

Relationship of Chronic Histologic Prostatic Inflammation in Biopsy Specimens With Serum Isoform [-2]proPSA (p2PSA), %p2PSA, and Prostate Health Index in Men With a Total Prostate-specific Antigen of 4-10 ng/mL and Normal Digital Rectal Examination

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OBJECTIVE	To investigate the relationship between serum [-2]proPSA (p2PSA) and derivatives with chronic histologic prostatic inflammation (CHPI) in men undergoing prostate biopsy for suspected prostate cancer (PCa).
METHODS	This nested case-control study resulted from an observational prospective trial for the definition of sensibility, specificity, and accuracy of p2PSA, %p2PSA, and Beckman Coulter Prostate Health Index (PHI), in men undergoing prostate biopsy, with a total prostate-specific antigen (PSA) of 4-10 ng/mL and normal digital rectal examination. CHPI was the outcome of interest and defined as the presence of moderate to large infiltration of lymphomononuclear cells with interstitial and/or glandular disruption in absence of PCa. p2PSA, %p2PSA, and PHI were considered the index tests and compared with the established biomarker reference standard tests: tPSA, fPSA, %fPSA.
RESULTS	Of 267 patients subjected to prostate biopsy, 73 (27.3%) patients were diagnosed with CHPI. Comparing CHPI with PCa patients, %p2PSA and PHI were found to be significantly lower, whereas fPSA and %fPSA were significantly higher. %p2PSA and PHI were the most accurate predictors of CHPI at biopsy, significantly outperforming tPSA, fPSA, and %fPSA. On the contrary, no significant differences were found in PSA, p2PSA, and derivatives between CHPI and benign prostatic hyperplasia (BPH) patients.
CONCLUSION	Our findings showed that p2PSA, %p2PSA, and PHI values might discriminate PCa from CHPI or BPH, but not CHPI from BPH, in men with a total PSA 4-10 ng/mL and normal digital rectal examination. p2PSA isoform and its derivatives could be useful in clinical decision making to avoid unnecessary biopsies in patients with CHPI and elevated tPSA value. UROLOGY ■: ■-■, 2013. © 2013 Elsevier Inc.

Since its introduction in clinical practice in the early 1990s, prostate-specific antigen (PSA) has been widely used for early prostate cancer (PCa)

detection. However, there are many conditions limiting the specificity of PSA testing for PCa. In fact, serum PSA levels might increase as a result of benign conditions, such as chronic prostatitis or benign prostatic hyperplasia (BPH). Moreover, PSA levels are also affected by biologic variability, which might be related to differences in androgen levels, prostate manipulation, or ejaculation.¹ Finally, alterations in PSA levels might be related to sample handling, laboratory processing, or assay standardization.²

Thus, nowadays up to two-thirds of patients who undergo a prostate biopsy will have a negative histologic result. Acute and chronic inflammations are one of the

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most common causes of increase in serum PSA levels. Therefore, the development of novel markers capable of accurately distinguishing between inflammation and PCa could definitely be of pivotal importance to better indicate the need of a prostate biopsy.

A recent European multicenter observational study³ demonstrated that [-2]proPSA (p2PSA), a serum isoform of PSA, and its derivatives, namely p2PSA over fPSA (%p2PSA) and the Hybritech Prostate Health Index (PHI), might improve discrimination between men with and without PCa at initial biopsy, potentially lowering the rate of unnecessary prostate biopsies.⁴

In this study, we tested the hypothesis that p2PSA and its derivatives (%p2PSA and PHI) might discriminate between PCa and chronic histologic prostatic inflammation (CHPI) in patients with a PSA between 4 and 10 ng/mL and a negative digital rectal examination (DRE), thus avoiding unnecessary prostate biopsies in these individuals.

MATERIALS AND METHODS

Study Population

The analysis consisted of a nested case-control study from a large monocentric study aimed to define the sensibility, specificity, and accuracy of p2PSA, %p2PSA ($[p2PSA/10]/fPSA$), and Beckman Coulter PHI ($[-2]proPSA/fPSA \times \sqrt{PSA}$) in predicting PCa. The hospital ethics committee approved the study (Protocol N. 2PROPSA/13.03.2010: Title: "Specificity, sensitivity and accuracy of [-2]proPSA for the diagnosis of prostate cancer in patients who are candidates for a prostatic biopsy"), and all patients signed written informed consent.

The study included patients undergoing ambulatory initial prostate biopsy for suspected PCa, with a total PSA of 4-10 ng/mL and a normal DRE, in the period from October 2010 to October 2011.

Exclusion criteria were the following: patients with bacterial acute prostatitis in the 3 months before biopsy, patients subjected to previous endoscopic surgery of the prostate, patients subjected to previous prostate biopsy, or patients being treated with dutasteride or finasteride were excluded. Furthermore, patients 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 might alter the concentration of p2PSA.⁵

Methods

A blood sample was drawn to measure the prebiopsy tPSA, fPSA, and p2PSA levels, before performing prostate biopsy, and, within 3 hours of the blood draw, the samples were centrifuged.⁶ The samples were then frozen at -80°C and centrally processed using an Access 2 Immunoassay System, an automated random-access analyzer that performs immunoassays on body fluid samples (Beckman Coulter, Brea, CA). tPSA and fPSA were determined using the Hybritech calibration.

A preliminary transrectal ultrasonography was performed in each patient to determine prostate volume and visualize possible abnormalities within the gland. Prostate volume was calculated using the ellipsoid volume formula: $\text{Length} \cdot \text{Height} \cdot \text{Width} \cdot \pi/6$. The same scheme of transrectal ultrasonography-guided

prostate biopsies was used for all patients and consisted in a standardized institutional saturation scheme of 18-22 biopsy cores taken from the peripheral portion of the prostate gland (apex, midgland, and base), with additional cores taken when necessary according to prostate volume, patients' age, and ultrasound visible abnormalities, to obtain the highest detection rate.⁷ Prostate biopsy specimens were placed in specific single-core specimen containers filled with 10% buffered formalin. All the specimens were analyzed by a single, experienced genitourinary pathologist.⁸

CHPI was pathologically defined as moderate to large infiltration of lymphomononuclear cells with interstitial and/or glandular disruption in absence of PCa.⁹

Outcomes

The primary outcome was to test the sensitivity, specificity, and accuracy of serum p2PSA, %p2PSA ($\{[p2PSA \text{ pg/mL}]/[fPSA \text{ ng/mL} \times 1000]\} \times 100$), and Beckman Coulter PHI ($[p2PSA/fPSA] \times \sqrt{PSA}$), in discriminating CHPI from PCa, compared with the established biomarker reference standard tests (tPSA, fPSA, and %fPSA), in patients with a PSA between 4 and 10 ng/mL and a negative DRE. Patients with CHPI were considered the cases, whereas patients with PCa or BPH were the controls.

The prospective reduction of unnecessary biopsies to discriminate between CHPI and PCa was reported as a secondary outcome.

Statistical Analysis

The Shapiro-Wilk test was used to assess the normality of variables. Owing to the skewness of variables distributions, the Kruskal-Wallis test followed by Dwass-Steel-Christchlow-Fligner test for posthoc analysis was used for comparisons between groups. Correlations were checked by the Spearman's rho coefficient analysis.

Multivariable logistic regression models were fit for the prediction of the presence of CHPI or PCa at biopsy, collinearity problems were corrected excluding predictors that strongly correlated with other explanatory variables. Hosmer-Lemeshow goodness-of-fit test was used to assess the goodness of logistic models (internal calibration). Odds ratios with 95% confidence intervals were also calculated. To reduce overfit bias, multivariable predictive accuracy tests were subjected to 200 bootstrap resamples.

Multivariable logistic regression models were complemented by predictive accuracy tests and decision curve analysis. Predictive accuracy was quantified as the area under the receiver operating characteristic curve (AUC). To test the ability of p2PSA, %p2PSA, and PHI to discriminate between CHPI and PCa at biopsy, these variables were added to the base multivariable model (including age, prostate volume, PSA, fPSA, and %fPSA). The gain in predictive accuracy was quantified, and AUCs were compared using the DeLong method.¹⁰ Finally, decision curve analysis was also integrated in the statistical analysis.¹¹

All statistical analyses were performed using IBM SPSS v. 20.0 software (IBM Corp., Armonk, NY). A 2-sided P value $<.05$ was considered significant. MedCalc release 9.3.7.0 software (MedCalc Software, Mariakerke, Belgium) was used to plot receiver operating characteristic curves. Decision curves were plotted using a macro developed in Microsoft Excel (Microsoft, Redmond, WA) by one of the authors (V.B.).

Table 1. Descriptive characteristics of the study population, including patients with a total prostate-specific antigen of 4-10 ng/mL and normal digital rectal examination (median and range)

Variables	Overall Population	Presence of CHPI	Presence of BPH	Presence of PCa
No. of patients (%)	267	73 (27.3%)	93 (34.8%)	101 (37.8%)
Age, y (range)	63.9 (43.7-84.8)	63.9 (43.7-77.7) <i>P</i> = .078* <i>P</i> = .953 [†]	62.0 (45.3-77.8) <i>P</i> = .093*	65.1 (47.5-84.8)
BMI (range)	25.2 (19.8-35.6)	25.3 (20.1-33.7) <i>P</i> = .820* <i>P</i> = .926 [†]	25.2 (19.8-30.5) <i>P</i> = .979*	25.2 (19.9-35.6)
Prostate volume, mL (range)	60.0 (18-190)	65.0 (21-172) <i>P</i> < .0001* <i>P</i> = .753 [†]	67.0 (23-190) <i>P</i> = .0002*	51.0 (18-135)
Adenoma volume, mL (range)	31.0 (6-150)	37.0 (7-143) <i>P</i> < .0001* <i>P</i> = .200 [†]	35.0 (9-150) <i>P</i> = .002*	25.75 (6-93)
Total PSA, ng/mL (range)	6.12 (4.01-9.91)	5.77 (4.01-9.78) <i>P</i> = .338* <i>P</i> = .997 [†]	6.45 (4.09-9.90) <i>P</i> = .298*	6.09 (4.01-9.91)
Free PSA, ng/mL (range)	1.02 (0.34-3.32)	1.12 (0.40-2.07) <i>P</i> = .022* <i>P</i> = .840 [†]	1.09 (0.35-3.32) <i>P</i> = .125*	0.87 (0.34-2.40)
%fPSA (range)	0.16 (0.02-0.42)	0.18 (0.08-0.38) <i>P</i> = .010* <i>P</i> = .501 [†]	0.16 (0.06-0.42) <i>P</i> = .164*	0.14 (0.02-0.38)
p2PSA, pg/mL (range)	15.98 (4.66-85.03)	16.07 (6.48-38.32) <i>P</i> = .966* <i>P</i> = .310 [†]	14.97 (4.66-64.09) <i>P</i> = .177*	17.79 (5.98-85.03)
%p2PSA (range)	1.64 (0-25.01)	1.46 (0.61-4.62) <i>P</i> < .0001* <i>P</i> = .999 [†]	1.44 (0-3.01) <i>P</i> < .0001*	1.93 (0.89-25.01)
PHI (range)	40.86 (15-141)	35.65 (17-111) <i>P</i> < .0001* <i>P</i> = .601 [†]	37.00 (15-84) <i>P</i> < .0001*	49.57 (22-141)

BMI, body mass index; BPH, benign prostate hyperplasia; CHPI, chronic histologic prostate inflammation; %fPSA, percentage of free PSA to total PSA; p2PSA, [-2]proPSA; %p2PSA, percentage of [-2]proPSA to free PSA; PCa, prostate cancer; PHI, Prostate Health Index; PSA, prostate-specific antigen.

* *P* values referred to PCa group.

† *P* values referred to BPH group.

RESULTS

Of 664 patients subjected to prostate biopsy, 267 had a PSA between 4 and 10 ng/mL and a negative DRE. In this subgroup, 73 of 267 (27.3%) patients were diagnosed with CHPI. Most frequently, CHPI was found to be associated with hyperplasia (90.4%), prostatic intraepithelial neoplasia (PIN) (6.8%), or atypical small acinar proliferation (ASAP) (1.4%). Conversely, BPH (without CHPI) and PCa were diagnosed in 93 (34.8%) and 101 (37.8%) patients, respectively. Demographic and clinical characteristics of the study population are listed in Table 1.

Comparing patients with CHPI with those with PCa, %p2PSA (1.46% vs 1.93%; *P* < .0001) and PHI (35.65 vs 49.57; *P* < .0001) were found to be significantly lower, whereas fPSA (1.12 vs 0.87 ng/mL; *P* = .022) and %PSA (18% vs 14%, *P* = .01) were significantly higher. Interestingly, PSA and p2PSA values were not significantly different in the two groups.

Univariable accuracy analysis revealed %p2PSA (AUC: 0.73) and PHI (AUC: 0.73; lower %p2PSA and

PHI = higher probability of CHPI) to be the most accurate predictors of CHPI at biopsy, significantly outperforming tPSA (AUC: 0.50; *P* < .001 vs both %p2PSA and PHI), fPSA (AUC: 0.62; *P* = .029 vs %p2PSA and *P* = .032 vs PHI), and %fPSA (AUC: 0.63; *P* = .044 vs PHI; Fig. 1A).

Information regarding sensitivity and specificity for CHPI is found in Table 2. At 90% specificity, the cutoff of %p2PSA and PHI were, respectively, 1.27 and 31.0 with a sensitivity of 34.3% and 32.9%. At a %p2PSA cutoff of 1.27, a total of 38 of 174 (21.8%) biopsies could have been avoided, but 12 of 101 (11.9%) cancers would have been missed: 9 with Gleason score (GS) 6 (3 + 3) and 3 cancers with a GS of 7 (3 + 4). At a PHI cutoff of 31.0, a total of 34 of 174 (19.5%) biopsies could have been avoided, but 10 of 101 (9.9%) cancers would have been missed: 7 with GS 6 (3 + 3) and 3 cancers with a GS of 7 (3 + 4).

In multivariable logistic regression models, %p2PSA and PHI (low values) achieved the independent predictor status for CHPI, significantly increasing the accuracy of the

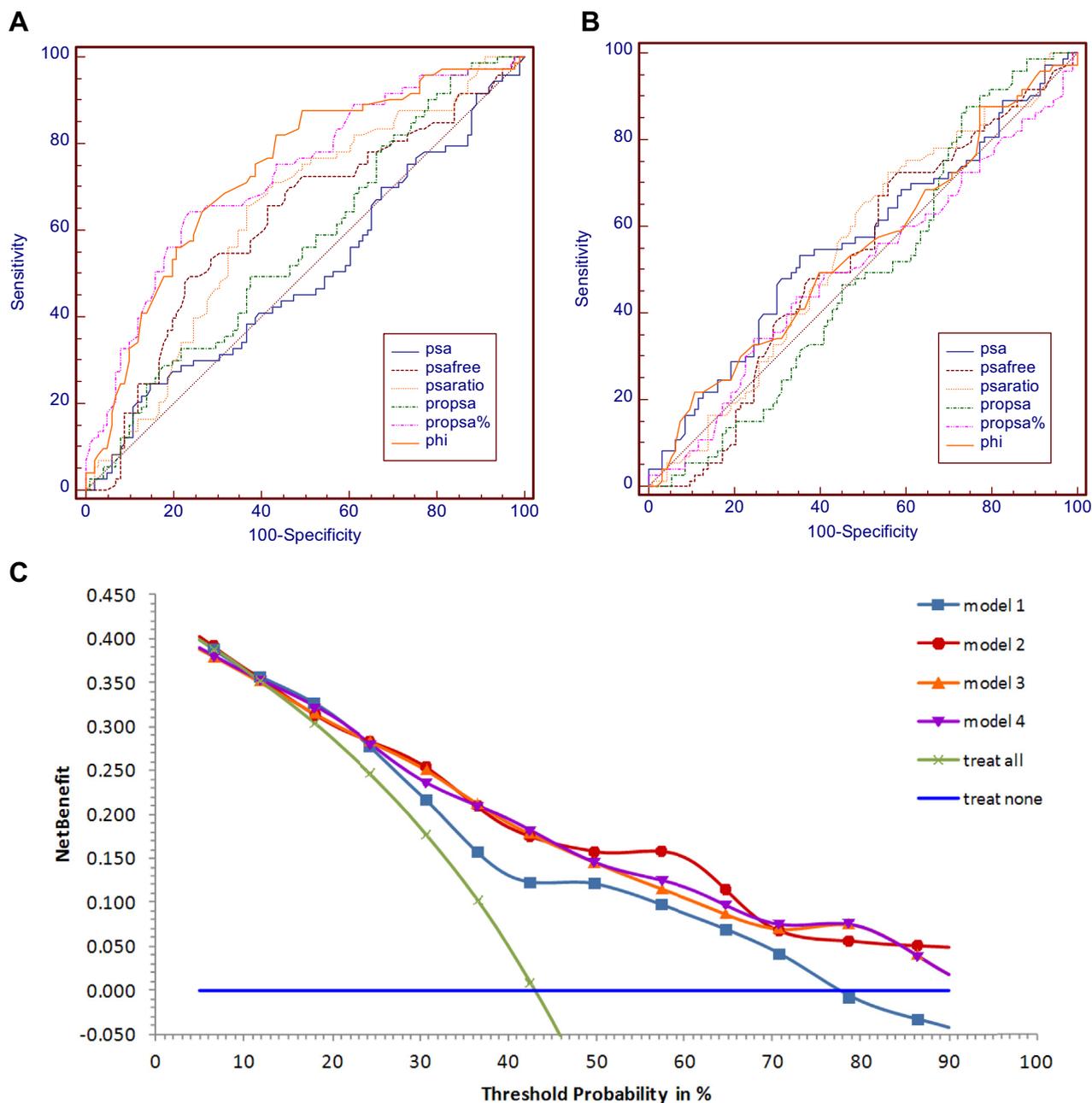


Figure 1. (A, B) Receiver operating characteristic curves depicting the accuracy of individual predictors of chronic histologic prostatic inflammation vs prostate cancer (A) and vs benign prostatic hyperplasia (B) at initial extended biopsies. (C) Decision curve analysis of the effect of prediction models. Net benefit is plotted against various threshold probabilities. A threshold probability indicates the probability of chronic histologic prostatic inflammation at which one would choose to not perform a biopsy. Model 1 is a basic model including age, prostate volume, total prostate-specific antigen, free prostate-specific antigen, and percent fPSA. Model 2 is a basic model including all factors in model 1 plus p2PSA. Model 3 is a basic model including all factors in model 1 plus %p2PSA to fPSA. Model 4 is a basic model including all factors in model 1 plus the Prostate Health Index (PHI).

multivariable base model (consisting of patient age, prostate volume, tPSA, fPSA, and %fPSA) by 7.2% ($P = .027$) and 7.6% ($P = .026$) extent, respectively (Table 3). Figure 1C presents the decision curve analysis for the models shown in Table 3. Models including p2PSA, %p2PSA, and PHI (models 2, 3, and 4) showed the highest net benefit in discriminating between patients with and

without PCa in a probability of pathologic outcome range (threshold probability) between 25% and 90%.

Finally, when comparing the CHPI with BPH subgroups, no significant differences were observed in PSA or p2PSA and derivatives (Table 1). Similarly, we found that all these markers did not have any predictive potential to discriminate CHPI from BPH (Fig. 1B).

Table 2. Sensitivities, specificities, positive predictive value, and negative predictive value in predicting the presence of chronic histologic prostatic inflammation at initial biopsy

Variables	Criterion	Sensitivity (%)	95% CI	Specificity (%)	95% CI	PPV	95% CI	NPV	95% CI
tPSA (ng/mL)	≥4.4	91.8	83.0-96.9	10.9	5.6-18.7	42.7	34.9-50.4	64.7	42.0-87.4
	≥5.9	46.6	34.8-58.8	47.5	37.5-57.7	39.1	28.8-49.3	55.2	44.7-65.6
	≥8.7	12.3	5.8-22.1	91.1	83.8-95.8	50.0	26.9-73.1	59.0	51.3-66.7
fPSA (ng/mL)	≥0.55	91.8	83.0-96.9	14.9	8.6-23.3	43.8	35.9-51.7	71.4	52.1-90.8
	≥1.00	60.3	48.1-71.5	59.4	49.2-69.1	51.8	41.1-62.4	67.4	57.7-77.2
	≥1.64	17.8	9.8-28.5	91.1	83.8-95.8	59.1	38.5-79.6	60.5	52.8-68.3
%fPSA	≥0.099	90.4	81.2-96.0	15.8	9.3-24.4	43.7	35.8-51.6	69.6	50.8-88.4
	≥0.162	65.8	53.7-76.5	63.4	53.2-72.7	56.5	45.9-67.0	71.9	62.6-81.2
	≥0.245	13.7	6.8-23.8	90.1	82.5-95.1	50.0	28.1-71.9	59.1	51.3-66.9
p2PSA (pg/mL)	≤26.0	90.4	81.2-96.0	21.8	14.2-31.1	45.5	37.4-53.6	75.9	60.3-91.4
	≤16.4	52.1	40.0-63.9	53.5	43.3-63.5	44.7	34.1-55.3	60.7	50.5-70.8
	≤9.5	15.1	7.8-25.4	90.1	82.5-95.1	52.4	31.0-73.7	59.5	51.7-67.3
%p2PSA	≤2.24	91.8	83.0-96.9	31.7	22.8-41.7	49.3	40.9-57.7	84.2	72.6-95.8
	≤1.67	65.8	53.7-76.5	72.3	62.5-80.7	63.2	52.3-74.0	74.5	65.9-83.1
	≤1.27	34.3	23.5-46.3	90.1	82.5-95.1	71.4	56.5-86.4	65.5	57.6-73.4
PHI	≤55.0	90.4	81.2-96.0	30.7	21.9-40.7	48.5	40.1-56.9	81.6	69.3-93.9
	≤41.0	68.5	56.6-78.9	68.3	58.3-77.2	61.0	50.4-71.5	75.0	66.2-83.8
	≤31.0	32.9	22.3-44.9	90.1	82.5-95.1	70.6	55.3-85.9	65.0	57.1-72.9

CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value; tPSA, total PSA; other abbreviations as in Table 1.

COMMENT

In this study, we demonstrated that low %p2PSA and PHI values might discriminate CHPI (cases) from PCa, but not CHPI from BPH, in patients with a serum PSA level between 4 and 10 ng/mL and a negative DRE.

Since its introduction in clinical practice, serum PSA testing showed a low specificity, as total PSA increase is possible in many clinical situations other than PCa, ranging from inflammation or BPH¹² to a preneoplastic lesion such as HG-PIN.^{13,14}

Prostatic inflammation is frequently diagnosed in biopsy, surgery, and autopsy histopathologic specimens. The reported inflammation rate was 44% in prostatic autopsy specimens, 44% for benign prostate biopsies, 95% in TURP specimens, and 100% in open prostatectomy specimens.¹⁵ Chronic prostatitis is thought to be one of the most common causes of increased serum PSA levels. Up to 10% of men suffer from the symptoms of prostatitis syndrome.^{16,17} However, the relationship between serum PSA levels and histologic prostatic inflammation is controversial.

According to Simardi et al,¹⁸ the presence of inflammation in more than 20% of the prostate gland might be responsible for a significant increase of serum PSA levels. However, Irani et al¹⁹ did not find any correlation between intensity or grade of inflammation and PSA level in asymptomatic men. Thus, prescribing antibiotics for asymptomatic men with a newly increased PSA, suspect for PCa, might not be an appropriate method of management. In fact, Baltaci et al²⁰ reported that antibiotics therapy will not decrease the risk of PCa at biopsy, even if the PSA decreases to <4 ng/mL.

Moreover, chronic prostatic inflammation might have an unclear role in carcinogenesis.²¹ Previous studies have found both positive²² and negative²³ associations between inflammation and PCa.

Recent studies demonstrated that serum isoform p2PSA and its derivate PHI could be valid tools for discriminating between men with or without PCa and would aid in the avoidance of overdiagnosis and overtreatment in patients with a tPSA between 2.0 and 10 ng/mL.^{4,24,25} Indeed, %p2PSA and PHI were shown to be the strongest predictors of PCa at initial and repeat extended biopsy, showing significantly greater accuracy than the currently used tests (tPSA, %fPSA, and PSA density) in determining the presence of PCa.

To our knowledge, there are no studies investigating the relationship between p2PSA (and derivatives) and CHPI. When we considered patients with CHPI as the cases, we demonstrated significantly lower levels of %p2PSA and PHI in CHPI compared with those measured in PCa patients, whereas no difference was observed between CHPI and BPH patients. This might be because of the fact that most of the CHPI diagnoses at biopsy specimen were also associated to BPH findings, but also proves that the presence of inflammation does not significantly alter p2PSA levels in comparison with other benign conditions.

The main strength of our study appears to be the prospective evaluation of p2PSA and its derivatives. Furthermore, diagnostic procedures were strictly monitored and developed according reproducible methods. Nevertheless, this study might pose some limitations. First, patients were included in the original trial for their risk of PCa and not primarily for their history of chronic prostatitis. We also did not consider the relationship between pathologic results (CHPI) and clinical information collectable through self-administered questionnaires (ie Chronic Prostatitis Symptom Index). In addition, we did not assess the grade of inflammation at pathologic samples. However, it is noteworthy that Irani et al¹⁹ were unable to determine a relationship between

Table 3. Bivariate and multivariate analyses predicting the probability of chronic histologic prostatic inflammation

Predictors	AUC of Individual Predictor Variables (95% CI)	Bivariate Analysis OR (95% CI); <i>P</i> Value	Multivariate Analysis			
			Base Model OR (95% CI); <i>P</i> Value	Base Model Plus p2PSA OR (95% CI); <i>P</i> Value	Base Model Plus %p2PSA OR (95% CI); <i>P</i> Value	Base Model Plus PHI OR (95% CI); <i>P</i> Value
Age	0.596 (0.519-0.670)	0.949 (0.911-0.990); <i>P</i> = .014	0.918 (0.875-0.963); <i>P</i> < .001	0.918 (0.871-0.966); <i>P</i> = .001	0.917 (0.872-0.964); <i>P</i> = .001	0.918 (0.873-0.965); <i>P</i> = .001
Prostate volume	0.701 (0.625-0.770)	1.025 (1.012-1.038); <i>P</i> < .001	1.031 (1.014-1.047); <i>P</i> < .001	1.027 (1.010-1.045); <i>P</i> = .001	1.027 (1.011-1.044); <i>P</i> = .001	1.027 (1.10-1.044); <i>P</i> = .001
Adenoma volume*	0.721 (0.646-0.788)	1.035 (1.018-1.052); <i>P</i> < .001	—	—	—	—
tPSA	0.497 (0.420-0.574)	1.006 (0.838-1.207); <i>P</i> = .950	0.963 (0.776-1.194); <i>P</i> = .729	1.291 (0.980-1.701); <i>P</i> = .069	0.905 (0.719-1.139); <i>P</i> = .394	1.060 (0.838-1.341); <i>P</i> = .628
fPSA [†]	0.618 (0.541-0.690)	2.147 (1.087-4.240); <i>P</i> = .028	—	—	—	—
%fPSA [‡]	0.630 (0.554-0.702)	1.870 (1.147-3.049); <i>P</i> = .012	1.227 (0.672-2.242); <i>P</i> = .506	4.117 (1.670-10.148); <i>P</i> = .002	1.023 (0.549-1.903); <i>P</i> = .944	1.002 (0.537-1.871); <i>P</i> = .994
p2PSA	0.565 (0.488-0.640)	0.962 (0.928-0.997); <i>P</i> = .032	—	0.869 (0.805-0.937); <i>P</i> < .001	—	—
%p2PSA	0.726 (0.653-0.790)	0.300 (0.164-0.550); <i>P</i> < .001	—	—	0.321 (0.158-0.651); <i>P</i> = .002	—
PHI	0.734 (0.662-0.798)	0.949 (0.926-0.973); <i>P</i> < .001	—	—	—	0.952 (0.925-0.980); <i>P</i> = .001
AUC of multivariate models (95% CI)			0.741 (0.668-0.806)	0.800 (0.731-0.858)	0.794 (0.725-0.853)	0.798 (0.729-0.856)
Gain in predictive accuracy (95% CI)			—	0.058 (0.004-0.113) [§]	0.053 (0.006-0.100) [§]	0.056 (0.007-0.106) [§]

AUC, area under the curve; OR, odds ratio; other abbreviations as in Tables 1 and 2.

The area under the curve reflects the predictive value of individual variables (columns) and of the multivariable models in predicting the probability of having chronic histologic prostatic inflammation.

* Not included in multivariate base model because the strong correlation with prostate volume ($\rho = 0.920$).

[†] Not included in multivariate base model because the strong correlations with percentage of free PSA to total PSA ($\rho = 0.825$) and $[-2]\text{proPSA}$ ($\rho = 0.708$).

[‡] Expressed as $\text{fPSA/PSA} \times 10$ to scaling OR in a more intelligible range.

[§] $P < .05$ (relative to the multivariate base model; DeLong method).

intensity or grade of inflammation and PSA levels in asymptomatic men. Conversely, Nadler et al²⁶ demonstrated a significant PSA and p2PSA increase in patients with chronic prostatitis compared with controls. Moreover, we did not arrange the study population according to age, race, and family history information, potentially underestimating the models predictive accuracy. Finally, we consider only one PSA time point, and consequently it was not possible to investigate how levels of PSA and its isoforms change over time in patients with CHPI compared with those with PCa. This could be an interesting point for future investigations.

CONCLUSION

In this study, we demonstrated that p2PSA, %p2PSA, and PHI values might discriminate between CHPI and PCa, but not between CHPI and BPH, in patients with a total PSA of 4-10 ng/mL and a normal DRE. As tPSA failed to distinguish PCa, BPH, and CHPI, p2PSA isoform and its derivatives could be useful in clinical decision making to prevent unnecessary biopsies in patients with CHPI and elevated tPSA value. However, further investigations are needed to find a biomarker able to discriminate between the two benign conditions.

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