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Prostate Cancer

Prediction of High-grade Prostate Cancer Following Multiparametric Magnetic Resonance Imaging: Improving the Rotterdam European Randomized Study of Screening for Prostate Cancer Risk Calculators

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Abstract

Background: The Rotterdam European Randomized Study of Screening for Prostate Cancer risk calculators (ERSPC-RCs) help to avoid unnecessary transrectal ultrasound-guided systematic biopsies (TRUS-Bx). Multivariable risk stratification could also avoid unnecessary biopsies following multiparametric magnetic resonance imaging (mpMRI).
Objective: To construct MRI-ERSPC-RCs for the prediction of any- and high-grade (Gleason score $\geq$3 + 4) prostate cancer (PCa) in 12-core TRUS-Bx $\pm$ MRI-targeted biopsy (MRI-TBx) by adding Prostate Imaging Reporting and Data System (PI-RADS) and age as parameters to the ERSPC-RC3 (biopsy-naïve men) and ERSPC-RC4 (previously biopsied men).
Design, setting, and participants: A total of 961 men received mpMRI and 12-core TRUS-Bx $\pm$ MRI-TBx (in case of PI-RADS $\geq$3) in five institutions. Data of 504 biopsy-naïve and 457 previously biopsied men were used to adjust the ERSPC-RC3 and ERSPC-RC4.
Outcome measurements and statistical analysis: Logistic regression models were constructed. The areas under the curve (AUCs) of the original ERSPC-RCs and MRI-ERSPC-RCs (including PI-RADS and age) for any- and high-grade PCa were compared. Decision curve analysis was performed to assess the clinical utility of the MRI-ERSPC-RCs.
Results and limitations: MRI-ERSPC-RC3 had a significantly higher AUC for high-grade PCa compared with the ERSPC-RC3: 0.84 (95% confidence interval [CI] 0.81–0.88) versus 0.76 (95% CI 0.71–0.80, $p < 0.01$). Similarly, MRI-ERSPC-RC4 had a higher AUC for high-grade PCa compared with the ERSPC-RC4: 0.85 (95% CI 0.81–0.89) versus 0.74 (95% CI 0.69–0.79, $p < 0.01$). Unlike for the MRI-ERSPC-RC3, decision curve analysis showed clear net benefit of the MRI-ERSPC-RC4 at a high-grade PCa risk threshold of $\geq$5%. Using a $\geq$10% high-grade PCa risk threshold to biopsy for the MRI-ERSPC-RC4, 36% biopsies are saved, missing low- and high-grade PCa, respectively, in 15% and 4% of men who are not biopsied.

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Conclusions: We adjusted the ERSPC-RCs for the prediction of any- and high-grade PCa in 12-core TRUS-Bx ± MRI-TBx. Although the ability of the MRI-ERSPC-RC3 for biopsy-naïve men to avoid biopsies remains questionable, application of the MRI-ERSPC-RC4 in previously biopsied men in our cohort would have avoided 36% of biopsies, missing high-grade PCa in 4% of men who would not have received a biopsy.
Patient summary: We have constructed magnetic resonance imaging-based Rotterdam European Randomized study of Screening for Prostate Cancer (MRI-ERSPC) risk calculators for prostate cancer prediction in transrectal ultrasound-guided biopsy and MRI-targeted biopsy by incorporating age and Prostate Imaging Reporting and Data System score into the original ERSPC risk calculators. The MRI-ERSPC risk calculator for previously biopsied men could be used to avoid one-third of biopsies following MRI.

1. Introduction

Men with a suspicion of prostate cancer (PCa) based on elevated prostate-specific antigen (PSA) and/or abnormal digital rectal examination (DRE) generally receive a transrectal ultrasound-guided systematic biopsy (TRUS-Bx). Nowadays, multiparametric magnetic resonance imaging (mpMRI) is increasingly being used due to its high negative predictive value for clinically significant PCa of approximately 90% [1–3]. The European Association of Urology (EAU) PCa guidelines recommend performing prebiopsy mpMRI in men with a suspicion of PCa after previous negative TRUS-Bx [3,4]. Since not all men with a clinical suspicion who receive mpMRI actually harbor high-grade PCa, a (targeted) biopsy following MRI could be avoided in some of these men using a risk calculator. The Rotterdam European Randomized Study of Screening for Prostate Cancer risk calculators (ERSPC-RCs) are well-validated models that help avoid 20–33% of unnecessary TRUS-Bx [5–13]. In the present study, we aim to construct MRI-ERSPC-RCs for patient selection for (targeted) biopsy following mpMRI by adding the Prostate Imaging Reporting and Data System (PI-RADS) score and age as parameters to the ERSPC-RC3 (in biopsy-naïve men) and ERSPC-RC4 (in previously biopsied men).

2. Patients and methods

2.1. Study population

A total of 1353 consecutive men with a clinical suspicion of PCa (no prior PCa diagnosis), who received mpMRI and subsequent TRUS-Bx and/or targeted biopsy (TBx) between 2012 and 2017, were included in the prospective institutional review board–approved databases of five institutions in Düsseldorf (n = 723), Rotterdam (n = 178), The Hague (n = 210), Amsterdam (n = 160), and Den Bosch (n = 82). Subgroups of the institutional cohorts from Düsseldorf, Rotterdam, and The Hague were reported previously [14–17].

2.2. Multiparametric MRI

All MRI scans were performed on a 3-T MRI scanner using a pelvic phased-array coil. The mpMRI protocol consisted of T2-weighted imaging (T2WI), diffusion-weighted imaging (DWI) with apparent diffusion coefficient reconstructions, and dynamic contrast enhanced imaging in four institutions (Düsseldorf, Rotterdam, The Hague, and Amsterdam). In Den Bosch (n = 82), a biparametric MRI protocol consisting of T2WI and DWI was used. All the institutional radiologists who reviewed the MRI-scans had years of experience in reading prostate MRI. All individual suspicious lesions were graded according to the PI-RADS score [18,19]. Since the time period for (MRI) data collection was predominantly before the publication of PI-RADSv2 [19], the majority of MR images in the present study were graded according to the PI-RADSv1 5-point scale [18].

2.3. Prostate biopsy

The prostate biopsy protocol varied among the institutions. In all institutions, MRI-TBx was performed for each PI-RADS ≥3 lesion. The technique used for MRI-TBx varied among institutions (Table 1): the MRI in-bore technique, as well as the MRI-TRUS fusion and cognitive fusion techniques were used. A total of 961 out of the 1353 men received a TRUS-Bx, with (in case of PI-RADS ≥3) or without (in case of PI-RADS 1–2) additional MRI-TBx. These men were included in the analyses of the present study. All biopsy procedures (targeted and systematic) were performed by a transrectal approach. The biopsy procedures were all performed by experienced operators, and all biopsy specimens were graded by dedicated uropathologists. All Gleason score (GS) 3 + 3 prostate cancers were classified as low-grade PCa, regardless of the maximum cancer core length. GS ≥3 + 4 PCa was classified as high-grade disease.

2.4. Adjustment of the ERSPC-RCs

ERSPC-RC3 and ERSPC-RC4 are prediction models for PCa in sextant TRUS-Bx based on the data of, respectively, 3624 men in the first screening round and 2896 men in the second screening round of the ERSPC Rotterdam (www.prostatecancer-riskcalculator.com) [7]. Both the ERSPC-RC3 and the ERSPC-RC4 use PSA, DRE (suspicious: no/yes), TRUS (suspicious: no/yes), and TRUS-measured prostate volume (continuous) as parameters. In addition, the ERSPC-RC4 takes the previous biopsy status (previous biopsy: no/yes) into account. ERSPC-RC3 + DRE and ERSPC-RC4 + DRE are simplified models in which TRUS (suspicious: no/yes) is not included as a parameter and the prostate volume is used (categorized into volume classes of 25, 40, or 60 ml), as can be assessed by DRE. ERSPC-RC3 (+DRE) and ERSPC-RC4 (+DRE) calculate the risk of any-grade and the risk of high-grade (GS ≥3 + 4) and/or locally advanced (T-stage ≥2C) PCa. In the present study, we aimed to augment the ERSPC-RC3 + DRE and ERSPC-RC4 + DRE by incorporating the overall PI-RADS score, for the prediction of any- and high-grade (GS ≥3 + 4) PCa in extended (12-core) TRUS-Bx ± MRI-TBx (in case of PI-RADS ≥3). In addition, as the ERSPC-RC3 + DRE and ERSPC-RC4 + DRE are developed based on the data of men aged 55–74 yr, age was included as a potential predictor in order to comply with the larger age range of men in daily clinical practice. Data from the 961 men from our cohort who received TRUS-Bx ± MRI-TBx (in case of PI-RADS ≥3) were used, of whom

Table 1 – Patient characteristics of all consecutive men with a suspicion of prostate cancer who received MRI and subsequent biopsy between 2012 and 2016 in Düsseldorf, Rotterdam, The Hague, Amsterdam, and Den Bosch

	Düsseldorf (*n* = 723)		Rotterdam (*n* = 178)		The Hague (*n* = 210)		Amsterdam (*n* = 160)		Den Bosch (*n* = 82)		Total cohort (*n* = 1353)	
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR
Age (yr)	66.1	59.7–72.0	67.0	61.8–70.5	66.8	62.0–71.4	65.0	60.0–69.0	62.0	58.0–65.0	66.0	60.0–71.0
PSA (ng/ml)	8.6	6.0–12.8	11.0	8.1–17.0	9.4	6.8–15.2	6.4	4.9–9.2	6.6	5.7–10.0	8.7	6.1–12.9
Prostate volume (ml)	49.0	36.0–71.0	47.0	33.0–73.3	51.0	37.8–73.3	51.9	37.9–67.0	45.0	31.0–60.0	49.7	36.0–70.0
PSA density	0.17	0.12–0.26	0.24	0.15–0.36	0.19	0.12–0.28	0.13	0.09–0.19	0.15	0.11–0.23	0.17	0.12–0.27
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
DRE												
Benign	202	28	136	76	101	48	111	69	58	71	608	45
Suspicious	133	18	42	24	56	27	49	31	24	29	304	22
Missing	388	54	0	0	53	25	0	0	0	0	441	33
Previous biopsy												
No	293	41	10	6	59	28	107	67	82	100	551	41
Yes	430	59	168	94	151	72	53	33	0	0	802	59
PI-RADS												
1–2	8	1	55	31	52	25	99	62	25	30	239	18
3	138	19	28	16	38	18	25	16	21	26	250	18
4	375	52	52	29	75	36	22	14	13	16	537	40
5	202	28	43	24	45	21	14	9	23	28	327	24
Biopsy procedure												
TRUS-Bx only	0	0	55	31	49	23	98	61	25	30	227	17
MRI-TBx only	206	29	62	35	124	59	0	0	0	0	392	29
TRUS-Bx + MRI-TBx	517	72	61	34	37	18	62	39	57	70	734	54
Included in MRI-ERSPC-RCs (TRUS-Bx ± MRI-TBx)	517	72	116	65	86	41	160	100	82	100	961	71
TBx method												
In bore	240	33	0	0	122	58	0	0	0	0	362	27
Fusion	483	67	123	69	0	0	58	36	57	70	721	53
Cognitive	0	0	0	0	39	19	4	3	0	0	43	3
No MRI-TBx	0	0	55	31	49	23	98	61	25	30	227	17
Overall GS												
No PCa	365	50	67	38	108	51	82	51	38	46	660	49
GS 3 + 3 PCa	79	11	42	24	41	20	24	15	24	29	210	16
GS 3 + 4 PCa	130	18	45	25	33	16	30	19	7	9	245	18
GS 4 + 3 PCa	67	9	13	7	13	6	11	7	8	10	112	8
GS ≥4 + 4 PCa	82	11	11	6	15	7	13	8	5	6	126	9
Total	723	100	178	100	210	100	160	100	82	100	1353	100

DRE = digital rectal examination; ERSPC-RCs = European Randomized study of Screening for Prostate Cancer risk calculators; GS = Gleason score; IQR = interquartile range; MRI = magnetic resonance imaging; MRI-TBx = MRI-targeted biopsy; PCa = prostate cancer; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; TRUS-Bx = transrectal ultrasound-guided systematic biopsy.

Table 2 – Patient characteristics of men included in MRI-ERSPC-RC3: model for the prediction of any- and high-grade PCa in TRUS-Bx MRI-TBx (in case of PI-RADS ≥3) in biopsy-naïve men

	Patient characteristics of biopsy-naïve men included in MRI-ERSPC-RC3 (n = 504)							
	No PCa (n = 210; 42%)		Any PCa (n = 294; 58%)		GS 3 + 3 PCa (n = 81; 16%)		GS ≥3 + 4 PCa (n = 213; 42%)	
	Median	IQR	Median	IQR	Median	IQR	Median	IQR
Age (yr)	62.0	56.0–67.8	66.1	60.9–72.2	65.0	58.3–70.0	67.0	61.9–73.0
PSA (ng/ml)	6.1	4.8–7.8	7.3	5.2–10.8	6.5	4.7–10.1	7.7	5.5–11.0
Prostate volume (ml)	56.5	39.8–77.0	40.0	30.0–52.0	42.0	29.5–58.0	40.0	30.0–51.0
	n	%	*n*	%	*n*	%	*n*	%
DRE								
Benign	116	55	116	39	44	54	72	34
Suspicious	23	11	102	35	18	22	84	39
Missing	71	34	76	26	19	23	57	27
PI-RADS								
1–2	66	31	39	13	26	32	13	6
3	67	32	32	11	13	16	19	9
4	66	31	97	33	26	32	71	33
5	11	5	126	43	16	20	110	52
Total	210	100	294	100	81	100	213	100

DRE = digital rectal examination; ERSPC-RC = European Randomized study of Screening for Prostate Cancer risk calculator; GS = Gleason score; IQR = interquartile range; MRI = magnetic resonance imaging; MRI-TBx = MRI-targeted biopsy; PCa = prostate cancer; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; TRUS-Bx = transrectal ultrasound-guided systematic biopsy.

504 biopsy-naïve men were included in the adjusted MRI-ERSPC-RC3 and 457 previously biopsied men were included in the MRI-ERSPC-RC4.

2.5. Statistical analysis

The multiple imputation by chained equations (MICE) algorithm was used to substitute missing DRE values. The MRI-measured prostate volume, calculated by the ellipsoid formula (length × width × height × π/6), was categorized into the known volume classes of the ERSPC-RC3 + DRE and ERSPC-RC4 + DRE with cutoff values of <30 ml (25 ml), 30–50 ml (40 ml), and >50 ml (60 ml). The original ERSPC-RCs were recalibrated (re-estimation of the intercept and slope of the linear predictor) to a clinical setting based on the data from the present cohort (n = 961). Logistic regression analysis was performed to estimate the coefficients of the overall PI-RADS score and age in addition to the recalibrated ERSPC-RC3 + DRE and ERSPC-RC4 + DRE. MRI-ERSPC-RCs included the linear predictor of the original ERSPC-RCs as a covariate. Bootstrap resampling (1000 samples) was used for internal validation of the MRI-ERSPC-RCs, and the calibration was explored graphically by the construction of calibration plots. Predictive accuracy of the original ERSPC-RCs and MRI-ERSPC-RCs was assessed by the area under the receiver operating characteristic curve (AUC), and the nested models were compared using the likelihood method after five times repeated complete data analysis. A sensitivity analysis was performed excluding men from the Den Bosch institution (n = 82) who received biparametric MRI. Decision curve analysis was performed to assess and compare the clinical utility of the original ERSPC-RCs and MRI-ERSPC-RCs. Clinical utility of the models is expressed by the net benefit ratio, which weighs the benefits of (high-grade) PCa detected against the harms of unnecessary biopsies performed [20,21]. A table was constructed displaying the number and percentage of biopsies saved versus (high-grade) PCa missed in those men who did not receive a biopsy at different risk thresholds (5–20%) to biopsy of the MRI-ERSPC-RCs with the number of patients standardized to 1000. Statistical tests were two sided, with the criterion of significance set at $p < 0.05$. Statistical analyses were performed with R version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patient characteristics

Table 1 shows the patient characteristics of all 1353 men with a clinical suspicion of PCa who received mpMRI and subsequent biopsy between 2012 and 2017 in the five institutions. Median age, PSA, and prostate volume were 66 (interquartile range [IQR] 60–71) yr, 8.7 (IQR 6.1–12.9) ng/ml, and 49.7 (36.0–70.0) ml, respectively. DRE values were missing in 33% (441/1353) men. A total of 82% (1114/1353) men had an overall PI-RADS score of ≥3. TRUS-Bx and MRI-TBx were performed with a median number of 12 cores (IQR 12–12; range 8–12) and four cores (IQR 3–6; range 2–6) per patient, respectively. MRI-TBx was performed using the in-bore technique in 32% (362/1126) men, and using MRI-TRUS fusion and cognitive fusion in 64% (721/1126) and 4% (43/1126) men, respectively. A total of 16% (210/1353) men had low-grade PCa and 36% (483/1353) had high-grade PCa. Patient characteristics of the 504 biopsy-naïve men who received TRUS-Bx ± MRI-TBx included in the MRI-ERSPC-RC3 and those of the 457 previously biopsied men included in the MRI-ERSPC-RC4 are shown in Tables 2 and 3, respectively. The median time between the previous TRUS-Bx and mpMRI + biopsy in men included in the MRI-ERSPC-RC4 was 1.6 (IQR 0.9–3.1) yr. In the 504 biopsy-naïve men included in the MRI-ERSPC-RC3, low- and high-grade PCa detection rates were 16% (81/504) and 42% (213/504), respectively (Table 2). Low- and high-grade PCa detection rates in the 457 previously biopsied men included in the MRI-ERSPC-RC4 were 14% (65/457) and 29% (132/457), respectively (Table 3).

Table 3 – Patient characteristics of men included in MRI-ERSPC-RC4: model for the prediction of any- and high-grade PCa in TRUS-Bx MRI-TBx (in case of PI-RADS ≥3) in previously biopsied men

	Patient characteristics of previously biopsied men included in MRI-ERSPC-RC4 (*n* = 457)							
	No PCa (*n* = 260; 57%)		Any PCa (*n* = 197; 43%)		GS 3 + 3 PCa (*n* = 65; 14%)		GS ≥ 3 + 4 PCa (*n* = 132; 29%)	
	Median	IQR	Median	IQR	Median	IQR	Median	IQR
Age (yr)	65.4	61.1–69.4	68.0	62.9–72.0	65.9	58.2–69.9	68.0	65.0–72.8
PSA (ng/ml)	9.4	6.8–13.6	11.0	7.4–16.0	9.0	6.5–14.8	11.7	7.7–17.5
Prostate volume (ml)	63.9	48.0–88.8	42.0	30.0–60.6	48.0	29.0–65.1	41.0	30.2–55.9
	n	%	*n*	%	*n*	%	*n*	%
DRE								
Benign	123	47	104	53	45	69	59	45
Suspicious	51	20	54	27	10	15	44	33
Missing	86	33	39	20	10	15	29	22
PI-RADS								
1–2	106	41	24	12	20	31	4	3
3	56	22	16	8	9	14	7	5
4	78	30	98	50	26	40	72	55
5	20	8	59	30	10	15	49	37
Total	260	100	197	100	65	100	132	100

DRE = digital rectal examination; ERSPC-RC = European Randomized study of Screening for Prostate Cancer risk calculator; GS = Gleason score; IQR = interquartile range; MRI = magnetic resonance imaging; MRI-TBx = MRI-targeted biopsy; PCa = prostate cancer; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; TRUS-Bx = transrectal ultrasound-guided systematic biopsy.

3.2. Predictive accuracy of the original and adjusted ERSPC-RCs

Both overall PI-RADS score and age added significantly to the original ERSPC-RC3 + DRE and ERSPC-RC4 + DRE. The discriminative ability of the MRI-ERSPC-RCs was significantly higher for both any- and high-grade PCa compared with the original ERSPC-RCs (Table 4). MRI-ERSPC-RC3 had a significantly higher AUC for high-grade PCa of 0.84 (95% confidence interval [CI] 0.81–0.88) compared with an AUC of 0.76 (95% CI 0.71–0.80, $p < 0.01$) of the ERSPC-RC3 + DRE. Sensitivity analysis showed no difference in the AUC of the MRI-ERSPC-RC3 for high-grade PCa when men from Den Bosch were excluded (AUC 0.84, 95% CI 0.80–0.88). Similarly, the AUC for high-grade PCa of the MRI-ERSPC-RC4 was significantly higher compared with the ERSPC-RC4 + DRE: AUC of 0.85 (95% CI 0.81–0.89) versus AUC of 0.74 (95% CI 0.69–0.79, $p < 0.01$).

3.3. Decision curve analysis

For the MRI-ERSPC-RC4, decision curve analysis showed net benefit (a potential net reduction in biopsies) compared with a biopsy-all strategy and the ERSPC-RC4 + DRE at a risk threshold of ≥5% for high-grade PCa (Fig. 1B). However, for the MRI-ERSPC-RC3, net benefit was observed only above a 10% risk threshold for high-grade PCa (Fig. 1A).

3.4. Biopsies saved versus (high-grade) PCa missed using the MRI-ERSPC-RCs

Table 5 depicts the number and percentage of biopsies saved versus low- and high-grade PCa missed in those who are not biopsied by applying different risk thresholds of the MRI-ERSPC-RC3 (Table 5) and MRI-ERSPC-RC4 (Table 5) for high-grade PCa in a standardized number of 1000 men. At a

Table 4 – Comparison of the predictive accuracy of the original ERSPC-RCs and MRI-ERSPC-RCs

	ERSPC-RC + DRE		MRI-ERSPC-RC (addition of PI-RADS + age)		
	AUC	95% CI	AUC	95% CI	*p*-value
Any-grade prostate cancer					
Biopsy naïve: ERSPC-RC3 (*n* = 504)	0.779	0.738–0.819	0.839	0.805–0.872	<0.01
Previously biopsied: ERSPC-RC4 (*n* = 457)	0.708	0.659–0.757	0.791	0.748–0.834	<0.01
High-grade (GS ≥3 + 4) PCa					
Biopsy naïve: ERSPC-RC3 (*n* = 504)	0.757	0.714–0.799	0.843	0.808–0.878	<0.01
Previously biopsied: ERSPC-RC4 (*n* = 457)	0.742	0.693–0.791	0.850	0.813–0.887	<0.01

AUC = area under the receiver operating characteristic curve; CI = confidence interval; DRE = digital rectal examination; ERSPC-RC = European Randomized study of Screening for Prostate Cancer risk calculator; GS = Gleason score; MRI = magnetic resonance imaging; PI-RADS = Prostate Imaging Reporting and Data System.

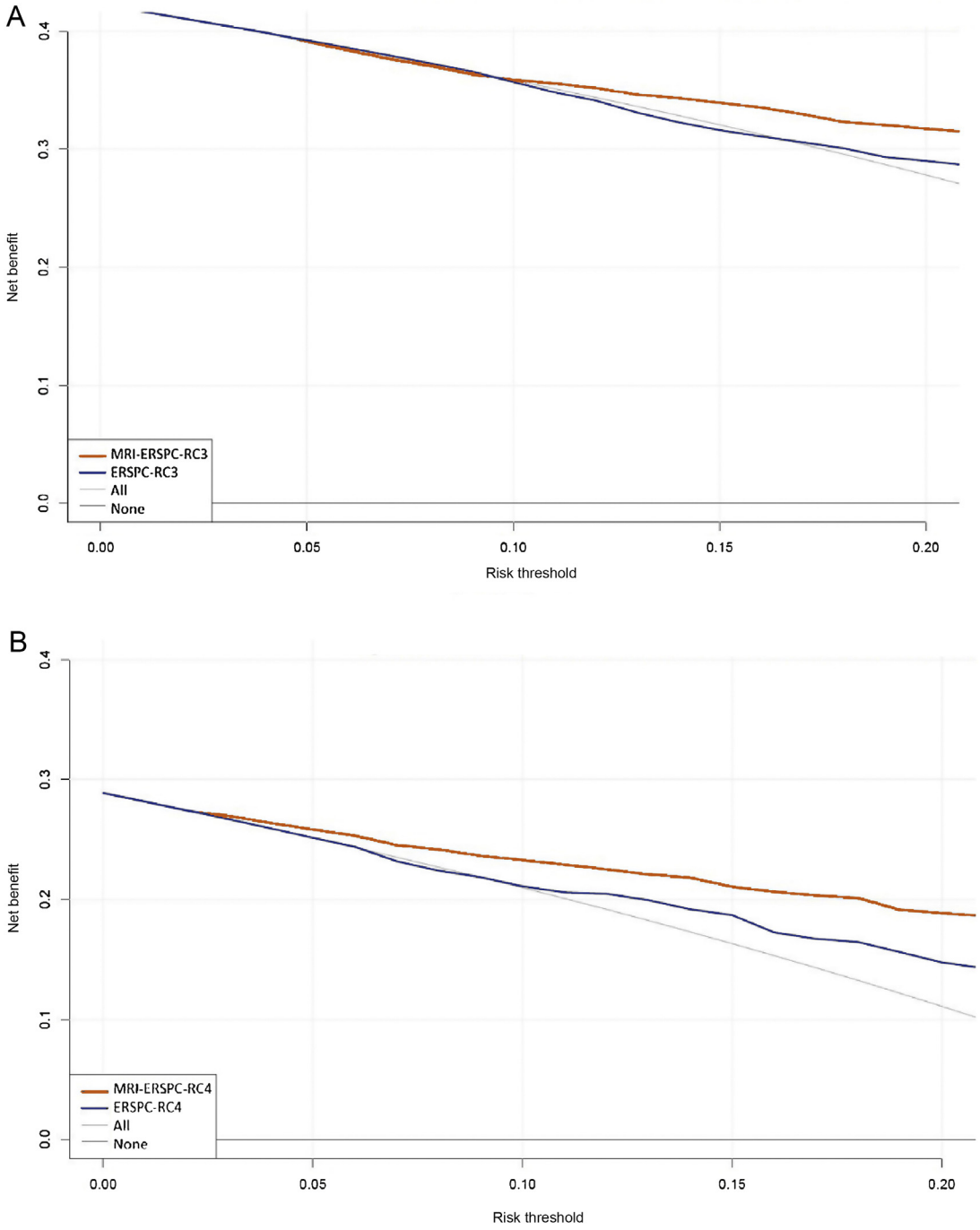

Fig. 1 – Decision curves for high-grade PCa in TRUS-Bx ± MRI-TBx (in case of PI-RADS ≥3) of the original and MRI-adjusted ERSPC-RCs in (A) biopsy-naïve men (*n* = 504) and (B) previously biopsied men (*n* = 457). ERSPC-RC = European Randomized Study of Screening for Prostate Cancer risk calculator; MRI = magnetic resonance imaging; MRI-TBx = MRI-targeted biopsy; PCa = prostate cancer; PI-RADS = Prostate Imaging Reporting and Data System; TRUS-Bx = transrectal ultrasound-guided systematic biopsies.

risk threshold to biopsy of ≥10% for the MRI-ERSPC-RC3, only 14% (143/1000) biopsies are avoided, missing low-grade PCa in 13% (18/143) of men and high-grade PCa in 10% (14/143) of men who are not biopsied. However, at a risk threshold to biopsy of ≥10% for the MRI-ERSPC-RC4, 36% (361/1000) of biopsies are avoided, missing low-grade PCa in 15% (55/361) of men and high-grade PCa in 4% (15/361) of men who are not biopsied.

4. Discussion

Risk-based patient selection for TRUS-Bx has been adopted in daily clinical practice, either by clinical judgment or by the use of risk calculators. Using a multivariable risk calculator similar to the original ERSPC-RCs has been shown to reduce the percentage of unnecessary TRUS-Bx by 20–33% in several external validation studies [7–13]. Nowadays,

Table 5 – Biopsies saved versus prostate cancer detected/missed using different risk thresholds for high-grade (GS ≥3 + 4) PCa of the MRI-ERSPC-RC3 for biopsy-naïve men and the MRI-ERSPC-RC4 for previously biopsied men in a standardized number of 1000 men

Risk threshold	(A) No. of men biopsied	(B) No. of biopsies saved (% of total A)	No. of GS 3 + 3 PCa detected (% of A)	No. of GS 3 + 3 PCa missed (% B)	No. of GS ≥3 + 4 PCa detected (% of A)	No. of GS ≥3 + 4 PCa missed (% B)
Biopsies saved vs prostate cancer detected/missed using different MRI-ERSPC-RC3 risk thresholds for high-grade (GS ≥3 + 4) PCa						
Total	1000	–	161 (16%)	–	423 (42%)	–
5%	980	20 (2%)	159 (16%)	2 (10%)	420 (43%)	3 (15%)
10%	857	143 (14%)	143 (17%)	18 (13%)	409 (48%)	14 (10%)
15%	762	238 (24%)	135 (18%)	26 (11%)	403 (53%)	20 (8%)
20%	675	325 (33%)	109 (16%)	52 (16%)	389 (58%)	34 (10%)
Biopsies saved vs prostate cancer detected/missed using different MRI-ERSPC-RC4 risk thresholds for high-grade (GS ≥3 + 4) PCa						
Total	1000	–	142 (14%)	–	289 (29%)	–
5%	735	265 (27%)	105 (14%)	37 (14%)	282 (38%)	7 (3%)
10%	639	361 (36%)	87 (14%)	55 (15%)	274 (43%)	15 (4%)
15%	586	414 (41%)	85 (15%)	57 (14%)	267 (46%)	22 (5%)
20%	525	475 (48%)	76 (14%)	66 (14%)	256 (49%)	33 (7%)

mpMRI is increasingly performed, especially in men with a sustained suspicion of PCa after previous negative TRUS-Bx [3,4]. The EAU PCa guidelines recommend risk stratification before the performance of MRI in previously biopsied men, and it was previously shown that stratification based on the ERSPC-RC4 could avoid unnecessary MRI scans in this setting [3,4,16]. In the present study, we aimed to augment the original ERSPC-RCs by incorporating the overall PI-RADS score and age, showing that a multivariable risk-based approach could also be used to avoid unnecessary biopsies after the performance of prebiopsy MRI. The original ERSPC-RC3 + DRE and ERSPC-RC4 + DRE already performed well in our cohort with AUCs for high-grade PCa of 0.76 (95% CI 0.71–0.80) and 0.74 (95% CI 0.69–0.79), respectively. Nevertheless, MRI-ERSPC-RCs had a significantly higher discriminative ability for high-grade PCa (AUC of 0.84 [95% CI 0.81–0.88] and 0.85 [95% CI 0.81–0.89] for the MRI-ERSPC-RC3 and MRI-ERSPC-RC4, respectively). Decision curve analysis showed clear net benefit of the MRI-ERSPC-RC4 at a ≥5% high-grade PCa risk threshold, proving the ability of the model to avoid unnecessary biopsies even after risk stratification before MRI with the original (recalibrated) ERSPC-RC4. Net benefit of the MRI-ERSPC-RC3 was observed only above the clinically reasonable high-grade PCa risk threshold of 10% to perform a biopsy. This reflects a higher added value of the MRI(-based model) in previously biopsied men as compared with biopsy-naïve men.

Obviously, the percentage of potentially avoidable biopsies after MRI is dependent on the composition of the cohort and thus on the degree of risk stratification before MRI. Our cohort used to develop the MRI-ERSPC-RCs consisted of men with a high clinical suspicion of PCa, reflected by a high percentage of men with any-grade (51%; 491/961) and high-grade (36%; 345/961) PCa. Nevertheless, the MRI-ERSPC-RC4 would still have avoided 36% of biopsies in previously biopsied men in our cohort using a ≥10% high-grade PCa risk threshold to biopsy, missing high-grade PCa in 4% of men who would not have been biopsied. The good discriminative ability of the original ERSPC-RCs in our cohort (AUCs for high-grade PCa of 0.76 and 0.74 for the ERSPC-RC3 + DRE and ERSPC-RC4 + DRE, respectively) is consistent with the recently reported AUCs for high-grade PCa of 0.81 and 0.76, respectively, for the ERSPC-RC3 and refitted ERSPC-RC4 in the large MRI study of Radtke et al [22]. Therefore, risk-based patient selection for mpMRI to avoid unnecessary MRI scans using the original (recalibrated) ERSPC-RCs seems justified [16].

Next to the present study, two recent studies presented new PCa prediction models incorporating both clinical and MRI parameters [22,23]. Van Leeuwen et al [23] constructed a model based on the data of 393 predominantly biopsy-naïve (88%) men undergoing transperineal template mapping biopsies (median 30 cores) incorporating the same parameters as used in the MRI-ERSPC-RCs, that is, PSA, DRE, prostate volume, previous biopsy status, overall PI-RADSv1 score, and age. The model had an AUC for significant PCa, defined as GS ≥3 + 4 PCa with >5% grade 4 and/or ≥20% cores positive and/or ≥7 mm of PCa in any core, of no less than 0.88 (95% CI 0.85–0.92) in the construction cohort and 0.86 (95% CI 0.81–0.92) in a validation cohort of 198 men [23]. Using a significant PCa risk threshold to biopsy of ≥10% would have avoided 28% of biopsy procedures in the cohort of van Leeuwen et al [23], missing 3% of significant PCa. Radtke et al [22] also used the previously mentioned parameters included in the MRI-ERSPC-RCs to fit new risk models for any- and high-grade (GS ≥3 + 4) PCa based on the data of 660 biopsy-naïve and 355 previously biopsied men who received transperineal template mapping biopsies (median 24 cores) + fusion MRI-TBx of all PI-RADSv1 ≥2 lesions. In accordance with the present study, the risk models of Radtke et al [22] including PI-RADSv1 and age performed significantly better than the probabilities of the original ERSPC-RCs, calculated manually per single patient online (www.prostatecancer-riskcalculator.com). However, with decision curve analysis, net benefit of these risk models was observed only beyond the ≥10% risk threshold for high-grade PCa [22].

Unlike the newly fitted models presented in the previously mentioned studies [22,23], MRI-ERSPC-RCs are constructed by augmenting the multiple externally validated original ERSPC-RCs. After recalibration, the linear predictor of the original ERSPC-RCs was included as a covariate together with the overall PI-RADS score and age.

MRI-ERSPC-RCs do not predict (high-grade) PCa in transperineal template mapping biopsy, but rather the more commonly used extended (12-core) TRUS-Bx in combination with MRI-TBx in case of PI-RADS ≥3 lesions. Of the total 1353 men in the cohort, only 961 men who received a TRUS-Bx were included in the MRI-ERSPC-RCs, as the EAU PCa guidelines recommend performing both TRUS-Bx and MRI-TBx (in case of suspicious lesions) following prebiopsy MRI [3,4]. Although the multicenter randomized controlled PRECISION trial recently showed superior significant PCa detection of MRI-TBx compared with TRUS-Bx in biopsy-naïve men [24], it is unlikely that the TRUS-Bx will be omitted in the near future as it still detects 10–20% of significant PCa not detected by MRI-TBx.

The strength of our study is the inclusion of data from five different institutions (two countries) using different TBx approaches. This makes our study results more generalizable, although it must be stated that no clear benefit of one TBx technique over another has been shown so far [25]. To limit the number of parameters included in the MRI-ERSPC-RCs, thereby improving their clinical applicability, the ERSPC-RCs + DRE (models without TRUS outcome as a parameter) were augmented instead of the ERSPC-RCs (models including TRUS outcome as a parameter). Our study has several limitations, one being the fact that one-third of cases had missing DRE values. These missing DRE values were imputed using the MICE algorithm. The analyses of multiply imputed data take into account the uncertainty in the imputations, leading to high standard errors in the analyses. Another limitation is the fact that the majority of MRI scans in our study were graded according to PI-RADSv1 [18], as the time period for (MRI) data collection was predominantly before the introduction of the PI-RADSv2 grading system [19], which might perform slightly better [26]. A final limitation is the fact that biparametric instead of multiparametric MRI was performed in one of five institutions with the smallest subcohort ($n = 82$, all men received an initial biopsy). However, sensitivity analysis excluding these men showed no impact on the predictive accuracy of the MRI-ERSPC-RC3.

External validation of the MRI-ERSPC-RCs is needed, preferably in cohorts of men who received mpMRI graded according to PI-RADSv2. Meanwhile, the MRI-ERSPC-RCs will become available for use in clinical practice on the ERSPC-RC website (www.prostatecancer-riskcalculator.com) with a mention of the necessity of external validation of the models and display of these results as soon as available.

5. Conclusions

Multivariable risk-based patient selection for biopsy after mpMRI can avoid unnecessary systematic and/or TBx, even after risk stratification before MRI. In the present study, we adjust the multiple externally validated ERSPC-RC-3 (for biopsy-naïve men) and ERSPC-RC-4 (for previously biopsied men) by incorporating the overall PI-RADS score and age. Although the ability of the MRI-ERSPC-RC3 for biopsy-naïve men to avoid biopsies remains questionable, application of the MRI-ERSPC-RC4 in previously biopsied men in our cohort would have avoided 36% of biopsies, missing high-grade PCa in 4% of men who would not have been biopsied.

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