European Randomized Study of Screening for Prostate Cancer Risk Calculator: External Validation, Variability, and Clinical Significance

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OBJECTIVE To externally validate the European Randomized Study of Screening for Prostate Cancer (ERSPC) risk calculator (RC) and to evaluate its variability between 2 consecutive prostate-specific antigen (PSA) values.

MATERIALS AND METHODS We prospectively catalogued 1021 consecutive patients before prostate biopsy for suspicion of prostate cancer (PCa). The risk of PCa and significant PCa (Gleason score ≥7) from 749 patients was calculated according to ERSPC-RC (digital rectal examination-based version 3 of 4) for 2 consecutive PSA tests per patient. The calculators' predictions were analyzed using calibration plots and the area under the receiver operating characteristic curve (area under the curve). Cohen kappa coefficient was used to compare the ability and variability.

RESULTS Of 749 patients, PCa was detected in 251 (33.5%) and significant PCa was detected in 133 (17.8%). Calibration plots showed an acceptable parallelism and similar discrimination ability for both PSA levels with an area under the curve of 0.69 for PCa and 0.74 for significant PCa. The ERSPC showed 226 (30.2%) unnecessary biopsies with the loss of 10 significant PCa. The variability of the RC was 16% for PCa and 20% for significant PCa, and a higher variability was associated with a reduced risk of significant PCa.

CONCLUSION We can conclude that the performance of the ERSPC-RC in the present cohort shows a high similitude between the 2 PSA levels; however, the RC variability value is associated with a decreased risk of significant PCa. The use of the ERSPC in our cohort detects a high number of unnecessary biopsies. Thus, the incorporation of ERSPC-RC could help the clinical decision to carry out a prostate biopsy. UROLOGY 102: 85–91, 2017. © 2016 Elsevier Inc.

Prostate cancer (PCa) has emerged as the most frequent cancer among men in Europe. It accounts for 22.8% of newly diagnosed cases of cancer in European men.[1] Since the introduction of prostate-specific antigen (PSA) for early detection of PCa, the rate of diagnosis has increased, and metastatic disease and specific mortality have been reduced in most western countries.[2] However, one of its drawbacks is that it is an organ-specific marker, but it has a bad specificity and high variability of up to 20% (10%-20%),[3] so at least 2 values are recommended before indicating a prostate biopsy.[4] Nowadays, there is no consensus-based recommendation with regard to population screening owing to the proven risk of overdiagnosis and overtreatment in a considerable number of patients.[5]

In an attempt to resolve these problems, many RNA, DNA, and protein-based biomarkers in urine, blood, and tissue samples have been studied. Also, some emerging areas of study including microRNA, long noncoding RNA, metabolomics, exosomes, and microbiota are being explored.[6-8] They are expensive and not routinely used in clinical practice, so usually a digital rectal examination (DRE) and PSA are the most widely used tools to select patients for prostate biopsy.

Nomogram-based PCa risk calculators (RC) are easy and accessible tools that have been developed to help clinicians in this selection process. Three of the most used are those from the Prostate Cancer Prevention Trial (PCPTcohort;

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PCPT-RC) (http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp), from the European Randomized Study of Screening for Prostate Cancer (ERSPC cohort; ERSPC-RC) (http://www.prostatecancer-riskcalculator.com/seven-prostate-cancer-riskcalculators), and from a local Canadian cohort (http://sunnybrook.ca/content/?page=occ-prostatecalc) whose original versions have been widely validated externally.[9] Recently, PCPT-RC and ERSPC-RC have incorporated some modifications,[10,11] which have not been externally validated to the same extent.[12] One of these validation cohorts has also shown that ERPSC-RC slightly outperformed PCPT-RC version 2.0 for significant PCa.[13] However, the variability of this RC between 2 consecutive PSA levels has not been analyzed, and further external validations are required.

The present study aimed to externally validate the new ERSPC-RC, analyze its variability between 2 consecutive PSA levels, and evaluate its clinical significance.

MATERIALS AND METHODS

Study Population and Design

An observational study was performed on patients from the ONCOVER cohort who underwent an ultrasound-guided prostate biopsy from January 2013 to July 2015. Clinical follow-up was 22 months (range 14-32).

The ONCOVER cohort is a group of 1021 patients who have donated blood and urine in the same morning conditions before undergoing prostate biopsy according to clinical practice.

The project was approved by the Reina Sofia Hospital Research Ethics Committee, and informed consent was obtained from all participants.

Inclusion criteria among the ONCOVER cohort are the following:

- The indications for undergoing a prostate biopsy were suspicious findings on DRE, PSA >10 ng/mL, or PSA 3-10 ng/mL if free PSA ratio <25% in those with a PSA of 3-10 ng/mL, and persistently elevated or rising PSA in those previously biopsied. Following European Association of Urology guidelines, at least 2 PSA levels were needed to indicate a prostate biopsy.
- PSA <50 ng/mL.
- full clinical and laboratory data to calculate ERSPC-RC
- 2 consecutive PSA levels within an interval of 12 weeks
- pathology biopsy results

Exclusion criterion was previously known PCa diagnosis.

Prostate Biopsy and Pathologic Analysis

A transrectal ultrasound (TRUS)-guided prostate biopsy was carried out under local anesthesia by using a standard periprostatic block, a TRUS transducer, and a 16-gauge automated needle biopsy instrument. The prostatic volume was measured, and 12 biopsy cores were obtained in patients undergoing their first biopsy, and a minimum of 16 cores were taken for those previously biopsied. All biopsy specimens were analyzed by a single urologic pathologist according to International Society of Urological Pathology 2005 modified criteria.[14]

Main Variables Description

Two PSA levels were measured within a variable period no higher than 12 weeks.

PSA 1: PSA level of biopsy indication.
PSA 2: PSA level before undergoing prostate biopsy.
Prostate volume: Prostate volume estimated by TRUS and categorized in 3 possible values, 25, 40, and 60 mL, as recommended[10] (TRUS volume <30 = 25, 30-50 = 40, and ≥50 = 60 mL).
Significant prostate cancer/high grade (HG): PCa with Gleason grade ≥7 on biopsy.
ERSPC-RC: ERSPC-RC 3 + DRE formula for patients at initial biopsy and the ERSPC-RC 4 + DRE for patients at repeat biopsy were used in this study. These calculators use PSA, prostate volume, and DRE examination as variables, with the information of a negative prostate biopsy in ERSPC 4 + DRE in patients previously biopsied. ERSPC-RC gives a probability of PCa and ERSPC/HG gives a probability of significant/high-grade or advanced PCa (Gleason ≥ 7 or T stage > 2B).
1 ERSPC/HG (1 Measure): Risk probability calculated by ERSPC-RC 3 or 4 ± DRE (depends on previous biopsy) for PCa using PSA 1/HG—for significant PCa (www.prostatecancer-riskcalculator.com).
2 ERSPC/HG (2 Measure): Risk probability calculated by ERSPC-RC 3 or 4 ± DRE (depends on previous biopsy) for PCa using PSA 2/HG—for significant PCa (www.prostatecancer-riskcalculator.com).

Biopsy indication according to ERSPC-RC recommendation: ≥20% of PCa or between 12.5% and 20% for any cancer and ≥4% for significant PCa.

Variability of PSA and ERSPC probability risk were calculated by this formula:

$$|1\ \text{Measure} - 2\ \text{Measure}|/1\ \text{Measure}$$

Statistical Analysis

A descriptive study was performed by calculating the median and interquartile ranges for the quantitative variables and the absolute frequencies and percentages for the qualitative variables.

The calibration and discrimination ability of the RC were assessed with both PSA measurements. The discrimination was measured using the receiver operating characteristic curve and summarized by the area under the curve (AUC). To compare the accuracy between the 2 receiver operating characteristic curves, the DeLong test was applied.

Calibration that shows the agreement between the frequency of observed outcome and the predicted probabilities was studied using graphical representations of the relationship between the 2 calibration curves.

Decision curve analyses were performed for the assessment of the net benefit according to different threshold probabilities that denote at which point one would consider a biopsy.

We analyzed age as a possible additional predictor within the RC. An evaluation with 250 repetitions of 10-fold cross validation was carried out.

To study the agreement between the RC with both PSA measures and the best cutoff value to diminish the variability, a Cohen kappa test was used.

A Cox proportional hazard model was used in multivariate analysis to assess the association of the ERSPC variability with the biopsy result adjusted by the calculated ERPSC risk.

SPSS Statistics 17.0 (SPSS Inc., Chicago, IL) and R version 3.2.3 software were used to analyze the data, and a *P* value of less than .05 was deemed to be significant.

RESULTS

External Validation

Of 1021 patients, 749 who met inclusion criteria were finally analyzed. Causes of patient exclusion for analysis are described in Supplementary Table S1. The median age was 66 years (interquartile range: 60-71). A total of 251 of 749 (33.5%) patients were diagnosed with PCa and 133 of 749 (17.8%) were diagnosed with significant PCa. Clinical and demographic variables are shown in Supplementary Table S2, and Table 1 shows them according to biopsy results. During follow-up, 105 patients underwent a new prostate biopsy, according to each clinician's indication, diagnosing 17 more patients with PCa, and only 10 of them are clinically significant.

The calibration plots of the ERSPC-RC showed that there is an acceptable parallelism at most axis values. Models underestimate the risk of small risk values and overestimate for higher risk values with both PSA 1 and 2 (Fig. 1).

The discriminative ability for the detection of PCa and significant PCa was not significantly different between 1 ERSPC and 2 ERSPC (as shown in Supplementary Fig. S1) with an AUC of 0.68 (95% confidence interval [CI]; 0.64-0.72) and 0.69 (95% CI; 0.65-0.74) for PCa and 0.74 (95% CI; 0.70-0.79) and 0.74 (95% CI; 0.70-0.79) for significant PCa, respectively. Taking into account PCa diagnoses during follow-up, we found that the discriminative ability of the RC did not change significantly.

The decision curve analyses revealed that RCs in both PSA groups provided a clinical net benefit from the threshold probability of 0.22 for PCa and from 0.09 for significant PCa (Fig. 2).

Taking into account ERSPC cutoff recommendations, accuracy when a prostate biopsy with 1 ERSPC was indicated was worse with an AUC of 0.64 (95% CI; 0.59-0.68) for significant PCa.

However, if 1 ERSPC had been calculated before indicating a biopsy in this cohort, 226 of 749 biopsies would have been avoided (30.2%), misdiagnosing 40 PCa of which only 10 would have been clinically significant (7.5% of all significant PCa). This means a negative predictive value (NPV) of 0.82 for PCa and 0.96 for significant PCa, with a lower positive predictive value of 0.40 and 0.24, respectively.

When only patients with PSA lower than 10 ng/mL in whom the nomogram is more relevant are considered, among 613 biopsies with 92 significant PCa diagnoses, 197 (32.1%) biopsies would have been avoided, misdiagnosing 7 significant PCa (7.6%) (NPV = 96.4% and positive predictive value = 20.4%).

Adding the age as a variable for the RC, we found the analysis shows improved accuracy of the 1 ERSPC for PCa (AUC 0.73 vs 0.69; $P < .05$) (Fig. S2) but not for significant PCa (data not shown).

Variability of ERSPC-RC

Considering all the cohort, we found that the accuracy of both ERSPC-RC probabilities was not different (Fig. S1). However, median variability of ERSPC-RC probabilities was 0.20 (0.0-0.5) for PCa and 0.17 (0.07-0.33) for significant PCa.

Concordance in the indication of a prostate biopsy between 1 ERSPC and 2 ERSPC was K = 0.71 ($P < .001$) (Table S3). The agreement between positive biopsy classifiers is locally maximal at 0.2, whereas there is no clear optimal threshold for high-grade tumor classifiers. Both coefficients become noisy for high thresholds, where neither classifier is useful (Fig. 3). Of the total cohort, 96 of 749 patients (12.8%) changed the indication of biopsy between 1 ERSPC-RC and 2 ERSPC-RC; 72 of 749 patients with an indication of prostate biopsy according to 1 ERSPC-RC had no indication in 2 ERSPC (Table S3), with 8 of 72 (11%) resulting in significant PCa.

A higher variability between probabilities of ERSPC/HG-RC was independently associated with a reduced

Table 1. Clinical and demographic characteristics categorized according to biopsy results

Variable	No PCa N = 498	PCa N = 251	Significant PCa N = 133
Age (y)	64.5 (59-7)	68 (63-73)	70 (64-76)
Family history	89 (17.9)	44 (17.8)	22 (16.5)
Positive DRE	53 (10.6)	79 (31.5)	49 (36.8)
PSA 1 (ng/mL)	5.7 (4.3-8.3)	6.4 (4.5-9.7)	7.0 (5.0-11.2)
PSA 2 (ng/mL)	5.1 (3.7-7.1)	5.9 (4.1-9.3)	6.2 (4.4-10.5)
Prostate volume (cm^3)	40 (25-60)	25 (25-40)	25 (25-40)
First biopsy	363 (72.9)	204 (81.3)	114 (85.7)
1 ERSPC	0.22 (0.13-0.36)	0.37 (0.22-0.59)	0.44 (0.27-0.70)
1 ERSPC/HG	0.06 (0.02-0.12)	0.12 (0.05-0.34)	0.17 (0.07-0.49)
2 ERSPC	0.19 (0.11-0.33)	0.34 (0.19-0.54)	0.44 (0.24-0.64)
2 ERSPC/HG	0.04 (0.02-0.10)	0.11 (0.04-0.29)	0.17 (0.06-0.41)

1 ERSPC/HG, probability of PCa and high-grade PCa using the 1° serum PSA; 2 ERSPC/HG, probability of PCa and high-grade PCa using the 2° serum PSA; DRE, digital rectal examination; PCa, prostate cancer; PSA 1, PSA level of biopsy indication; PSA 2, PSA level before undergoing prostate biopsy; PSA, prostate-specific antigen; Significant PCa, Gleason ≥7 on biopsy.
Values expressed in median and interquartile range for quantitative variables, and absolute and percentage for qualitative variables.

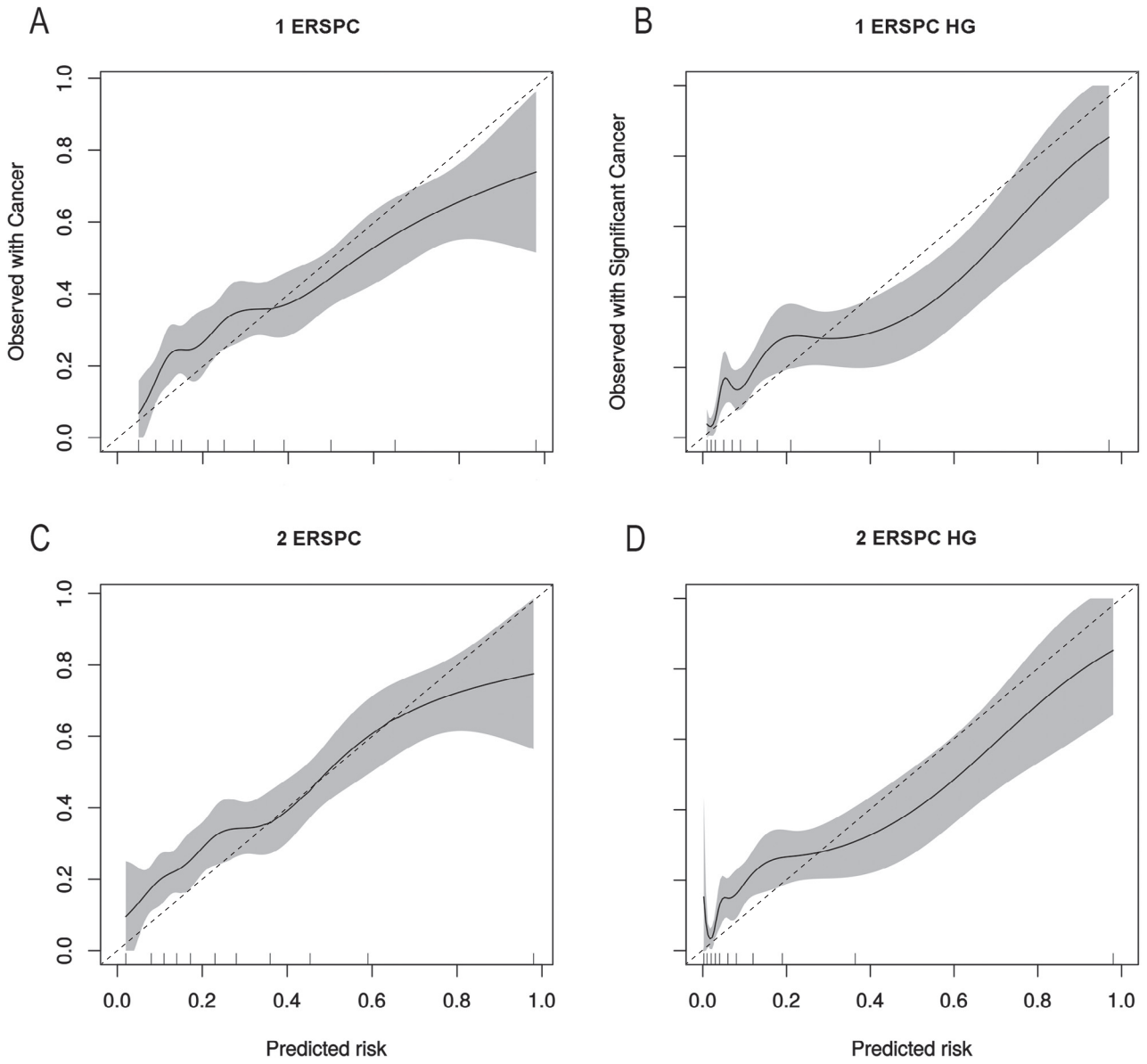

Figure 1. Calibration plots for the European Randomized Study of Screening for Prostate Cancer risk calculator (ERSPC-RC). The x-axis shows predicted probabilities of the models and the y-axis shows observed probabilities. The dashed line represents perfect predictions. The solid line refers to predicted vs observed event rates with grouped patients and the gray area refers to the confident interval. **(A,B)** Results for cancer and significant prostate cancer for 1 ERSPC, respectively. **(C,D)** Results for cancer and significant prostate cancer for 2 ERSPC, respectively. HG, high grade. (Color version available online.)

risk of significant PCa on biopsy as shown in Table S4, but its addition to the nomogram did not increase the accuracy of the RC with an AUC of 0.73 (95% CI; 0.67-0.78).

DISCUSSION

Nowadays, there is still a real problem when dealing with a patient with high PSA levels. It is well known that despite PSA organ-specific properties, its accuracy for PCa diagnoses is not too accurate; 2 of its problems are specificity and variability.[15]

PSA variability has been calculated by different authors to be around 10%-20% between different periods in theoretical basal situations.[16,17] Thus, it is recommended not to perform a prostate biopsy with only 1 PSA value and to confirm its levels again, with no specific time between the 2 measures.[3,4]

PCa RCs improved PSA accuracy and are easily available simple tools, which can be used in clinical practice. Recently, Poyet et al[13] and Foley et al[18] carried out a direct comparison and validation of a new version of ERSPC and PCPT RC, showing less accuracy than in their original cohorts and ERSPC-RC outperformed PCPT-RC for significant PCa.

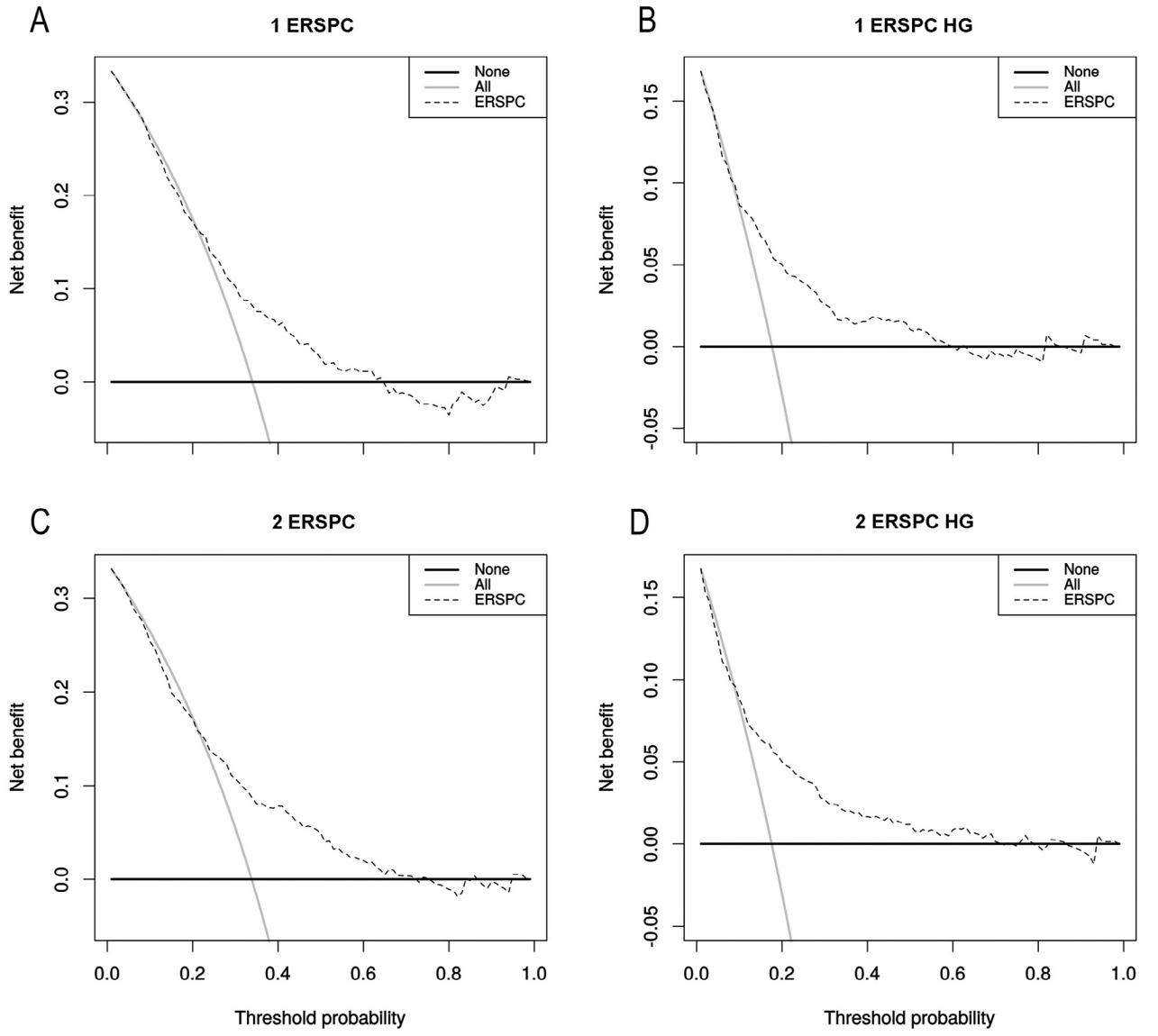

Figure 2. Decision curve analysis for the prediction of prostate cancer (PCa) or significant PCa using the European Randomized Study of Screening for Prostate Cancer risk calculator (ERSPC-RC). The horizontal line along the x-axis assumes that no patient will have significant prostate cancer, whereas the solid gray line assumes that all patients will have PCa or significant PCa. **(A,B)** Results for PCa and significant PCa for 1 ERSPC, respectively. **(C,D)** Results for PCa and significant PCa for 2 ERSPC, respectively.

One of the reasons for the improved accuracy of ERSPC-RC, and its outperformance of others such as PCPT, is the use of prostate volume calculated by TRUS.[9,18] Including TRUS as a predictor in a risk model to be used in a routine screening program could pose some problems as currently this would require general practitioners to refer patients to urology specialists, and not all urologists have TRUS available in the clinic. Also, despite not being painful or invasive, this could increase psychosocial distress that may already occur from screening or opportunistic diagnoses.[19] The use of prostate volume estimation by DRE categorized in 3 possibilities has been incorporated to the ERSPC-RC, showing a good correlation with the median volume calculated by TRUS and also maintaining their predictive accuracy.[10]

Our study methodology is similar to that used by Poyet et al[13] and Foley et al[18] with the same limitation, categorizing prostate volume from TRUS measures and not from DRE estimation. This allows a direct comparison in the performance of the RC in our different cohorts. As shown in our results, the accuracy of the RC in our cohorts is similar to theirs, around 0.7 for PCa and 0.74 for significant PCa. These results are in accordance with the knowledge of reduced accuracy capacity of nomograms in external validations.[20]

When we evaluated the correspondence between the predicted probabilities of the model in our validation series and the real incidence of PCa, we observed that the model has an acceptable parallelism for most values but underestimates the real number of cancers in low-risk values and

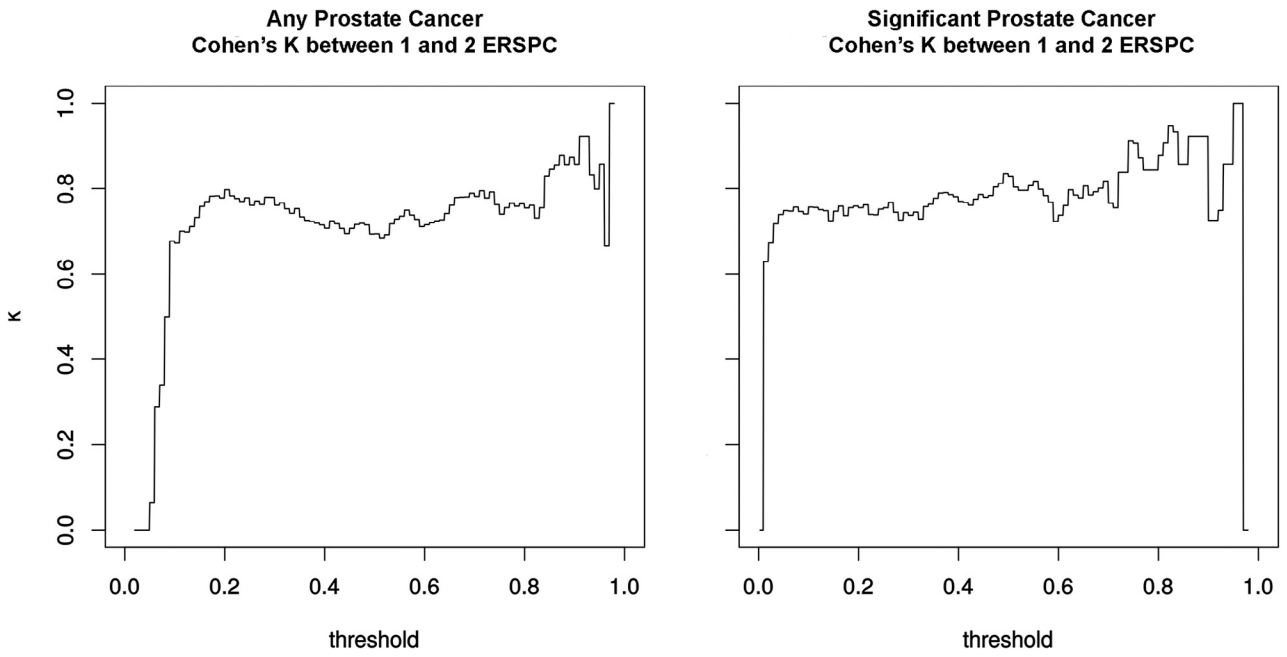

Figure 3. Cohen κ inter-rater agreement coefficient between prostate-specific antigen (PSA) 1 and PSA 2 classifiers as a function of the decision threshold.

overestimates in high-risk values as described in the calibration plots.

The variability of the RC between 2 consecutive PSA values is not insignificant. The median of absolute variability of the RC was 0.16 for PCa and 0.2 for significant PCa, which was similar to the variability published for PSA,[3,16,17] emphasizing the high weight of this variable in the RC. This result of variability implied a change in biopsy indication in approximately 100 patients, which mean that although the accuracy of RC with both PSA were similar in all the cohort, taking an individual approach would have changed the indication of biopsy in a considerable amount of patients. Nevertheless, in our cohort, Cohen κ test result suggests that the use of a threshold near 0.2 would make the classifier robust to variations in measured PSA for positive biopsy diagnoses, in agreement with ERSPC recommendations.

Furthermore, a higher absolute variation in the risk value between the 2 measures was associated with a decreased risk of significant PCa, but it did not increase the accuracy of the RC for PCa or significant PCa. Similar results, but only taking into account the PSA value, have recently been published by Nordstrom et al.[21] They found that those patients with a PSA of 3-10 ng/mL and an increase or decrease of more than 20% in 8 weeks were associated with a reduced probability of Gleason 7 or higher.

Our results show that the introduction of this RC could save a considerable number of prostate biopsies without misdiagnosing a great number of significant PCa, reaching an NPV of 0.96. These results emphasize the need to encourage urologists to use these easily available tools in clinical practice. Despite the fact that with the introduction of magnetic resonance imaging (MRI) the utility of these RCs could be reduced,[22] Alberts et al[23] have recently shown that a risk-based patient selection for MRI-targeted prostate biopsy, after a negative biopsy, could avoid unnecessary MRI scans.

Finally, this study has a few limitations that should be addressed. First, this is a retrospective study, which results in categorizing prostate volume calculated by TRUS instead of by DRE estimation. Second, the interval of PSA measures was not the same for all patients. This fact means we should interpret with caution the variability of the PSA, but it also reflects real clinical practice and is a similar approach as other authors have used, such as Komatsu et al,[16] in which the interval of time between PSA measures is not exact.

Despite the limitations of our study, we can conclude that the use of ERSPC-RC would improve our management and clinical decision to indicate prostate biopsies, avoiding an important number of unnecessary biopsies and overdiagnoses. The ERSPC-RC thresholds fit well with our Mediterranean cohort, and the PSA variations have less influence. Finally, a higher RC variability between 2 consecutive PSA measures is associated with a decreased risk of Gleason 7 or more.

Thus, further studies are necessary to clarify the role of this RC with novel biomarkers and imaging techniques and to study prospectively the role of its variability.

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APPENDIX

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.urology.2016.11.004.