psa	0.948	0.023	0.000	0.904	0.992
PHI	0.954	0.021	0.000	0.913	0.995

In the accuracy analysis, the AUCs of tPSA and its various parameters %fPSA, %p2PSA and PHI were 0.656, 0.345, 0.948 and 0.954, respectively. PHI was the most accurate predictor of PCa in the study population. There was a significant difference between the AUCs of PHI and tPSA. AUC (Area Under the Curve) for tPSA - 0.656 (AUC=0.656, CI 95% 0.532-0.780), compared to AUC (Area Under the Curve) for PHI - 0.954 (AUC=0.954, CI 95% 0.913-0.995).

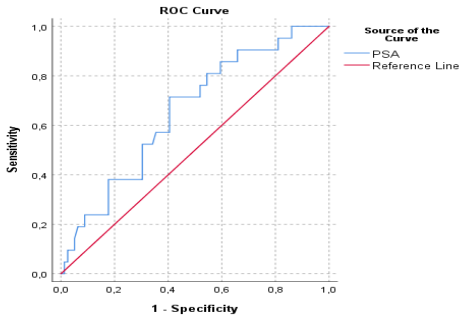
Table 7. Cut-off values, sensitivity and specificity including all the prostate markers (PSA, fPSA,%fPSA, p2PSA, %p2PSA and PHI)

variable	Area	p value	received cut off values	chosen cut off values	Sn	Sp
PSA	0.656 (0.532 – 0.780)	0.029	6.54		61.9	59.5
fpsa	0.390 (0.250 – 0.529)	0.121	1.335		38.1	39.2
%fpsa	0.345 (0.197 – 0.493)	0.029	21.91		33.3	32.9
p2psa	0.753 (0.642 – 0.865)	0.000	26.05		66.7	65.8
%p2psa	0.948 (0.904 – 0.992)	0.000	1.745	 1.36 2.15	85.7 100 76.19	86.1 63.29 94.94
PHI	0.954 (0.913 – 0.995)	0.000	42.8	 26.99 35.99 54.99	85.7 100 100 66.67	86.1 29.11 68.35 96.2

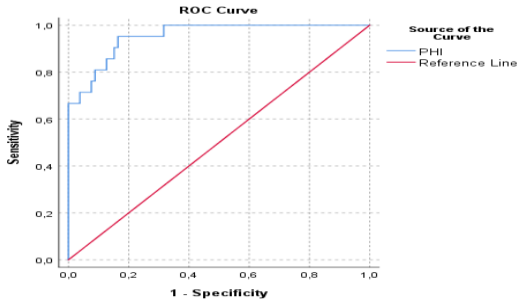
The optimal cut-off for PHI in this study population was 42.8 with sensitivity of 85.7% (95% CI: 54.8-90.6) and specificity of 86.1% (CI 95%, 0.913-0.995). Whereas, the tPSA for cut-off 6.54 sensitivity is 61.9 and specificity 59.5, respectively.

We also tested the manufacturer's recommended PHI range (taken from the manufacturer's package insert) into our study population. For PHI value below 26.99, chances for prostate biopsy will be negative in more than 90% as stated in the manufacturer insert.

Our study findings were in agreement with the manufacturer for PHI below 26.99. As the PHI values increased, the percentage of PCa and GS >7 cases detected correspondingly increased. In the high-risk group (PHI >35.99), 50% of cases that underwent prostate biopsy were positive.



Graph 2. Sensitivity and specificity for PSA



Graph 3. Sensitivity and specificity for PHI

Table 8. Comparison of PHI values divided in two groups between patients with Gleason score less and more than 7

PHI	**Gleason**			**p value**
	n	< 7 n (%)	≥ 7 n (%)	
36 – 54.99	7	4 (50)	3 (23.08)	X^2=
>55	14	4 (50)	10 (76.92)	p=0.
total	21	8	13	

X^2 (Pearson Chi-square)

Table 9. Correlation between Gleason score and PHI

Gleason	**PHI**			**p value**
	mean ± SD	min- max	median (IQR)	
<7	74.29 ± 36.4	41.89 – 133.3	63.61(45.89-100.1)	Z=0.47
≥7	81.91 ± 32.5	36.8 – 131.82	79.43(59.4-103.1)	p=0.00638
	79.01 ± 33.4	36.8 – 133.3	73.04(48.31-103.1)	

Z(Mann-Whitney U Test)

Among the 21 patients with positive biopsy, a mean age of 70.8 ± 4.8 years (range: 61 to 77) (Table 1). A clinically significant PCa (Gleason score 7 (3 + 4) or higher) was observed in 13 patients (61.9%). PHI preserved a significant association with the presence of csPCa, respectively. PHI was higher in csPCa 79.43(59.4-103.1) vs 63.61(45.89-100.1) (p=0.00638).

The optimal cut-off for the identification of csPCa was 42.7 with sensitivity: 85.7% and specificity 86.1%.If biopsy was restricted to patients with PHI≥42.7, 33.3% of biopsy could be avoided, but three csPC patients were missed. Furthermore, if biopsy was restricted to patients with PHI≥42.8, up to 50% of biopsy could be avoided with only one csPC patient being missed.

Discussion

The usefulness of PHI was evaluated. Our findings support previous results regarding that biomarker. Large studies from the U.S., Europe and Asia have uniformly demonstrated that PHI improves specificity and provides a greater net benefit for prostate cancer detection compared to total and free PSA. [10].

Deciding when to biopsy a man with non-suspicious DRE findings and tPSA in the 4–10 ng/ml range (gray zone) can be challenging, because two-thirds of such biopsies are typically found to be benign. Currently, PSA is widely used for PCa screening, but the limitations of PSA as a biomarker for PCa detection have been well demonstrated. It is necessary to distinguish PCa from benign prostatic disease and to clarify the aggressiveness of cancers, but PSA cannot completely predict the presence and biological behavior of PCa. [11].

The early detection of PCa using PSA results in a large number of negative biopsies and a high proportion of patients diagnosed with clinically low aggressive tumors (over-diagnosis) followed by unnecessary treatment (over-treatment) and morbidity related to complications. [12-13].

PHI as a combination of all three markers, showed the superiority in increasing the sensitivity and specificity in diagnoses of PCa. This study showed the AUC ROC curve for PHI, %p2PSA, and tPSA was

0.954, 0.948, and 0.656, respectively. PHI showed the highest sensitivity of 85.7% (compared with tPSA 61.9% and p2PSA 66.7%), and highest NPV of 91.57% (compared with %p2PSA 80.0% and tPSA 72.8%,). The highest specificity was observed for PHI - 96.20% followed by %p2PSA - 94.94%. A lower specificity was noted for tPSA 59.5%. The AUC for PHI was 0.954, which is a comparable value with the data from other authors with similar inclusion criteria, such as Lughezzani G, Lazzeri M, et al. [14].

Data from the meta-analysis (including 12 studies) of Filella et al. showed AUCs for PHI between 0.703 and 0.77, which increases the specificity for prostate cancer detection and reduces the number of unnecessary biopsies, maintaining a high cancer detection rate [15].

Boegemann et al, in their multicenter study, showed that in comparison with tPSA, %fPSA, and %pro2PSA, PHI had a superior diagnostic performance for detecting prostate cancer in men with tPSA in the range 1.6–8.0 ng/mL.[16].

Using a PHI threshold for biopsy of 28.6 led to a 90% sensitivity and avoidance of 30% unnecessary biopsies, with indolent or no prostate cancer,[17] which is quite consistent to our study.

This is also consistent with the observations made by Catalona et al. [18] showing a 26% specificity for the PHI at 90% sensitivity with the cut-off as low as 24, according to our study with specificity of 29.11% for the PHI at 100% sensitivity with the cut-off 26.99. The authors also concluded that most studies do not state recommended cut-offs. In addition, the European Association of Urology (EAU) guidelines published in 2016 suggested that the PHI could be used as an additional diagnostic option for men with a serum PSA level between 2 and 10 ng/mL and a negative DRE [19].

As a specific biomarker that could increase predictive validity and risk stratification, PHI is needed to identify patients who may have PCa and reduce morbidity due to unnecessary diagnosis and treatment. PHI showed higher predictive performance in the detection of PCa compared to standard reference methods, and they were better able to distinguish aggressive (GS ≥ 7) from clinically indolent PCa.

As the PHI increased, the ratio of high GS also increased. GS ≥7 began to appear in groups with PHI ≥36.0, particularly for GS 8 and 9 patients, who were distributed only in the groups with PHI ≥54.99. In, our study for the PHI levels (36-54.99) only 23.08 of patients had Gleason score ≥ 7.In patients with PHI levels >55, 76.92% of patients had Gleason score ≥ 7. Wang et al, in a meta-analysis found significantly higher PHI values observed in patients with GS ≥ 7 (PHI ≥ 60) compared with GS < 7 (PHI < 53; p = 0.0018). [20].

Median PHI for patients with Gleason score ≥ 7 in our study was 79.43(59.4-103.1) vs 63.61(45.89-100.1) for group with GS<7. This clinically important finding was also confirmed by Abrate et al.[21] and Filella et al,[22] who reported significantly higher PHI (median: 69.75 vs. 48.04) values in patients with prostate cancer, (p < 0.001) confirmed with a prostate biopsy with GS ≥ 7.

Tosoian et al. reported similar findings with PHI testing in their large academic center practice at Johns Hopkins University. A prospective registry of 345 men receiving a PHI result was compared to a contemporary cohort of 1318 men who did not undergo PHI testing.

Their comparative analysis showed that PHI testing reduced the rate of biopsy procedures performed without changing the frequency of higher-grade cancers detected. Overall, 39% of men in their registry underwent a biopsy when PHI was included in the assessment, representing a 9% reduction in the rate of prostate biopsy procedures performed compared to the control group (48%, P < 0.001). 91% of men with PHI 55+ had Gleason score ≥7 cancers. [23].

Many studies reported similarities compared to our study. Sanda and colleagues evaluated PHI in a group of 658 men with PC. The authors reported that PHI improved the prediction of high-grade PC in a group with the range of PSA from 4 to 10 ng/mL.

The PHI correlated significantly with the bioptic GS [24]. One of the largest projects in recent times has been the Multicentric European Study (PROMETHEUS), which confirmed that PHI is one of the strongest predictors of PC which correlates with biopsy GS.

The aim of this study was to investigate the PHI as a marker for tumor aggressiveness in prostate biopsy and the optimization of correct indications for treatment options [25]. In spite of that, all studies agreed that PHI was more superior then current standard biomarkers and may potentially reduce unnecessary prostate biopsies and biopsy-related morbidities. [26, 27, 28, 29].

The main limitation of this study was the relatively small sample size. The examined patients do not represent a screening population. It is done in a single secondary referral center and patients were enrolled due to the increased suspicion of csPCa. The number of examined patients is also limited. To conclusively prove that PHI is a superior marker, larger prospective studies are needed. This issue is clinically relevant.

Conclusions

In conclusion, the new PHI test outperforms its individual components of total, free and (-2)proPSA for the identification of clinically significant prostate cancer. PHI may be useful as part of a multivariable approach to reduce prostate biopsies and overdiagnosis.

Abbreviations

PHI- prostate health index; fPSA-free PSA; PCa-prostate cancer; nonPCa-no significant prostate cancer;PSA-prostate-specific antigen, pPSA: proPSA; p2PSA: [−2]proPSA; DRE-digital rectal examination; CI-confidence interval; AUC-area under curve; TRUS-transrectal ultrasound; Gleason score-GS; FDA-Federal Drug Administration; (EAU)- European Association of Urology; csPCa.- clinical significant PCa

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