



Comparing the prediction of prostate biopsy outcome using the Chinese Prostate Cancer Consortium (CPCC) Risk Calculator and the Asian adapted Rotterdam European Randomized Study of Screening for Prostate Cancer (ERSPC) Risk Calculator in Chinese and European men

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Abstract

Purpose To externally validate the clinical utility of Chinese Prostate Cancer Consortium Risk Calculator (CPCC-RC) and Asian adapted Rotterdam European Randomized Study of Screening for Prostate Cancer Risk Calculator 3 (A-ERSPC-RC3) for prediction prostate cancer (PCa) and high-grade prostate cancer (HGPCa, Gleason Score $\geq 3+4$) in both Chinese and European populations.

Materials and methods The Chinese clinical cohort, the European population-based screening cohort, and the European clinical cohort included 2,508, 3,616 and 617 prostate biopsy-naive men, respectively. The area under the receiver operating characteristic curve (AUC), calibration plot and decision curve analyses were applied in the analysis.

Results The CPCC-RC's predictive ability for any PCa (AUC 0.77, 95% CI 0.75–0.79) was lower than the A-ERSPC-RC3 (AUC 0.79, 95% CI 0.77–0.81) in the European screening cohort ($p < 0.001$), but similar for HGPCa ($p = 0.24$). The CPCC-RC showed lower predictive accuracy for any PCa (AUC 0.65, 95% CI 0.61–0.70), but acceptable predictive accuracy for HGPCa (AUC 0.73, 95% CI 0.69–0.77) in the European clinical cohort. The A-ERSPC-RC3 showed an AUC of 0.74 (95% CI 0.72–0.76) in predicting any PCa, and a similar AUC of 0.74 (95% CI 0.72–0.76) in predicting HGPCa in Chinese cohort. In the Chinese population, decision curve analysis revealed a higher net benefit for CPCC-RC than A-ERSPC-RC3, while in the European screening and clinical cohorts, the net benefit was higher for A-ERSPC-RC3.

Conclusions The A-ERSPC-RC3 accurately predict the prostate biopsy in a contemporary Chinese multi-center clinical cohort. The CPCC-RC can predict accurately in a population-based screening cohort, but not in the European clinical cohort.

Keywords Prostate cancer · Biopsy · Risk calculators · Asian populations · Net benefit · Clinical prediction model · External validation

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Introduction

Prostate cancer (PCa) is the most prevalent malignancy in male in western countries, and account for one-quarter of new malignancy diagnoses in men in the United States [1]. The PCa incidence is lower in Asian countries [2, 3]. This could be caused by racial differences and/or different screening strategies [4]. In western populations, PCa screening with a purely PSA based biopsy indication leads to unnecessary biopsies [5]. Would prostate cancer screening with a comparable PSA cut-off be applied in the Chinese population it would likely lead to even more unnecessary biopsies,

giving the lower PCa detection rate at similar PSA levels in the Chinese population [6].

Risk calculators (RC) have been developed to aid physicians in shared decision making before taking the actual prostate biopsy and have shown to reduce unnecessary biopsies by more than 30% [7]. However, the application of western-developed risk calculators in Asian countries might yield lower predictive performance. Recently published studies in Korean [8] and Chinese populations [9] showed that the Rotterdam European Randomized Study of Screening for Prostate Cancer Risk Calculator 3 (ERSPC-RC3) and Prostate Cancer Prevention Trial risk calculator (PCPT-RC) overestimate the risk of PCa. Therefore, the development of Asian-specific RCs for Asians including Chinese is desired. The Chinese Prostate Cancer Consortium Risk Calculator (CPCC-RC) was developed using multi-center clinical data from Chinese men to predict biopsy outcomes. This RC showed good predictive performance after external validation [10]. Recently, the ERSPC-RC3 was adapted to the Asian setting, showing excellent discrimination and calibration in Hong Kong-based development and external validation cohorts [11].

In this study, we assessed the generalizability and clinical usefulness of both the CPCC-RC and the Asian-adapted ERSPC-RC3 (A-ERSPC-RC3) by externally validating these RCs in a contemporary multi-center Chinese clinical cohort and a multi-center European clinical cohort. In addition, considering the lower prevalence of PCa in Asia, we also evaluated the performance of the CPCC-RC in the ERSPC Rotterdam population-based screening cohort. All men included in this study were biopsy naive.

Methods

Study population

This study is approved by Ethical review board of Changhai Hospital. The Chinese validation cohort included 2,508 referred men from five hospitals who were enrolled from January 2010 to December 2013. These men were not included in the development cohort of the CPCC-RC [10]. Biopsy indication was PSA ≥ 4.0 ng/ml, abnormal digital rectal examination (DRE), or a suspicious lesion on transrectal ultrasound (TRUS) imaging. They received 8–12 systematic TRUS-guided biopsy cores, with no targeted biopsies were performed. Patient's characteristics were prospectively gathered; %freePSA (freePSA/total PSA) and prostate volume was missing in 116 and 33 men, respectively. Missing data were imputed using all variables which were used in the development of both models. Imputation was executed by Multivariate Imputation by Chained Equations (MICE) and was repeated five times [12].

The European screening cohort consists of 3616 men biopsied at the first round of screening in the Rotterdam ERSPC section from November 1993 to March 2000. Biopsy indication was PSA ≥ 3.0 ng/ml or abnormal DRE finding. All patients underwent lateral sextant biopsies and extra biopsies whether a hypo-echogenic lesion was found. Detailed characteristics of this study and data management have been described previously [5, 13]. This cohort is the development cohort of the original ERSPC-RC3.

The European clinical cohort consisted of 617 men from four different sites (Berlin, Münster, Paris, Rennes). Men were referred for further assessment based on a PSA ≥ 4.0 ng/ml and/or suspicious DRE. These men were not a part of the development of the ERSPC-RCs. They received standard clinical health care at each participating site (≥ 10 cores transrectal ultrasound biopsies). Data on PSA, %freePSA, DRE, prostate volume and biopsy outcome were collected. Two men had no data on prostate volume and DRE finding; in these men the mean value of the prostate volume was used and DRE was set on normal.

Outcome measurements and prediction models

The primary endpoint was the presence of histologic adenocarcinoma on biopsy graded with Gleason score [14]. High-grade (HG) PCa was defined as Gleason score ≥ 7 , other prostate cancers were defined as low-grade prostate cancer (LGPCa) [15]. The A-ERSPC-RC3 was adjusted for the Asian setting by changing the intercept of the constant and was validated in more than 2000 Chinese men [16]. The A-ERSPC-RC3 includes PSA, TRUS measured prostate volume, DRE and TRUS abnormality. The CPCC-RC included PSA, TRUS measured prostate volume and DRE abnormality, but no TRUS abnormality, while age and %freePSA were included in the model.

Statistical analysis

Baseline characteristics of patients with PCa, LGPCa, and HGPCa were compared using the Mann–Whitney *U* test for continuous data and chi-square test for categorical data. For each risk calculator, the predicted probabilities for the presence of any PCa and HGPCa were calculated. The accuracy of the prediction models was assessed in each cohort by discrimination and calibration properties. The discriminative power of the prediction models for the presence of any PCa or HGPCa versus men without PCa was determined by the area under the receiver operating characteristic curve (AUC). Thousand bootstrap samples were created to test significance between the AUCs.

For calibration, the observed percentages of men with presences of PCa were plotted against the predicted probability of men having PCa after dividing the predicted

probabilities into deciles. For every decile, we calculated the 95% CI of the observed percentage of responders. In addition, a histogram was made for the actual frequency of the predicted probabilities. The goodness-of-fit of the data to the predictions was evaluated by the Hosmer–Lemeshow test. Statistical analyses were performed in R statistical package, version 3.3.1. A p value < 0.05 was considered statistically significant.

Results

Comparison of patients' characteristics

Men in the Chinese cohort had a median age of 69 years (IQR 63–75) and the median number of biopsy cores of 10 (IQR 8–12). PCa was found in 857 (34%) men and 599 (24%) men had HGPCa. In the European screening cohort and the clinical cohort, the median age was 64 years and 65 years, respectively. PCa was present in 885 (25%) and 290 (47%) men, while HGPCa was present in 313 (9%) and 142 (23%) men, respectively. Furthermore, men from the Chinese cohort had a larger prostate volume and a higher PSA level (Table 1).

External validation in the European screening cohort

The CPCC-RC had slightly lower predictive ability for any prostate cancer (AUC 0.77, 95% CI 0.75–0.79) than the A-ERSPC-RC (AUC 0.79, 95% CI 0.77–0.81, $p < 0.01$). For HGPCa, similar predictive ability between the CPCC-RC (AUC 0.86, 95% CI 0.83–0.88) and the A-ERSPC-RC (AUC 0.86, 95% CI 0.84–0.89, $p = 0.24$) was found (Table 2). Calibration plots showed that the CPCC-RC would generally underestimate the risk of any PCa in the European screening cohort by 10–15%. However, the CPCC-RC showed good calibration for HGPCa, especially at lower risk thresholds (Fig. 1a, b). Decision curve analysis showed a higher net benefit for the CPCC-RC above the risk threshold of 7.5% for any PCa and 4% for HGPCa in comparison to a biopsy all scenario men, (Fig. 2a, b). Net-benefit for the A-ERSPC-RC3 was even higher than the CPCC-RC.

External validation in the European clinical cohort

Validation of the CPCC-RC in the European clinical cohort had a moderate discriminative ability in predicting any PCa (AUC 0.65, 95% CI 0.61–0.70), and good discriminative ability in predicting HGPCa (AUC 0.73, 95% CI 0.69–0.77). The A-ERSPC-RC had a similar discrimination for any PCa (AUC 0.65, 95% CI 0.60–0.69, $p = 0.79$) and lower discrimination for HGPCa (AUC 0.69, 95% CI 0.65–0.73, $p < 0.01$).

Calibration analyses showed that the CPCC-RC would generally underestimate the risk of both any PCa and HGPCa in the European clinical cohort (Fig. 1c, d). Decision curve analysis for any PCa and HGPCa showed no improvement in net benefit when using the CPCC-RC or the A-ERSPC-RC in the European clinical dataset (Fig. 2c, d).

External validation in the Chinese cohort

External validation of A-ERSPC-RC3 in the Chinese clinical cohort showed an AUC of 0.74 (95% CI 0.72–0.76) in predicting any PCa, and a similar AUC of 0.74 (95% CI 0.72–0.76) in predicting HGPCa. These AUC's are significantly lower than the AUC's of the CPCC-RC (0.77, 95% CI 0.74–0.77, $p < 0.001$) and 0.77 (95% CI 0.75–0.79, $p < 0.001$), respectively. Calibration plots showed that the A-ERSPC-RC3 underestimated the risk of any PCa in the risk range of 0–40% and overestimated the risk in the risk range over 60%. The CPCC-RC, on the contrary, underestimated the risk of any PCa in higher risk ranges (30%–100%) but was well-calibrated in the risk range of 0–30% (Fig. 1e). Also for the prediction of HGPCa, the CPCC-RC was better calibrated than the A-ERSPC-RC3 in most risk ranges. The A-ERSPC-RC3 underestimated the risk of HGPCa in the risk range of 0–40% and overestimated the risk in the risk range of 60–100% (Fig. 1f). Improvement in net benefit was found for the CPCC-RC at risks of 12.5% and above for any PCa and 8% or more for HGPCa (Fig. 2e, f). For the A-ERSPC-RC, an improvement in net benefit was found from a risk threshold of 20% onward for any PCa and 15% for HGPCa. Higher net benefit was found for the CPCC-RC than for the A-ERSPC-RC3. At a 10% risk threshold for predicting HGPCa, the biopsy reduction is 25% for the CPCC-RC and 28% for A-ERSPC-RC. This threshold would result in missing 8% (CPCC-RC) and 10% (A-ERSPC-RC) of the HGPCa diagnoses (Table 3). The use of CPCC-RC would avoid an additional 6.8 biopsies per 1000 men at risk compared to the A-ERSPC-RC. At the 10% risk threshold the CPCC has a net benefit of 0.16. This implies that to avoid one unnecessary biopsy, without increasing the percentage of missed diagnoses of HGPCa, the CPCC-RC should be applied to six men.

Discussion

The A-ERSPC-RC3 which originated from the original ERSPC-RC can accurately predict the outcome of prostate biopsy in a contemporary Chinese multi-center clinical cohort [11]. However, the calibration plots showed an underestimation of the probability of detecting PCa on biopsy in the Chinese external validation cohort used in the current analyses. This underestimation is probably attributable to

Table 1 Characteristics of patients with and without prostate cancer in the Chinese cohort, European screening and clinical cohort

Characteristics	Chinese clinical cohort, <i>n</i> = 2508			EU screening cohort, <i>n</i> = 3616			EU clinical cohort, <i>n</i> = 617			
	No PCa <i>n</i> = 1651 (66%)	LGPCa <i>n</i> = 258 (10%)	HGPCa <i>n</i> = 599 (24%)	No PCa <i>n</i> = 2731 (76%)	LGPCa <i>n</i> = 572 (16%)	HGPCa <i>n</i> = 313 (9%)	No PCa <i>n</i> = 327 (53%)	LGPCa <i>n</i> = 148 (24%)	HGPCa <i>n</i> = 142 (23%)	<i>p</i> value
Age, median (IQR) (years)	67 (61–74)	70 (66–75)	72 (65–77)	<0.001	66 (61–70)	68 (64–71)	63 (57–68)	62 (58–68)	67 (61–71)	<0.001
PSA, median (IQR), (ng/ml)	10.0 (6.5–15.3)	11.3 (7.5–17.1)	15.7 (9.1–24.9)	<0.001	4.0 (2.5–5.7)	5.1 (3.7–7.4)	7.8 (4.8–16.0)	4.6 (3.6–5.7)	5.6 (4.4–6.8)	<0.001
Free PSA ratio, median (IQR)	15.0 (10.3–21.4)	13.6 (8.8–20.2)	11.3 (7.5–17.0)	<0.001	21.8 (16.9–27.9)	17.0 (11.9–23.7)	12.1 (8.2–17.4)	14.8 (11.0–19.4)	11.4 (8.7–15.4)	<0.001
No. of biopsy cores, median (IQR)	10 (8–12)	10 (8–12)	8 (8–12)	<0.001	NA	NA	NA	12 (10–12)	10 (10–12)	<0.001
Prostate volume, median (IQR), (ml)	47 (32–69)	37 (27–54)	34 (25–48)	<0.001	43 (33–57)	37 (29–50)	37 (29–47)	41 (25–54)	31 (25–41)	<0.001
No. of suspicious DRE, <i>n</i> (%)	403 (24)	77 (30)	228 (38)	<0.001	836 (31)	236 (41)	207 (66)	49 (33)	58 (41)	<0.001

p value is calculated between LGPCa/no PCa and HGPCa

PSA prostate-specific antigen, DRE digital rectal examination, IQR interquartile range, PCa prostate cancer, HGPCa high-grade prostate cancer, LGPCa low-grade prostate cancer, EU European, NA not available

Table 2 Area under the receiver operating characteristic curve for the Chinese Prostate Cancer Consortium Risk Calculator and the Asian adapted Rotterdam European Randomized Study of Screening for Prostate Cancer Risk Calculator 3 predicting any PCa or HGPCa in the three cohorts

Cohort-RC	Any PCa (95% CI)	<i>p</i> value	HGPCa (95% CI)	<i>p</i> value
EU screening				
CPCC-RC	0.77 (0.75–0.79)		0.86 (0.83–0.88)	
A-ERSPC-RC3	0.79 (0.77–0.81)	< 0.01	0.86 (0.84–0.89)	0.24
EU clinical				
CPCC-RC	0.65 (0.61–0.70)		0.73 (0.69–0.77)	
A-ERSPC-RC3	0.65 (0.60–0.69)	0.79	0.69 (0.65–0.73)	< 0.01
Chinese				
CPCC-RC	0.77 (0.74–0.77)		0.77 (0.75–0.79)	
A-ERSPC-RC3	0.74 (0.72–0.76)	< 0.01	0.74 (0.72–0.76)	< 0.01

PCa prostate cancer, HGPCa high-grade prostate cancer, EU European, CPCC-RC Chinese Prostate Cancer Consortium Risk Calculator, A-ERSPC-RC3 Asian adapted Rotterdam European Randomized Study of Screening for Prostate Cancer Risk Calculator 3

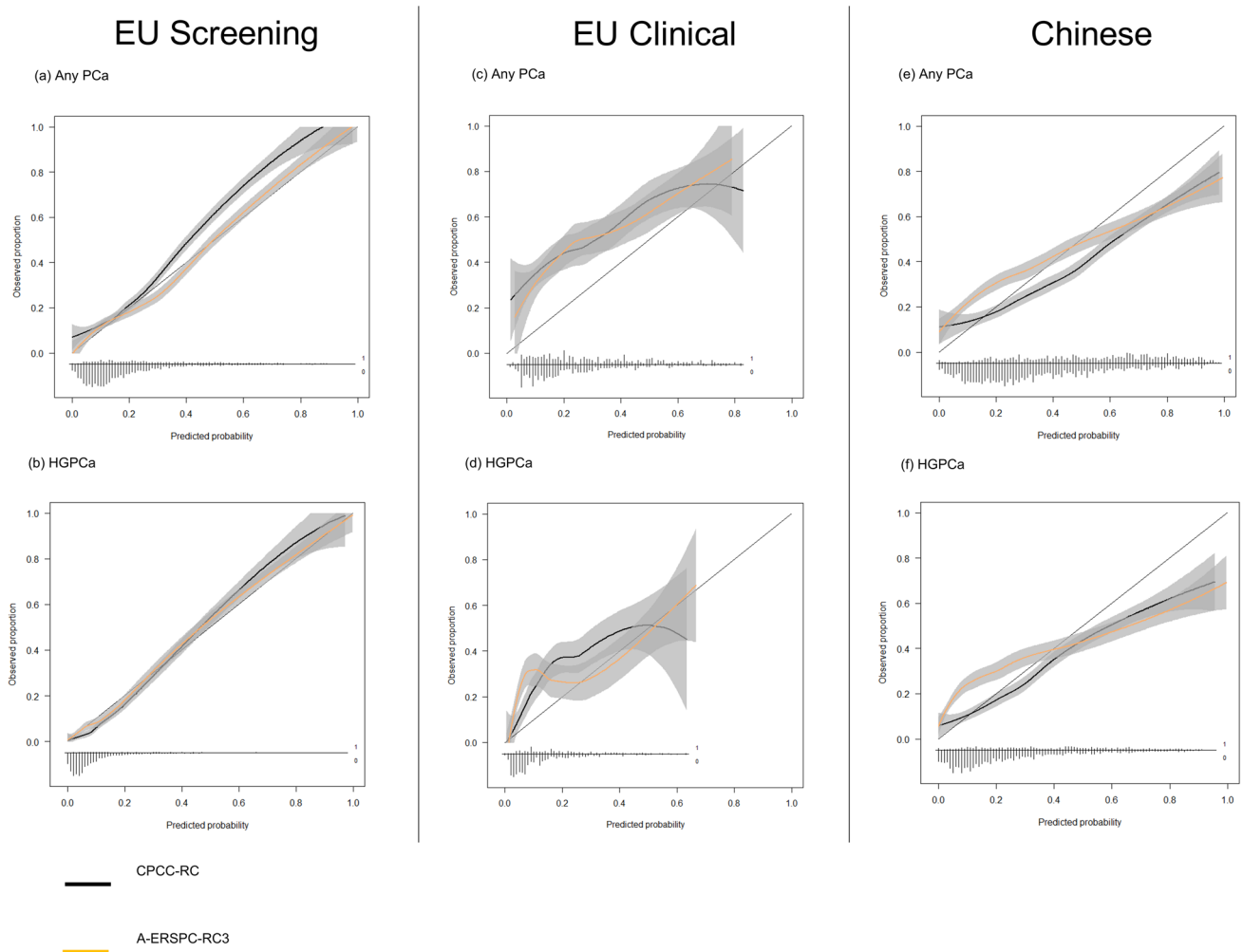


Fig. 1 Calibration plot for **a** predicting any prostate cancer in the European screening cohort, **b** predicting high-grade prostate cancer in the European screening cohort, **c** predicting any prostate cancer in the European clinical cohort, **d** predicting high-grade prostate cancer in the European clinical cohort, **e** predicting any prostate cancer in the

Chinese clinical cohort, **f** predicting high-grade prostate cancer in the Chinese clinical cohort. The yellow line is for A-ERSPC-RC3 and the black line is for the CPCC-RC. PCa prostate cancer, HGPCa high-grade prostate cancer

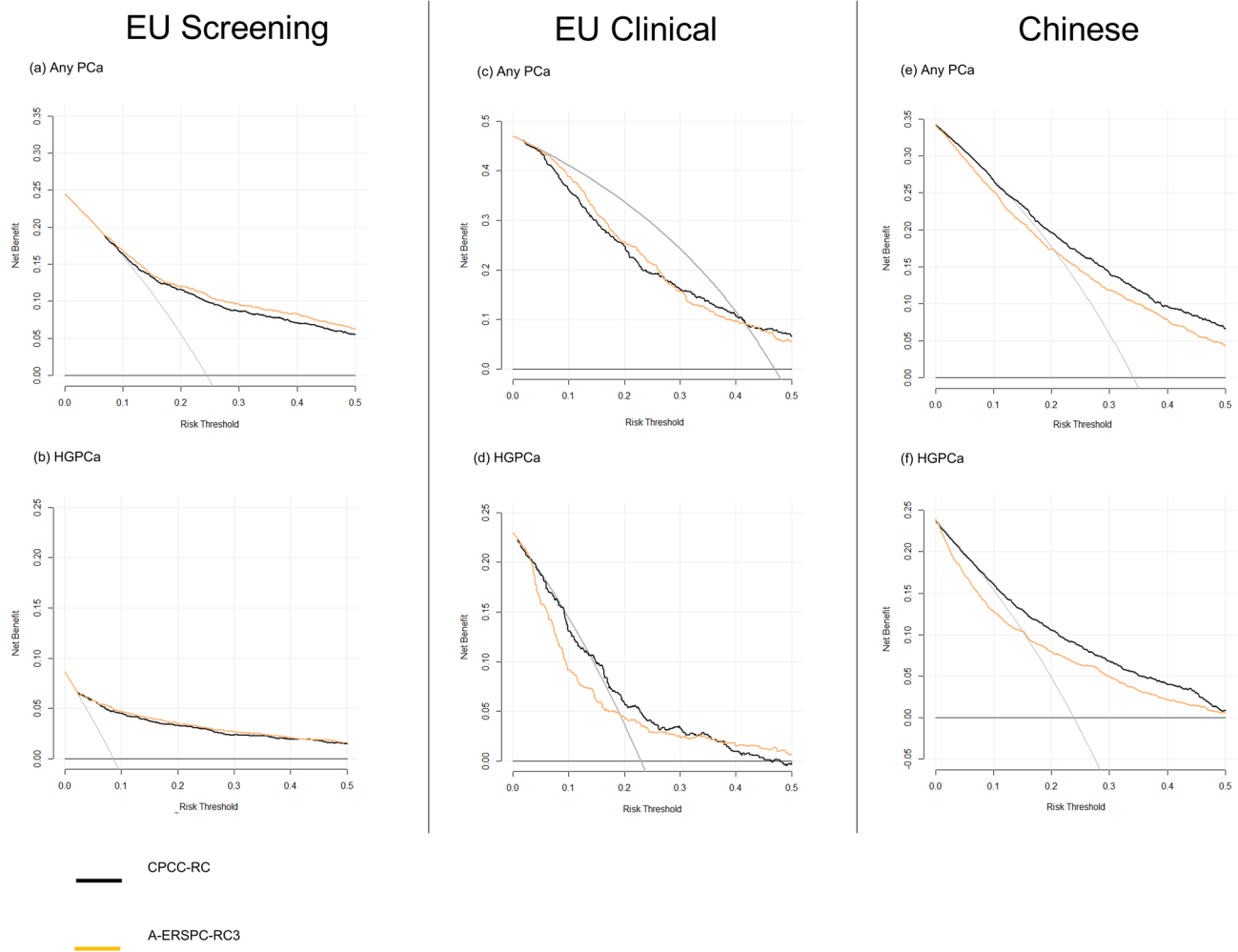


Fig. 2 Decision curve analysis for **a** any prostate cancer in the European screening cohort, **b** high-grade prostate cancer in the European screening cohort, **c** any prostate cancer in the European clinical cohort, **d** high-grade prostate cancer in the European clinical cohort,

e predicting any prostate cancer in the Chinese clinical cohort, **f** high-grade prostate cancer in the Chinese clinical cohort. The yellow line is for A-ERSPC-RC3 and the black line is for the CPCC-RC. *PCa* prostate cancer, *HGPCa* high-grade prostate cancer

differences between a population-based screening setting as compared to a referral population [17]. In addition, the number of cores, age and the PSA levels differ between the cohort on which the A-ERSPC-RC was updated (Hong Kong origin). These differences could explain the underestimation of the A-ERSPC-RC. In comparison with the original ERSPC-RC, Zhu, et al. found that it overestimated the probability of PCa and HGPCa by approximately 20% [9]. Yoon et al. validated the ERSPC-RC in a Korean cohort and showed the predicted probabilities were nearly 20% higher than the actual rate [8]. The over-estimation of the original ERSPC-RC and under-estimation of the A-ERSPC-RC indicates that the A-ERSPC-RC could need a more region-specific adaptation or addition of other relevant predictors, e.g. age. When evaluating RCs in other settings, the risk factors distribution in relation to the outcome should be taken

into consideration: i.e. the case mix of a cohort. This could explain the differences in the predictive performance of the tested RCs. For example, the PSA-PCa ratio might contribute to a good predictive capability in the Chinese cohort and the European screening cohort, while it could be the reason for a poor prediction in the EU clinical cohorts.

For the CPCC-RC, the predictive performance was good in the independent Chinese cohort as well as in the European screening cohort, but not in the European clinical cohort. This suggests that the CPCC-RC is applicable outside its development setting in Asia, but as expected less suitable in the European clinical setting with in general a higher prevalence of PCa and significant PCa. This observation is confirmed by Ankerst et al. in where an internationally validated risk calculator for patients in North America and Europe was developed [17]. They found a substantial deviation between

Table 3 Biopsy reduction, delayed prostate cancers diagnosis and net true positives using the Chinese Prostate Cancer Consortium Risk Calculator and the Asian adapted Rotterdam European Randomized Study of Screening for Prostate Cancer Risk Calculator 3 compared to biopsy all in 1000 Chinese men

Threshold Clinical significant PCa	Number of biopsies		Number of indolent cancers		Number of high-grade cancers		Additional net true reduction of biopsies compared to ERSPC strategy (G) × 1000 men
	(A) Performed	(B) Reduced (% total A)	(C) Detected (% A)	(D) Not detected (% B)	(E) Detected (% A)	(F) Missed diagnosis (% B)	
Biopsy all	1000	0	342	0	239 (24)	0	
5%							
CPCC-RC	900	100 (10)	330 (37)	12 (12)	231 (26)	8 (8)	0.7
A-ERSPC-RC3	873	127 (13)	335 (38)	7 (6)	229 (26)	10 (8)	–
10%							
CPCC-RC	752	248 (25)	310 (41)	32 (13)	220 (29)	19 (8)	6.8
A-ERSPC-RC3	725	275 (28)	325 (45)	17 (6)	211 (29)	28 (10)	–
15%							
CPCC-RC	612	388 (39)	285 (47)	57 (15)	202 (33)	37 (10)	7.4
A-ERSPC-RC3	604	396 (40)	313 (52)	29 (7)	194 (32)	45 (11)	–
20%							
CPCC-RC	512	488 (49)	258 (50)	84 (17)	184 (36)	55 (11)	3.9
A-ERSPC-RC3	515	485 (49)	295 (57)	47 (10)	182 (35)	57 (12)	–

CPCC-RC Chinese Prostate Cancer Consortium Risk Calculator, A-ERSPC-RC3 Asian adapted Rotterdam European Randomized Study of Screening for Prostate Cancer Risk Calculator 3

the predicted risk and the actual risk when applying the Prostate Cancer Prevention Trial risk calculator (developed in the US) to data from European centers. Using the data from eight North American medical centers, a new comprehensive risk prediction model was established and validated in three European centers. Less deviation was found with the newly developed Prostate Biopsy Collaborative Group model. Although they did not look at predictive performance in an Asian cohort, the message was similar to ours: external validation and recalibration are necessary before implementing RCs in daily clinical practice. Similarly, this study indicated the inapplicability of a European risk calculator in an Asian population. The CPCC-RC has shown to be well-calibrated in an East Asian population [10]. There are several other RCs in East Asian populations, such as Chinese [18], Korean [19, 20], and Japanese RCs [21]. Head-to-head comparison is required to compare these several RCs in clinical utility.

Development of numerous RCs is not helping the implementation of these useful tools. Instead, adapting existing RCs known to have good discriminative capability or constructing an internationally based risk calculator taking into account of ethnicity and heterogeneity between populations would be the way to go to optimize prostate cancer prediction on biopsy worldwide. The additional benefit of an international risk calculator would be a uniform patient selection for PCa, making it easier to compare study outcomes. In

addition, existing and externally validated (international) RCs must be constantly updated with new findings that potentially can improve predictive capability. Multiparametric magnetic resonance imaging and novel biomarkers as four kallikrein, Prostate Cancer Antigen (PCA3) and Prostate Health Index (PHI) are promising additions in RCs that are used to select men with an elevated risk of having HGPCa and should be incorporated in multivariable prediction tools to analyze their potential improvement of the clinical utility [22, 23]. Importantly, MRI has evolved as a powerful test in the diagnostic situation [24], which has been recommended by the latest EAU guidelines for initial biopsy setting.

There are several limitations to our study. First, currently, ISUP classification was adopted in the assessment of risk for PCa RCs just as our previous studies which incorporate ISUP classifications [7], however, we did not apply ISUP standards due to the lack of the detailed Gleason scores. Further validation of ISUP classifications should be applied. Second, the three cohorts of patients differ in testing methodology, mainly in the nature of the participants and the indication for biopsy. It is important to note that the Chinese cohort is limited to men referred for a prostate cancer evaluation and do not reflect the general (screening) population, thus there is sensible risk of selection in the clinical cohort. Furthermore, the design to external validation of the RCs is retrospective; however, the data is prospectively collected for

the European screening cohort. In the Chinese cohort there were some missing variables, but due to imputation could still be used for analysis. In general, it has been shown in many studies that instead of using a PSA cut-off for patient selection risk calculators should be used, as these tools can reduce one-third of the unnecessary biopsies [7].

Conclusion

The Asian-adapted ERSPC-RC3 performed well in a contemporary Chinese multi-center clinical cohort. The CPCC-RC performed well in a European PSA based screening setting, but less in a multi-center European clinical cohort. Both RCs reduce unnecessary biopsies compared to a PSA-decision-based strategy. External validation and calibration are very necessary before implementing RCs.

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Author contributions RC: protocol/project development, data collection or management, manuscript writing/editing. JMV: protocol/project development, data collection or management, data analysis, manuscript writing/editing. YY: data collection or management, manuscript editing. ZS: data collection or management, manuscript editing. YS: protocol/project development. MJR: protocol/project development.

Compliance with ethical standards

Conflict of interest The authors have no potential conflicts of interest to disclose.

Research involving human participants This study is approved by Ethical review board of Changhai Hospital.

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