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ORIGINAL ARTICLE

Validation of the prostate health index in a predictive model of prostate cancer☆

A. Sanchís-Bonet[a,*], M. Barrionuevo-González[b], A.M. Bajo-Chueca[c], L. Pulido-Fonseca[a], L.E. Ortega-Polledo[a], J.C. Tamayo-Ruiz[a], M. Sánchez-Chapado[a,c]

[a] *Departamento de Urología, Hospital Universitario Príncipe de Asturias, Alcalá de Henares (Madrid), Spain*
[b] *Departamento de Bioquímica y Análisis Clínicos, Hospital Universitario Príncipe de Asturias, Alcalá de Henares (Madrid), Spain*
[c] *Departamento de Biología de Sistemas, Facultad de Medicina, Universidad de Alcalá de Henares, Alcalá de Henares (Madrid), Spain*

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Abstract
Objectives: To validate and analyze the clinical usefulness of a predictive model of prostate cancer that incorporates the biomarker ''[-2] pro prostate-specific antigen'' using the prostate health index (PHI) in decision making for performing prostate biopsies.
Material and methods: We isolated serum from 197 men with an indication for prostate biopsy to determine the total prostate-specific antigen (tPSA), the free PSA fraction (fPSA) and the [-2] proPSA (p2PSA). The PHI was calculated as p2PSA/fPSA $\times \sqrt{}$tPSA. We created 2 predictive models that incorporated clinical variables along with tPSA or PHI. The performance of PHI was assessed with a discriminant analysis using receiver operating characteristic curves, internal calibration and decision curves.
Results: The areas under the curve for the tPSA and PHI models were 0.71 and 0.85, respectively. The PHI model showed a better ability to discriminate and better calibration for predicting prostate cancer but not for predicting a Gleason score in the biopsy $\geq$7. The decision curves showed a greater net benefit with the PHI model for diagnosing prostate cancer when the probability threshold was 15–35% and greater savings (20%) in the number of biopsies.

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* Corresponding author.
E-mail address: asanchisbonet@yahoo.es (A. Sanchís-Bonet).

Conclusions: The incorporation of p2PSA through PHI in predictive models of prostate cancer improves the accuracy of the risk stratification and helps in the decision-making process for performing prostate biopsies.

PALABRAS CLAVE
Cáncer de próstata;
Índice de salud prostática;
Modelos predictivos;
Curvas de decisión;
Biopsia de próstata

Validación del índice de salud prostática en un modelo predictivo de cáncer de próstata

Resumen

Objetivos: Validar y analizar la utilidad clínica de un modelo predictivo de cáncer de próstata que incorpora el biomarcador «[−2] proantígeno prostático específico» a través del índice de salud prostática (PHI) en la toma de decisión para realizar una biopsia de próstata.

Material y métodos: Se aisló suero de 197 varones con indicación de biopsia de próstata para la determinación del antígeno prostático específico total (tPSA), fracción libre de PSA (fPSA) y [-2] proPSA (p2PSA); el PHI se calculó como p2PSA/fPSA $\times \sqrt{}$tPSA. Se crearon 2 modelos predictivos que incorporaban variables clínicas junto a tPSA o a PHI. Se evaluó el rendimiento de PHI usando análisis de discriminación mediante curvas ROC, calibración interna y curvas de decisión.

Resultados: Las áreas bajo la curva para el modelo tPSA y el modelo PHI fueron de 0,71 y 0,85, respectivamente. PHI mostró mejor capacidad de discriminación y mejor calibración para predecir cáncer de próstata, pero no para predecir un grado de Gleason en la biopsia $\geq$7. Las curvas de decisión mostraron un beneficio neto superior del modelo PHI para el diagnóstico de cáncer de próstata cuando el umbral de probabilidad está entre 15 y 35% y un mayor ahorro (20%) en el número de biopsias.

Conclusiones: La incorporación de p2PSA a través de PHI a los modelos predictivos de cáncer de próstata mejora la exactitud en la estratificación del riesgo y ayuda en la toma de decisión sobre realizar una biopsia de próstata.

Introduction

Serum prostate-specific antigen (PSA) was the first marker used for the early diagnosis of prostate cancer (PCa); however, it is not very specific, with the consequences that this entails.[1] The free PSA fraction (fPSA) and the percentage of fPSA (% fPSA) significantly improve the discrimination between PCa and other benign situations, especially in patients with tPSA levels between 4 and 10 ng/ml.[2] The p2PSA molecule, an isoform of fPSA, and the prostate health index (PHI), which incorporates tPSA, fPSA and p2PSA in its calculation, improve the diagnostic accuracy of PCa and of clinically significant or aggressive disease.[3,4]

However, the calculation of the diagnostic accuracy in terms of reliability indexes, or the calculation of the area under the curve (AUC) are not enough to answer the following questions: what is the probability that a patient has of suffering from PCa? Or how can I stratify a patient's risk of having PCa? And, therefore, to whom should I biopsy and who benefits from the prostate biopsy?

The development of predictive models that make it possible to stratify and discriminate the risk, its calibration, and the development of decision curves could be more useful in clinical practice.[5,6] The purpose of this study is to analyze and validate the clinical usefulness of a predictive model of PCa that incorporates the biomarker '[-2] prostate-specific proantigen' through the PHI in the decision-making process to perform a prostate biopsy.

Material and methods

Prospectively and through an observational cohort design, between January 2015 and December 2016, 197 men were included with indication of first or successive prostate biopsy, who signed an informed consent for the inclusion in the study and for the extraction of a blood sample. The study was approved by the Hospital Ethics Committee. A tPSA 2–20 ng/ml or the presence of a suspicious digital rectal examination in men over 45 years of age was fixed as inclusion criterion. Patients with a history of taking 5-α-reductase inhibitors in the last 6 months and patients with a history of urinary tract infection or lower urinary tract manipulation in the 3 months prior to the biopsy indication were excluded from the study.

The clinical variables of interest (first or successive biopsy, age of the patients, and digital rectal examination), the laboratory variables (tPSA, fPSA, and p2PSA) and the findings in the analyzed biopsy samples (presence of cancer or not in biopsy and presence of at least one Gleason grade $\geq$7 in the biopsy) were collected. Two models were defined: PSA model (age, digital rectal examination, previous biopsy, and tPSA) and PHI model (age, digital rectal examination, previous biopsy, and PHI).

Blood samples were taken immediately before the biopsy, they were ultracentrifuged and frozen at −80° in the first 2 h after extraction to minimize the low stability of p2PSA at room temperature in serum.[7] Blindness was maintained for