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Predictive Value of Four Kallikrein Markers for Pathologically Insignificant Compared With Aggressive Prostate Cancer in Radical Prostatectomy Specimens: Results From the European Randomized Study of Screening for Prostate Cancer Section Rotterdam

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Abstract

Background: Treatment decisions can be difficult in men with low-risk prostate cancer (PCa).
Objective: To evaluate the ability of a panel of four kallikrein markers in blood—total prostate-specific antigen (PSA), free PSA, intact PSA, and kallikrein-related peptidase 2—to distinguish between pathologically insignificant and aggressive disease on pathologic examination of radical prostatectomy (RP) specimens as well as to calculate the number of avoidable surgeries.
Design, setting, and participants: The cohort comprised 392 screened men participating in rounds 1 and 2 of the Rotterdam arm of the European Randomized Study of Screening for Prostate Cancer. Patients were diagnosed with PCa because of an elevated PSA $\geq$3.0 ng/ml and were treated with RP between 1994 and 2004.
Outcome measurements and statistical analysis: We calculated the accuracy (area under the curve [AUC]) of statistical models to predict pathologically aggressive PCa (pT3–T4, extracapsular extension, tumor volume $>$0.5 cm^3, or any Gleason grade $\geq$4) based on clinical predictors (age, stage, PSA, biopsy findings) with and without levels of four kallikrein markers in blood.
Results and limitations: A total of 261 patients (67%) had significant disease on pathologic evaluation of the RP specimen. While the clinical model had good accuracy in predicting aggressive disease, reflected in a corrected AUC of 0.81, the four kallikrein

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markers enhanced the base model, with an AUC of 0.84 ($p < 0.0005$). The model retained its ability in patients with low-risk and very-low-risk disease and in comparison with the Steyerberg nomogram, a published prediction model. Clinical application of the model incorporating the kallikrein markers would reduce rates of surgery by 135 of 1000 patients overall and 110 of 334 patients with pathologically insignificant disease. A limitation of the present study is that clinicians may be hesitant to make recommendations against active treatment on the basis of a statistical model.

Conclusions: Our study provided proof of principle that predictions based on levels of four kallikrein markers in blood distinguish between pathologically insignificant and aggressive disease after RP with good accuracy. In the future, clinical use of the model could potentially reduce rates of immediate unnecessary active treatment.

1. Introduction

A high proportion of patients with screen-detected prostate cancer (PCa) do not have aggressive disease. It can be questioned whether a patient found to have pathologically insignificant disease on pathologic analysis of the radical prostatectomy (RP) specimen should have undergone immediate active treatment or should have been managed with surveillance. A commonly used definition of *pathologically insignificant PCa* in RP specimens is the one suggested by Epstein et al: organ-confined cancer with a volume ≤ 0.5 cm^3 without poorly differentiated elements (Gleason score ≤ 6) [1].

Prediction tools exist that take into account several clinical features that help to preoperatively distinguish pathologically insignificant from aggressive disease. These tools include prostate-specific antigen (PSA) and clinical stage, as well as biopsy variables such as transrectal ultrasound prostate volume, Gleason grade, number of positive biopsy cores, percentage of cancer in any core sample, total cancer length, and noncancer tissue in biopsy cores [2–6].

Currently available prediction tools have a discrimination in the area under the curve (AUC) range of 0.70–0.80; hence, there is room for improvement. Current models will classify some men as having pathologically insignificant disease who will eventually present with aggressive disease while on surveillance and will advise men to have invasive treatment who may actually have pathologically insignificant disease. There is a need for more optimal pretreatment decision tools that aim at reducing possible overtreatment of pathologically insignificant disease.

We have previously shown that a model based on levels of four kallikrein markers in blood—total PSA, free PSA, intact PSA, and kallikrein-related peptidase 2 (hK2)—has the ability to predict the result of prostate biopsy and that discrimination is improved for low-grade compared with high-grade disease [7,8]. We therefore hypothesized that this four-kallikrein model would also help distinguish between pathologically insignificant and aggressive disease on pathologic examination of the RP specimens, when used in addition to standard clinical predictors. We also aimed to evaluate whether this model could be used as a treatment decision aid, particularly in low-risk patients.

2. Methods

The cohort emerges from the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer (ERSPC). Men were invited for screening every fourth year. PCa was detected by lateralized sextant transrectal ultrasound–guided biopsy because of an elevated PSA $\geq$3.0 ng/ml. Our cohort comprised 392 screened men participating in rounds 1 and 2 (the first round took place during 1993–2000, and the second round 4 yr later for every participant) who were treated with RP between 1994 and 2004. The outcome, pathologically aggressive (nonindolent) disease on RP specimens, was defined as disease not confined to the prostate, tumor volume >0.5 cm^3, or Gleason grade >3.

The TNM 2002 classification was used for PCa staging. The volume of tumor foci was measured by computer-assisted morphometric analysis after carefully encircling tumor areas on the glass slides.

We built a base model predicting pathologically aggressive disease using logistic regression, including the following standard clinical features: age (age at blood draw for 369 men, age at clinical examination for 29 men), total PSA, number of positive biopsy cores, and millimeters of cancerous tissue (all modeled continuously) as well as Gleason score ($\leq$6, 7, and $\geq$8) and clinical stage (lower than T2b compared with T2b or higher). Originally 398 patients were included in the analysis before dropping 3 that were missing outcome data and 3 that were missing required clinical model data, leaving 392 men for analysis. The length of PCa in single-needle biopsies was calculated based on the tumor percentage of the total microscopic needle biopsy length. Discontinuous cancer foci within a single biopsy were considered as separate foci.

Clinically insignificant tumors preoperatively were defined according to the Epstein criteria [1] as PSA $<$10 ng/ml, biopsy Gleason score $\leq$6, clinical stage T2a or lower, two or fewer positive cores, and $\leq$50% of any one core involved with tumor.

The nomogram developed by Steyerberg et al [2] is frequently used in predicting pathologically insignificant disease on RP, building on the nomograms from Kattan et al [4]. The Steyerberg nomogram, however, requires more extensive pathologic examination (such as the length of noncancerous tissue in individual biopsy cores), which is not common practice at all hospitals. We therefore created our base model on clinical parameters that are available at virtually any hospital in which RPs are performed.

2.1. Laboratory methods

All laboratory analyses were conducted blind to biopsy results [9]. Serum samples were retrieved from the archival serum bank in Rotterdam, The Netherlands, where they were stored frozen at -80 °C after their initial processing $\leq$3 h from venipuncture. The samples were shipped frozen on dry ice to Malmö, Sweden, in 2005–2007. Analyses of free, total, and intact PSA, along with hK2, were done in Hans Lilja's laboratory at the Wallenberg Research Laboratories (Department of Laboratory Medicine, Lund University, Skåne University Hospital, Malmö, Sweden) during