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Original article

Clinical performance of prostate health index in men with tPSA > 10 ng/ml: Results from a multicentric European study

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Abstract

Background: Evidence regarding the diagnostic accuracy of a [-2]proPSA derivative, namely, the prostate health index (PHI), to predict the presence of prostate cancer (PCa) in individuals with high total prostate-specific antigen (tPSA) levels is lacking. We tested the hypothesis that these markers could assist clinicians in the biopsy decision path of patients with tPSA > 10 ng/ml.

Methods: The primary endpoint was to evaluate the sensitivity, specificity, and diagnostic accuracy of PHI in determining the presence of PCa at biopsy in comparison to tPSA, free PSA, and % of free to total PSA. We calculated the number of prostate biopsies that could have been spared by using this marker to decide whether or not to perform a biopsy. A secondary endpoint was to determine the relationship between PHI and PCa characteristics.

Results: The PCa was diagnosed in 136 of 262 patients (51.9%). Total PSA and PHI values were significantly higher ($P < 0.005$) and % of free to total PSA values significantly lower ($P < 0.0001$) in patients with PCa relative to those with a negative biopsy. In multivariable logistic regression models, PHI achieved the independent predictor status and significantly increased the accuracy of the base multivariable model by an extent of 8.2% ($P = 0.0005$). The inclusion of PHI in the biopsy decision path would decrease the number of unnecessary biopsies by an extent of 50.0%, while missing only few cases with clinically significant PCa. Finally, Gleason score was significantly related to PHI levels.

Conclusions: The results of our study support the diagnostic effectiveness of PHI even in patients with tPSA > 10 ng/ml. Further validation studies with larger sample size are needed to corroborate our findings.

Keywords: Prostate health index; PHI; Prostate cancer; Prostate biopsy; High total PSA

1. Introduction

Prostate-specific antigen (PSA) is widely known as a serum biomarker for the early detection of prostate cancer (PCa). Its introduction in clinical practice in the early 1990s changed PCa diagnosis and management [1]. However, while PSA is recognized as an organ-specific marker, it cannot be considered an accurate PCa predictor owing to its

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low specificity and sensitivity. The PSA levels may increase because of benign conditions, such as benign prostatic hyperplasia (BPH) and chronic prostatitis [2,3]. Moreover, PSA levels are also affected by biologic variability that may be related to differences in androgen levels, prostate manipulation, or ejaculation [4]. Finally, sample handling, laboratory processing, or assay standardization could alter PSA measurement [5].

In consequence, considerable efforts have been made to find new markers capable of accurately detecting the presence of PCa. Recently, prostate health index (PHI), a derivative of a [-2]proPSA (p2PSA), has been shown to be more accurate than reference standard tests (total PSA [tPSA], % of free to total PSA [%fPSA]) in the detection of clinically significant PCa at biopsy [6]. However, most of these studies aimed to determine the diagnostic performance of this marker in the tPSA range between 2 and 10 ng/ml, also known as the diagnostic "gray zone" [7–9]. Conversely, only few studies reported about the accuracy of PHI even in patients with high tPSA levels (>10 ng/ml) [10]. A nonnegligible proportion of patients with tPSA $>$ 10 ng/ml may not harbor PCa, as this elevation of tPSA levels may result as a consequence of large prostate volume or asymptomatic prostatic inflammation [11,12]. In consequence, we tested the hypothesis that PHI could be more accurate than tPSA and %fPSA even in this subgroup of patients.

2. Materials and methods

2.1. Study population

The data analysis consisted of a nested case-control study from the PROPSA Multicentric European Study (PROMEtheuS) project (detailed descriptions of study design, setting, ethics, centers, and patients are available at http://www.controlled-trials.com/ISRCTN04707454). The study was designed according to the Standards for the Reporting of Diagnostic Accuracy Studies (STARD) methodology (http://www.stard-statement.org) to test the sensitivity, specificity, and accuracy of PHI [(p2PSA/fPSA)$\sqrt{}$tPSA)] in men with a tPSA $>$ 10 ng/ml. Detailed descriptions of study design, setting, centers, and patients are available online (http://www.controlled-trials.com, ref. ISRCTN04707454).

The current study population included patients undergoing ambulatory prostate biopsy for suspected PCa according to indications from their referring physicians. Inclusion criteria were the following: patients >45 years of age with or without a positive digital rectal examination (DRE), with or without a previous negative biopsy with a tPSA $>$ 10 ng/ml. Exclusion criteria were the following: patients with bacterial acute prostatitis in the 3 months before biopsy and patients subjected to previous endoscopic surgery of the prostate. Patients being treated with dutasteride or finasteride were excluded. Furthermore, subjects with chronic renal failure, marked blood protein alterations (plasma normal range: 6–8 g/100 ml), hemophiliacs, or those previously multiply transfused were not included in the study, as these conditions may alter the concentration of p2PSA [13].

Before prostate biopsy, blood was drawn to measure the prebiopsy tPSA, fPSA, and p2PSA levels and blood samples were managed as previously described [14]. Patients underwent transrectal ultrasound-guided prostate biopsies according to a standardized extended scheme consisting of at least 12 biopsy cores taken from the peripheral portion of the prostate gland. Transrectal ultrasound determination of prostate and adenoma volumes was obtained with the prolate ellipsoid formula ($\pi/6 \times$ width [longest section on transverse scan] $\times$ length [greatest anteroposterior distance on sagittal scan] $\times$ height [longest cephalocaudal dimension in sagittal plane]). The adenoma volume was calculated starting from the inner part of the capsule to the limit of the transition zone at the veru montanum. Prostate biopsy specimens were placed in specific single-core specimen containers. The specimens were processed and evaluated at each center by an experienced genitourinary pathologist. The PCa was identified and graded according to the 2005 consensus conference of the International Society of Urological Pathology definitions [15]. Patients, diagnosed with high-grade prostatic intraepithelial neoplasia and atypical small acinar proliferation according to the contemporary diagnostic criteria, were not considered positive for the outcome of interest.

2.2. Statistical analysis

The primary endpoint was to evaluate the sensitivity, specificity, and diagnostic accuracy of PHI (index test) in determining the presence of PCa at prostate biopsy in comparison to tPSA, fPSA, and %fPSA (standard tests). The number of prostate biopsies that could have been spared by using PHIs in the prostate biopsy decision path was calculated. A secondary endpoint was to determine the relationship between PHI and pathologic characteristics at biopsy.

The multicentric nature of this study resulted in a complex sample that was derived not from simple random sampling but rather with each sample having an unequal probability of extraction. It was therefore necessary to adjust the data using inverse probability weighting according to the population size of each country (2012 EUROSTAT Census: http://epp.eurostat.ec.europa.eu). The Shapiro-Wilk test was used to assess the normality of variables. The student t-test, Mann-Whitney U test, and χ^2 test with Yate continuity correction were used, respectively, for comparisons of normally and not normally distributed continuous variables, as well as categoric frequencies. Correlations were checked by the Spearman rho coefficient