OBJECTIVE: The study aimed at assessing the potential benefit of prostate health index (PHI) for early detection of prostate cancer (PCa) and the use of PHI as a marker predicting the presence of PCa before performing prostate biopsy.

METHODS: The study comprised 55 males who underwent prostate biopsy. Before the procedure, blood samples were collected to test prostate specific antigen (PSA) and free/total PSA ratio (%fPSA) and PHI was calculated. Receiver operating characteristic (ROC) analysis was used to assess the benefit of these values for predicting the presence of PCa.

RESULTS: Based on histological examination 31 males were diagnosed with PCa, the remaining 24 were negative. Among the PCa patients, 39% had a Gleason score of 6, 26% had a score of 7 and 35% had a score of 8–10. There were statistically significant differences in PHI and PSA between males with and without PCa. The areas under the ROC curve for %fPSA, total PSA and PHI were 0.712, 0.746 and 0.789, respectively. PHI showed the best predictive ability to estimate biopsy results. If the cut-off criterion PHI > 36.4 (77.42% sensitivity, 66.67% specificity) had been used, 41.7% of males would have avoided unnecessary biopsy.

CONCLUSION: The use of PHI may considerably improve the accuracy of PCa detection in patients with elevated PSA and thus reduce the number of unnecessary biopsies.

Key words: prostate cancer, prostate specific antigen, prostate health index, biopsy

Address for correspondence: V. Janout, Faculty of Health Sciences, Palacký University Olomouc, Hněvotínská 976/3, 775 15 Olomouc, Czech Republic. E-mail: vladimir.janout@upol.cz

https://doi.org/10.21101/cejph.a5720

INTRODUCTION

Prostate cancer (PCa) is currently the most frequent malignancy in males (1). The incidence of PCa has increased four-fold over the last decades and this steep increase is attributed to the introduction of the prostate specific antigen (PSA) test into clinical practice. Early detection and subsequent effective treatment of PCa are important for prolonging patient lives. A prostate biopsy plays a key role in confirming the diagnosis and early initiation of therapy. With the prostate biopsy, PCa may be histologically confirmed. Before the biopsy is performed, its benefit for the particular patient must be considered. The main indications for performing the biopsy are a suspicious digital rectal examination (DRE) or other abnormal parameters assessing the risk of PCa such as PSA or prostate health index (PHI).

PSA is a glycoprotein produced by prostatic acinar and ductal epithelial cells. The antigen is an enzyme; its primary function is to liquefy human semen. It is an organ-specific marker. Under normal circumstances, its level is low; it is measured in ng/mL. The cut-off for performing a biopsy is 3.5 ng/mL*. The amount of PSA is strongly influenced by androgen production. Increased PSA may be contributed to by multiple factors, for instance impaired cell integrity in prostate diseases such as infection or benign prostatic hyperplasia and mechanical manipulation of the prostate during examination. Thus, elevated PSA does not necessarily mean the presence of PCa. In blood serum, PSA is in a free (fPSA) and bound (tPSA) forms, at a ratio of 1 : 4 (2, 3). The PSA value itself has a very low specificity with a positive predictive value of approximately 25%, leading to high rates of false-positive results and 75% of unnecessary prostate biopsies (4).

In clinical practice, the PSA test is easily available and, when combined with DRE, it has improved PCa detection. Although the serum PSA cut-off has been set at 4 μg/L, as many as 20% of PCa patients have lower levels. With regard to cancer detection, the PSA sensitivity and specificity are reported to be 68–80% and 49–90%, respectively. In case of benign prostatic disease, serum PSA is usually higher. The f/t PSA ratio may be considered useful particularly with total PSA ranging from 4 to 10 ng/mL; the predictive value decreases with lower values (5, 6).

ProPSA is produced by prostate cells as a precursor of PSA and gradually transformed to the definitive form of PSA by enzymatic processes. It exists in several isoforms in blood and its
normal level accounts for approximately 30% of the total tPSA amount. ProPSA is very sensitive and it aids in decision-making about performing a biopsy if PSA is increased. The [-2]proPSA isoform (also written as p2PSA) is useful in case of a suspicious DRE and elevated PSA as it increases clinical significance in cancer detection. Compared to tPSA and f/tPSA, its specificity is higher. With immunohistochemistry staining, its activity is higher in tumor than benign tissue. This value is used to determine PHI and %2PSA calculated as p2PSA/PSA (7).

In recent years, research in urology has focused on novel serum biomarkers potentially improving PCa diagnosis. PHI, a novel promising test based on PSA, has been the subject of many studies. Since approximately 75% of prostate biopsies are performed unnecessarily, it is important to find a test that is as specific as possible to reduce unnecessary biopsies. This is what PHI offers (8). PHI is a value determined by a mathematical calculation combining tPSA, fPSA and the [-2]proPSA isoform. The index is calculated using the following formula: ([-2]proPSA/fPSA) × VPSA (9). PHI also helps predict an individual’s risk of PCa. The highest predictive value is when tPSA ranges between 2 and 10 ng/mL (10). The introduction of this marker into PCa diagnosis reduces the potential risk of unnecessary biopsies and subsequent wrong diagnosis and treatment. Studies on errors in the diagnosis of PCa have produced varied results. A study by Welch and Albertsen reported the overdiagnosis of 1.3 million males in the USA in 1987–2005 (11). Given its high accuracy in predicting PCa, PHI value based on calculation using p2PSA might considerably contribute to a lower rate of negative prostate biopsies, reducing the costs of diagnosis and therapy (12). Moreover, prostate biopsy puts a lot of mental stress on the patient and there is a risk of consequences (hemorrhagic complications, potency problems and infection risk).

The study aimed at assessing the benefit of PHI for PCa diagnosis and the use of PHI as a marker in the diagnostic process when making decision about performing prostate biopsy. The key assessments were sensitivity, specificity and diagnostic accuracy of PHI (as a test) for predicting the presence of PCa as compared with tPSA and %PSA (standard tests).

MATERIALS AND METHODS

Patients suspected of having PCa were examined at the Urology Department of Havířov Hospital between January and June 2015. Before biopsies were performed, blood was collected from all participants to determine PSA and its derivatives key for subsequent assessment of relationships between these values and the presence of PCa. During the biopsy procedure tissue samples were obtained from both prostate lobes. In more than half of patients, sextant biopsies were performed, with 6 tissue samples taken from each lobe, that is, a total of 6+6 samples. Biopsy indication criteria were not limited by age, level of PSA or other, because the aim of the study was not to find new cases of PCa. Biopsy indication criteria was established by attending urologist (high level of PSA or progression of PSA with respect to size of prostate gland). All males who volunteered to participate gave written informed consent to anonymous data analysis in the study. Basic descriptive statistics were used to characterize the participants (median, arithmetic mean, minimum, maximum and standard deviation – SD). Differences in values between the groups with and without PCa were analyzed with an independent t-test assessed at a level of significance of 5%. Data were statistically analyzed using MedCalc (Version_12.4.0.0*). For individual values of the sample, total PSA, %PSA and PHI, receiver operating characteristic (ROC) analysis was performed (test sensitivity, specificity, area under the curve – AUC, SD, confidence interval).

ROC analysis is an instrument for the assessment and optimization of a classification system (test) that shows a relationship between specificity and sensitivity of the test for all possible threshold values. The higher the specificity and sensitivity are, the more useful the test (diagnostic method) is. In an ROC graph, the best diagnostic test has the largest AUC. In the literature, AUC classifications quantifying the diagnostic power of a test may be found. According to the most frequently used classification, a test with an AUC greater than 0.75 may be considered able to provide satisfactory discrimination (13).

RESULTS

The study comprised 55 male patients suspected of having PCa. Prior to biopsy, blood samples were analyzed in the laboratory. All participants underwent a prostate biopsy for elevated PSA. Based on histological examination of prostate tissue biopsy samples, PCa was confirmed in 31 males. In the remaining 24 males, the biopsy yielded negative results. In patients with both positive and negative findings, the distribution of PHI was as follows: a total of 15 males (3 positive, 12 negative) in the PHI ≤ 28 category (according to Beckman Coulter); a total of 6 males (4 positive, 2 negative) in the PHI 29–36 category; a total of 12 males (6 positive, 6 negative) in the PHI 37–54 category; and a total of 22 males (18 positive, 4 negative) in the PHI ≥ 55 category. In males with positive PCa findings, PHI ≥ 55 prevailed; in those with negative results, by contrast, PHI ≤ 28 was most common (Fig. 1).

Males with positive results had a median PSA of 12.8 ng/L as compared with 5.94 ng/L in those with negative results; their median prostate tissue volumes were 36 mL and 39 mL, respectively. There was a clear difference in the median PHI between males with positive (59.40) and negative (30.85) findings (Table 1). Among 31 patients diagnosed with PCa, 12 (39%) had a Gleason score of 6, 8 (26%) had a score of 7 and the remaining 11 (35%) had a score of 8 or more (Fig. 2).

![Fig. 1. Distribution of PHI in individual subgroups.](http://www.medcalc.org)
ROC analysis showed the best diagnostic accuracy for predicting the presence of PCa in PHI. The AUC was 0.789, p < 0.001 (95% CI: 0.658–0.887). Each possible value of PHI in the sample was assigned test specificity and sensitivity. The best compromise between sensitivity and specificity was a cut-off criterion for early PCa detection of PHI > 36.4 with 77.42% sensitivity and 66.67% specificity of the test (Fig. 3). If this cut-off criterion had been used in the sample, 23 males (41.8%) would have avoided a prostate biopsy and there would have been 7 false-negative cases.

Just the second, after PHI, was the PSA test, with an AUC of 0.746, p < 0.001 (95% CI: 0.611–0.854). The best cut-off discriminating between positive and negative findings was PSA > 9.57 ng/mL with 67.74% sensitivity and 75% specificity (Fig. 4). Had this cut-off criterion been used in the sample, 28 males (50.9%) would have avoided an unnecessary prostate biopsy; however, the number of false-negative cases would have been 10.

For the %fPSA test, the AUC was 0.712, p = 0.0027 (95% CI: 0.573–0.850). The best cut-off discriminating between positive and negative findings was %fPSA < 11.22 with 58.06% sensitivity and 91.67% specificity (Fig. 5). With this cut-off criterion, 32 males (58.2%) would have avoided a prostate biopsy but 14 of them would have been false-negatively diagnosed.

The ROC analysis is summarized in Table 2. Comparison of %PSA, tPSA and PHI values suggests that the PHI test showed the best diagnostic accuracy for predicting PCa and thus potentially the greatest impact on reducing the number of unnecessary biopsies. When considering the need for a biopsy, PHI together with PSA seem to be very beneficial as compared with PSA alone.

For patients, ROC analysis was performed using all values in the sample. For comparison, analysis was conducted for males with PSA ranging from 1 to 10 ng/mL. The results are summarized in Table 3. For the entire sample, the largest AUC was seen in PHI (AUC 0.789, p < 0.001), followed by PSA (AUC 0.746, p < 0.001) and %fPSA (AUC 0.712, p = 0.003). For males with PSA below 10 ng/mL (n = 28), the largest AUC was seen in PHI (AUC = 0.711, p = 0.037), followed by %fPSA (AUC = 0.650, p = 0.196), and PSA (AUC = 0.567, p = 0.564). In both subgroups, PHI was superior to both PSA and %fPSA, suggesting that it carries the greatest weight when considering a biopsy.
DISCUSSION

The most frequent incentive for considering the presence of PCa is an increased PSA level. However, this may be frequently confounded by many factors such as age, benign prostatic hyperplasia or prostatitis. Elevated PSA levels are associated with a higher risk for PCa, namely 25% for PSA 4 ng/mL and as much as 50% for PSA > 10 ng/mL (14).

Vukotic et al. (15) reported the risk of the presence of PCa of 20% for patients with PSA 4–10 ng/mL and as much as 33% for those with PSA 10–20 ng/mL. In the present study, 49% of males had PSA > 10 ng/mL which is consistent with the above facts. Based on biopsy results, 31 males were diagnosed with PCa, that is over half of the entire sample (55 males). Histological examination showed GS 6 in 39%, GS 7 in 26% and GS 8–10 in 35% of males. According to the Institute of Health Information and Statistics of the Czech Republic, the number of early detected cases with low-grade PCa has dramatically increased since 2012. The increase is attributed to introduction of routine PSA tests into clinical practice and novel diagnostic tests.

Recently, studies have focused on novel, clinically more important markers shown to provide better diagnostic yield such as fPSA, %fPSA and PHI. Theoretically, there are 7 proPSA isoforms, with p2PSA being clinically the most significant. This marker is used for calculating PHI. A considerable benefit of p2PSA has been reported by authors of numerous studies. In their

Table 2. Summary of ROC analysis

<table>
<thead>
<tr>
<th>Marker</th>
<th>Area under ROC curve</th>
<th>SE</th>
<th>95% CI</th>
<th>p-value</th>
<th>Cut-off criterion</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHI</td>
<td>0.789</td>
<td>0.0621</td>
<td>0.658–0.887</td>
<td>&lt;0.001</td>
<td>&gt;36.40</td>
<td>77.42%</td>
<td>66.67%</td>
</tr>
<tr>
<td>tPSA</td>
<td>0.746</td>
<td>0.0665</td>
<td>0.611–0.854</td>
<td>&lt;0.001</td>
<td>&gt;9.57</td>
<td>67.74%</td>
<td>75.00%</td>
</tr>
<tr>
<td>%fPSA</td>
<td>0.712</td>
<td>0.0706</td>
<td>0.573–0.850</td>
<td>0.003</td>
<td>&lt;11.22</td>
<td>58.06%</td>
<td>91.67%</td>
</tr>
</tbody>
</table>

*a* DeLong et al., 1988 (18)  
*b* AUC ± 1.96 SE

Table 3. Analysis of ROC curves for individual values

<table>
<thead>
<tr>
<th>PCa – AUC (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
</table>
| Entire sample (all PSA values) n = 55 | Positive findings: 31  
Negative findings: 24 |
| %fPSA 0.712 (0.537–0.850) | 0.003 |
| PSA 0.746 (0.611–0.854) | <0.001 |
| PHI 0.789 (0.658–0.887) | <0.001 |
| Sample with PSA 1–10 ng/mL n = 28 | Positive findings: 10  
Negative findings: 18 |
| %fPSA 0.650 (0.448–0.819) | 0.196 |
| PSA 0.567 (0.367–0.751) | 0.564 |
| PHI 0.711 (0.510–0.865) | 0.037 |
study of 157 males with normal DRE findings undergoing their first prostate biopsy, Tan et al. analyzed various markers including p2PSA. They found a statistically significant difference in p2PSA between males with and without cancer (p = 0.001). ROC analysis of p2PSA determined the AUC at 0.695 (95% CI: 0.592–0.797), p = 0.004, indicating a discriminating test (16).

The present study assessed PSA, %fPSA, prostate volume and PHI. There were statistically very significant differences in PSA and PHI (p > 0.001) between males with and without PCa.

The best diagnostic accuracy for predicting cancer was observed in PHI. ROC analysis showed AUC = 0.789 (95% CI: 0.658–0.887), p > 0.001. This was the largest AUC in the sample, clearly confirming the expected fact that PHI had the best diagnostic effect in these patients. The cut-off criterion was found to be PHI > 36.4 with 77.42% sensitivity and 66.67% specificity. Had this cut-off criterion been used in the sample, 23 males (41.8%) would have avoided an unnecessary prostate biopsy. Available studies assessing the role of various PSA derivatives in predicting the presence of PCa showed superiority of PHI and its AUC over the others. In a recent study of 154 males with PSA between 4 and 10 ng/mL undergoing biopsy, PHI was diagnosed in 36 patients. There were statistically significant differences in %fPSA, %p2PSA and PHI between males with and without PCa. The best diagnostic test was PHI, with an AUC of 0.77. The best cut-off criterion was PHI > 29.6. If this cut-off criterion had been used in the sample, 88 males would have avoided an unnecessary prostate biopsy and there would have been 8 false-negative cases (17).

CONCLUSION

The study aimed to assess the benefit of PHI for diagnosing PCa and its use as a marker of this cancer when considering a prostate biopsy. In a sample comprising 55 males, %fPSA, PSA and PHI were determined and prostate tissue biopsy was performed. Cancer was confirmed in 31 patients. There were statistically significant differences in PSA and PHI between males with and without PCa. ROC analysis showed the best diagnostic accuracy for predicting the presence of PCa in PHI. Compared to the others, PHI had the largest AUC, which made it superior to %fPSA and PSA. Consistently with authors of other studies, the test had higher sensitivity and specificity. If the cut-off criterion PHI > 36.4 with 77.42% sensitivity and 66.67% specificity had been used, nearly half of the patients would have avoided an unnecessary prostate biopsy; this would have reduced costs spent on this procedure by health insurance companies.

Conflict of Interests

None declared

REFERENCES


Received February 20, 2019
Accepted in revised form October 17, 2019