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Research Article

Magnetic Resonance Imaging (MRI)—Adapted Prostate Cancer Risk Tool Incorporating Cribriform and Intraductal Carcinoma

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ABSTRACT

Current prostate cancer risk stratification tools are not adapted for magnetic resonance imaging (MRI)—targeted biopsies and do not include the presence of cribriform carcinoma/intraductal carcinoma (CC/IDC), an independent predictor of adverse clinical outcomes. We developed an MRI-adapted prostate cancer risk tool (MAPCaRT), which incorporates CC/IDC presence to the Cancer of the Prostate Risk Assessment (CAPRA) tool. We compared the prognostic power of MAPCaRT with that of CAPRA in MRI-targeted biopsies ($n = 266$, 2015–2023) and systematic-only biopsies ($n = 1291$, 2010–2018) that had matched radical prostatectomy. MAPCaRT employs the aggregate core count method for MRI-targeted lesions to calculate percent positive biopsy cores and uses the radiological stage when assessing MRI-targeted biopsies. Point attribution for CC/IDC presence and Gleason score was determined using a Cox proportional hazards model that included the CAPRA score, Gleason score, and CC/IDC status. Based on calculated MAPCaRT and CAPRA scores, patients were classified into the low-risk (0–2), intermediate-risk (3–5), or high-risk (6+) group. Model performance was assessed via the Kaplan-Meier curves, Harrell C-indices, and decision curve analysis for biochemical recurrence-free survival (BCR-FS) and event-free survival (EFS) (metastasis/cancer-specific death). CC/IDC was present in 84 of 266 (32%) MRI-targeted biopsies and 293 of 1291 systematic-only biopsies (23%). The median follow-up time was 3.4 years (IQR, 2.3–5.5 years) for the MRI-targeted biopsy cohort and 5.9 years (IQR, 3.4–8.1 years) for the systematic biopsy cohort. In the MRI-targeted biopsy cohort, MAPCaRT showed substantial improvement of the C-index compared with CAPRA (0.635 vs 0.574, $P = .045$) and greater net clinical benefit for 4-year BCR-FS. In the systematic biopsy cohort, MAPCaRT demonstrated improved C-index for BCR-FS (0.696 vs 0.655, $P < .001$) and greater net clinical benefit for 5-year BCR-FS and EFS. Other model performance metrics were marginally better with MAPCaRT. In summary, we developed MAPCaRT (prostatecancercalculator.imp.utoronto.ca),

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a modified version of CAPRA incorporating CC/IDC presence, which demonstrated improved BCR-FS and EFS predictions. This may result in better clinical guidance for disease management decisions.

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Introduction

The Cancer of the Prostate Risk Assessment (CAPRA) risk stratification tool is used to guide management in prostate cancer.¹ It yields a risk score of 0 to 10 using patient age, serum prostate-specific antigen (PSA) level at biopsy, biopsy Gleason score, clinical tumor stage based on digital rectal examination (DRE), and percent positive biopsy (PPB) cores.¹ The original study by Cooperberg et al¹ demonstrated each 2-point increase to be associated with a 2-fold increase in recurrence risk. The CAPRA tool was developed before the widespread adoption of magnetic resonance imaging (MRI)—targeted prostate biopsies and before mandatory pathology reporting of cribriform carcinoma (CC) and intraductal carcinoma (IDC).²

Combined MRI-targeted and systematic biopsies are superior to systematic biopsies alone to detect clinically significant prostate cancer.³ However, calculation of PPB cores as an estimate of carcinoma extent is arbitrary in MRI-targeted biopsies. An individual core count for MRI targets may overestimate tumor extent, and the number of cores sampled in each target can vary within and between cases. PPB core calculation is further complicated in cases with core fragmentation. An aggregate core count method for tumor extent has been adopted by some pathologists for MRI-targeted lesions,⁴ but many pathologists and clinicians still use the individual core count method.⁵ That said, the optimal core count method for determination of the CAPRA score is not well established. Moreover, DRE is less and less used by clinicians and being replaced by multiparametric MRI (mpMRI). DRE lacks reproducibility⁶ and sensitivity for determination of clinical tumor stage, identifying only palpable lesions located in the posterior wall of the gland.⁷

There is robust and accumulating evidence that CC and IDC are associated with greater tumor volume, higher stage carcinomas, and worse clinical outcomes,^{8–13} but they are not included in any contemporary risk stratification tools. Previously, we demonstrated that the addition of CC/IDC presence into the CAPRA, National Comprehensive Cancer Network (NCCN), and CAPRA postsurgical tools further stratifies patients for disease-free survival probabilities.^{14–16} Here, we sought to develop an MRI-adapted prostate cancer risk tool (MAPCaRT) incorporating CC/IDC presence for predicting biochemical recurrence-free survival (BCR-FS) and event-free survival (EFS) in MRI-targeted biopsies and systematic-only biopsies by modifying the CAPRA tool.

Materials and Methods

Cohort Selection

Retrospective searches of laboratory information systems were performed to identify therapy-naïve MRI-targeted prostate biopsy and systematic-only biopsies that had matched radical prostatectomy. The MRI-targeted biopsy cohort comprised patients with Prostate Imaging Reporting and Data System ≥ 3

lesions who underwent MRI-targeted biopsy with/without systematic sampling at the University Health Network (n = 266, 2015–2023). The systematic-only biopsy cohort (n = 1291) was described in previous studies^{14–16} and comprised patients from the Sunnybrook Health Sciences Centre (n = 212, 2010–2017), University Health Network (n = 400, 2010–2017), Medical College of Wisconsin (n = 507, 2013–2018), and Erasmus University Medical Centre (n = 172, 2010–2017).

Clinicopathological Review

Biopsies were assessed for CC/IDC presence by academic uropathologists (M.R.D., T.H.v.d.K., K.A.I., and G.J.L.H.v.L.) based on hematoxylin and eosin slides, with the aid of immunostains as needed. The 2021 International Society of Urological Pathology definition of CC¹⁷ and the 2022 World Health Organization definition of IDC^{18,19} were employed to identify these lesions. Through electronic patient records and laboratory information system searches, the following clinicopathological features were collected: patient age at biopsy, serum PSA level at biopsy, radiological/clinical tumor stage, biopsy Gleason score, number of MRI-targeted lesions, total number of cores, number of positive cores, International Society of Urological Pathology grade group at radical prostatectomy, surgical margin status, pathological tumor stage (pT), and nodal stage (pN).

Clinical endpoints were BCR and events. BCR was defined as at least 2 consecutive serum PSA ≥ 0.2 ng/mL after radical prostatectomy. An event was defined as regional lymph node metastasis, distant metastasis, or cancer-specific death. Nodal disease at radical prostatectomy was considered an event. Time to BCR corresponded to the interval between radical prostatectomy and BCR. Time to event corresponded to the interval between the biopsy and the event. Follow-up time was the time from radical prostatectomy to the first clinical endpoint or last follow-up date.

Clinicopathological characteristics were summarized using descriptive statistics. Differences in distribution by cohort were assessed using the Mann-Whitney *U* test and χ^2 test for continuous and categorical data, respectively.

Development of the Magnetic Resonance Imaging–Adapted Prostate Cancer Risk Tool

We developed and compared different modified CAPRA scores to determine the best variables to include in MAPCaRT. First, we determined the ability of the original CAPRA scores for predicting BCR-FS and EFS in the MRI-targeted cohort and the systematic biopsy cohort using the traditional variables.¹ As for all the other risk stratification systems included in this study, the radiological tumor stage was used for MRI-targeted biopsies, and the clinical tumor stage based on DRE was used for systematic-only biopsies.²⁰ PPB core of MRI-targeted biopsies was calculated via the individual core count method similar to how one would normally determine PPB cores in systematic biopsies.

Table 1
M1 CAPRA and M2 CAPRA scoring systems

Clinicopathological variable	Value	M1 CAPRA point attribution	M2 CAPRA point attribution
Patient age (y)	<50	0	0
	≥50	1	1
Serum PSA at biopsy (ng/mL)	2.1-6	0	0
	6.1-10	1	1
	10.1-20	2	2
	20.1-30	3	3
	>30	4	4
Percent positive biopsy cores using the aggregate core count method for MRI-targeted lesions	<34%	0	N/A
	≥34%	1	N/A
Radiological/clinical tumor stage	T1 or T2	0	0
	T3a	1	1
Gleason score and CC/IDC status on biopsy	No pattern 4 or 5	0 ^a	0 ^a
	Secondary pattern 4 or 5, CC/IDC negative	0 ^a	0 ^a
	Secondary pattern 4 or 5, CC/IDC positive	2 ^a	2 ^a
	Primary pattern 4 or 5, CC/IDC negative	2 ^a	2 ^a
	Primary pattern 4 or 5, CC/IDC positive	4 ^a	4 ^a

CC, cribriform pattern 4 carcinoma; IDC, intraductal carcinoma; MRI, magnetic resonance imaging; M1 CAPRA, modified 1 Cancer of Prostate Risk Assessment; M2 CAPRA, modified 2 Cancer of Prostate Risk Assessment; N/A, not applicable; PSA, prostate-specific antigen.

^a These variables and point attributions differ from the original CAPRA.

Second, we assessed the prognostic power of CAPRA MRI-targeted (CAPRA-T) score, which is essentially based on the traditional CAPRA variables and originally assigned points, but it uses the aggregate core count method instead of the individual core count method for MRI-targeted lesions to determine PPB cores. Therefore, each MRI-targeted lesion with any number of positive cores was considered as 1 of 1 positive core (1/1). When all cores from an MRI-targeted lesion were negative, this was documented as a single negative core (0/1).

Third, we evaluated the prognostic power of modified 1 (M1) CAPRA, which incorporates CC/IDC presence while using the aggregate core count method for MRI-targeted lesions similar to CAPRA-T. Based on the full cohort, point attribution for CC/IDC presence and Gleason score was determined using a Cox proportional hazards model that included the original CAPRA score, Gleason score, and CC/IDC status. Because of the small number of patients with CC/IDC but without Gleason pattern 4 or 5, all such patients were combined into a single group. Nomograms and the logarithm of the hazard ratio for the Gleason and CC/IDC parameters were then used to assign point values for these variables in the M1 CAPRA model. M1 CAPRA's model performance was assessed in both the MRI-targeted biopsy cohort and the systematic-only biopsy cohort. Finally, we determined the prognostic power of modified 2 (M2) CAPRA, which consists of M1 CAPRA but with removal of PPB cores.

The original CAPRA, M1 CAPRA, and M2 CAPRA scores were calculated for all patients. In addition, CAPRA-T scores were generated for patients in the MRI-targeted biopsy cohort. Table 1 shows the clinicopathological variables used in the modified CAPRA scores and the assigned points. Based on the calculated scores, patients were classified into the low-risk (scores 0-2), intermediate-risk (scores 3-5), or high-risk (scores 6-10) group.

BCR-FS and EFS were summarized using the Kaplan-Meier method, and differences in survival by risk group were assessed using the log-rank test. Survival probabilities and their 95% CI were tabulated using a 4-year period for MRI-targeted biopsies and a 5-year period for systematic-only biopsies. The Harrell optimism-corrected C-index was estimated for each classification method using 1000 bootstrap resamples, and differences in

C-indices were formally assessed using z-score tests. Decision curve analysis (DCA) assessing the net clinical benefit of each classification method was conducted and visualized based on BCR-FS and EFS probabilities. Statistical analyses were completed using R version 4.3.0 (R core team 2023). *P* values of <.05 was considered significant. To compare the models' ability to predict adverse pathology at radical prostatectomy (defined as pN1, pT3+, and/or GG3+), a bar chart illustrating the proportions of patients with adverse pathology at radical prostatectomy within each risk group was built.

Results

Cohort Characteristics

Clinicopathological characteristics of the MRI-targeted biopsy cohort and systematic biopsy cohort are described in Table 2. The MRI-targeted biopsy cohort comprised 231 (89.9%) combined systematic and MRI-targeted biopsies, and 28 (11%) MRI-targeted only biopsies. There were 1 to 6 targets per specimen (mean, 1.8) and 1 to 7 cores per target (mean, 3.3).

Most biopsies were grade group 2 in both cohorts. The MRI-targeted biopsy cohort was more enriched in grade group 2 biopsies and had lower grade group 1 frequency than the systematic biopsy cohort.

Table 3 shows the risk group distribution in the MRI-targeted biopsy cohort and the systematic biopsy cohort using the original CAPRA, CAPRA-T, M1 CAPRA, and M2 CAPRA. Using any classification system, the intermediate-risk group was dominant in both cohorts; however, the MRI-targeted biopsy cohort had a higher proportion of patients classified in the intermediate-risk group and a lower proportion of patients in the low-risk group compared with the systematic biopsy cohort. Compared with the original CAPRA, modified CAPRA scores had significantly more men in the low-risk group (*P* < .001 for both M1 CAPRA and M2 CAPRA).

In the MRI-targeted biopsy cohort, 4-year BCR-FS probability was 0.79 (95% CI, 0.74-0.85), and 4-year EFS probability was 0.94 (95% CI, 0.91-0.97). In the first 4 years of follow-up, there were 48

Table 2

Clinicopathological characteristics of the MRI-targeted biopsy cohort and systematic-only biopsy cohort

Clinicopathological characteristics	MRI-targeted biopsy cohort (n = 266)	Systematic-only biopsy cohort (n = 1291)	P
Patient age (y)			.55
Mean (SD)	63.1 (6.8)	62.8 (6.8)	
Median (Q1-Q3)	64 (59-68)	63.5 (58.0-68.0)	
Range (min-max)	(36-77)	(39.7-83.0)	
Serum PSA at biopsy (ng/mL)			.16
Mean (SD)	9.0 (6.4)	9.3 (10.6)	
Median (Q1-Q3)	7.1 (5.2-11.1)	6.8 (5.0-10.1)	
Range (min-max)	(0.4-51.0)	(0.5-154.0)	
Grade group at biopsy, n (%)			<.001 ^a
1	34 (13)	270 (21)	
2	186 (70)	682 (53)	
3	34 (13)	200 (15)	
4	6 (2)	58 (4)	
5	6 (2)	81 (6)	
CC/IDC presence at biopsy, n (%)	84 (32)	292 (23)	.002 ^a
Grade group at radical prostatectomy			.004 ^a
1	30 (11)	130 (11)	
1t4	0 (0)	11 (1)	
2	180 (68)	677 (56)	
2t5	0 (0)	8 (1)	
3	42 (16)	235 (20)	
3t5	0 (0)	19 (2)	
4	5 (2)	36 (3)	
4t5	0 (0)	2 (0)	
5	9 (3)	85 (7)	
Missing	0	88	
Pathological tumor stage, n (%)			<.001 ^a
2	174 (65)	814 (63)	
3	3 (1)	0 (0)	
3a	80 (30)	319 (25)	
3b	9 (3)	157 (12)	
Missing	0	1	
Pathological tumor stage, n (%)			<.001 ^a
pN0	163 (61)	857 (66)	
pN1	3 (1)	92 (7)	
pNx	100 (38)	342 (26)	
Positive surgical margin, n (%)	66 (25)	392 (30)	.083
Follow-up time (y)			<.001 ^a
Mean (SD)	4.0 (2.1)	6.1 (3.8)	
Median (Q1-Q3)	3.4 (2.3-5.5)	5.9 (3.4-8.1)	
Range (min-max)	(0.1-9.3)	(0.0-14.9)	

BCR, biochemical recurrence; CC, cribriform pattern 4 carcinoma; IDC, intraductal carcinoma; MRI, magnetic resonance imaging; N/A, not applicable; PSA, prostate-specific antigen; Q1, quartile 1; Q3, quartile 3; t, tertiary/minor pattern.

^a Significant P value.

BCR (126 censored) and 14 events (132 censored). Over the full follow-up period (mean, 4.0 years; median, 3.4 years), a total of 54 patients experienced BCR (212 censored) and 15 patients had an event (251 censored).

In the systematic biopsy cohort, 5-year BCR-FS probability was 0.78 (95% CI, 0.76-0.81), and 5-year EFS probability was 0.89 (95% CI, 0.87-0.91). In the first 5 years of follow-up, there were 236 BCR (440 censored) and 130 events (448 censored). Over the full follow-up period (mean, 6.1 years; median, 5.9 years), 291 patients experienced BCR (1000 censored) and 166 patients had an event (1125 censored).

Comparison of the Risk Classification Systems

The Kaplan-Meier curves for BCR-FS and EFS using the original CAPRA, CAPRA-T, M1 CAPRA, and M2 CAPRA in the MRI-targeted biopsy cohort are illustrated in Figure 1. The M2 CAPRA plot for

BCR-FS showed limited separation between the intermediate-risk and high-risk groups (Fig. 1D). Survival curves for EFS using the original CAPRA and CAPRA-T revealed poor distinction between the low-risk and intermediate-risk groups (Fig. 1E, F). In the systematic biopsy cohort, the original CAPRA, M1 CAPRA, and M2 CAPRA in the systematic biopsy cohort discriminated the 3 risk groups for BCR-FS and EFS (Fig. 2).

Table 4 presents the BCR-FS and EFS probabilities across risk groups in the MRI-targeted biopsy cohort and the systematic biopsy cohort, as well as the C-indices of the different risk classification models. CAPRA-T, M1 CAPRA, and M2 CAPRA C-indices were all higher than the original CAPRA C-indices, either significantly or nonsignificantly (Table 4). In the MRI-targeted biopsy cohort, there was a statistically significant increase in C-indices for BCR-FS using CAPRA-T, M1 CAPRA, and M2 CAPRA and a significant increase in the C-index for EFS using CAPRA-T and M2 CAPRA. In the systematic biopsy cohort, there was statistically significant improvement of C-indices using M1 CAPRA for BCR-FS.

Table 3

Risk group distribution in the MRI-targeted biopsy cohort and systematic biopsy cohort

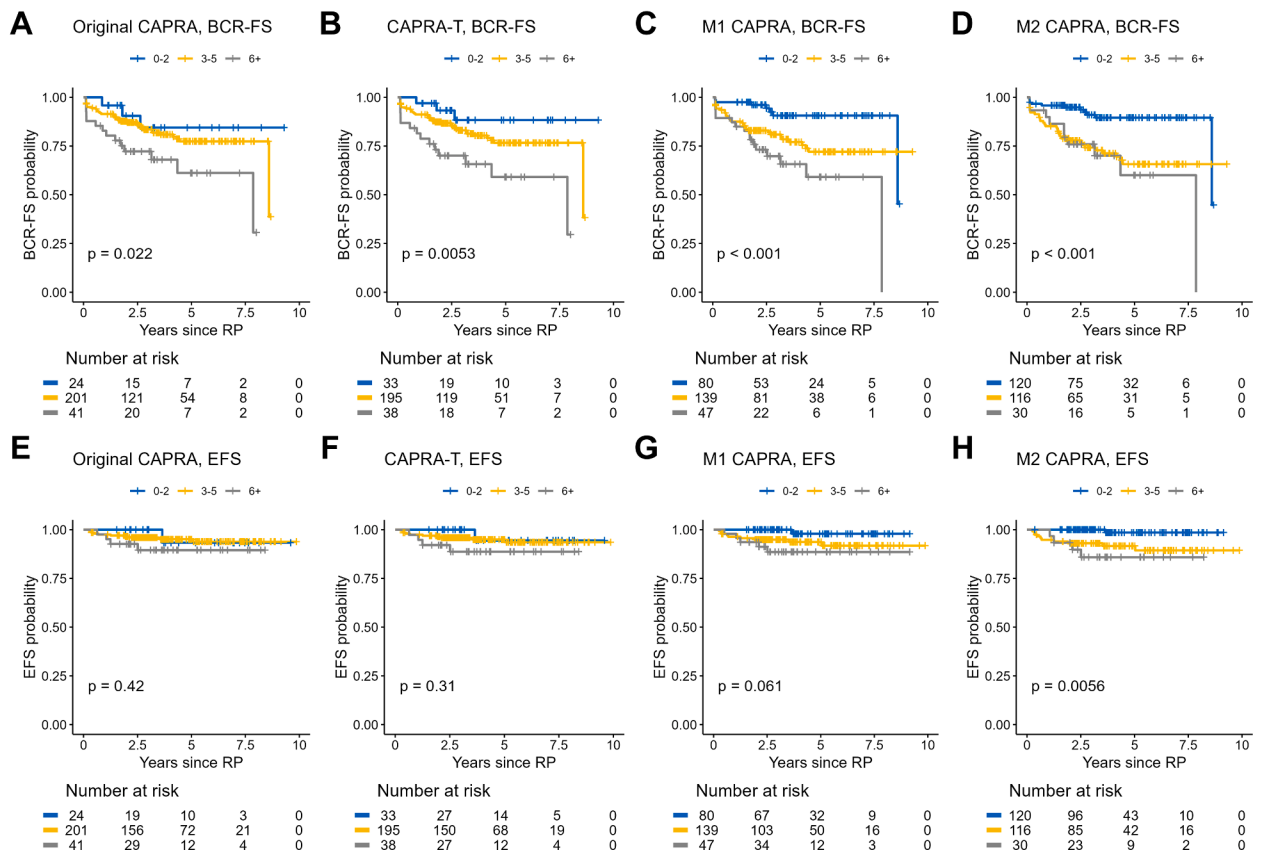
Risk groups	MRI-targeted biopsy cohort (n = 266), n (%)	Systematic biopsy cohort (n = 1291), n (%)	P
Original CAPRA			<.001 ^a
Low-risk group (scores 0-2)	28 (11)	312 (24)	
Intermediate-risk group (scores 3-5)	160 (60)	659 (51)	
High-risk group (scores 6+)	78 (29)	320 (25)	
CAPRA-T			N/A
Low-risk group (scores 0-2)	33 (12)	N/A	
Intermediate-risk group (scores 3-5)	195 (73)	N/A	
High-risk group (scores 6+)	38 (14)	N/A	
M1 CAPRA			.007 ^a
Low-risk group (scores 0-2)	80 (30)	518 (40)	
Intermediate-risk group (scores 3-5)	139 (52)	556 (43)	
High-risk group (scores 6+)	47 (18)	217 (17)	
M2 CAPRA			.080
Low-risk group (scores 0-2)	120 (45)	669 (52)	
Intermediate-risk group (scores 3-5)	116 (44)	470 (36)	
High-risk group (scores 6+)	30 (11)	152 (12)	

CAPRA, Cancer of the Prostate Risk Assessment; CAPRA-T, CAPRA MRI-targeted; MRI, magnetic resonance imaging; M1 CAPRA, modified 1 CAPRA; M2 CAPRA, modified 2 CAPRA; N/A, not applicable.

^a Significant P value.

The DCA for BCR-FS and EFS in the MRI-targeted biopsy cohort is shown in Figure 3. Regarding BCR-FS, CAPRA-T demonstrated a marginal increase in the net clinical benefit compared with the original CAPRA. Both M1 CAPRA and M2 CAPRA showed substantial improvement of the net clinical

benefit for BCR-FS compared with the original CAPRA and CAPRA-T. With regard to EFS, M2 CAPRA had the greatest net clinical benefit, followed by M1 CAPRA. CAPRA-T had a marginal increase in the net clinical benefit for EFS compared with the original CAPRA.

**Figure 1.**

Kaplan-Meier curves for BCR-FS and EFS in the MRI-targeted biopsy cohort. (A-D) Four-year BCR-FS probabilities in the MRI-targeted biopsy cohort using the original CAPRA, CAPRA-T, M1 CAPRA, and M2 CAPRA, respectively. (E-H) Four-year EFS probabilities in the MRI-targeted biopsy cohort using the original CAPRA, CAPRA-T, M1 CAPRA, and M2 CAPRA, respectively. BCR-FS, biochemical recurrence-free survival; CAPRA, Cancer of the Prostate Risk Assessment; CAPRA-T, CAPRA MRI-targeted; EFS, event-free survival; MRI, magnetic resonance imaging; M1 CAPRA, modified 1 CAPRA; M2 CAPRA, modified 2 CAPRA; RP, radical prostatectomy.

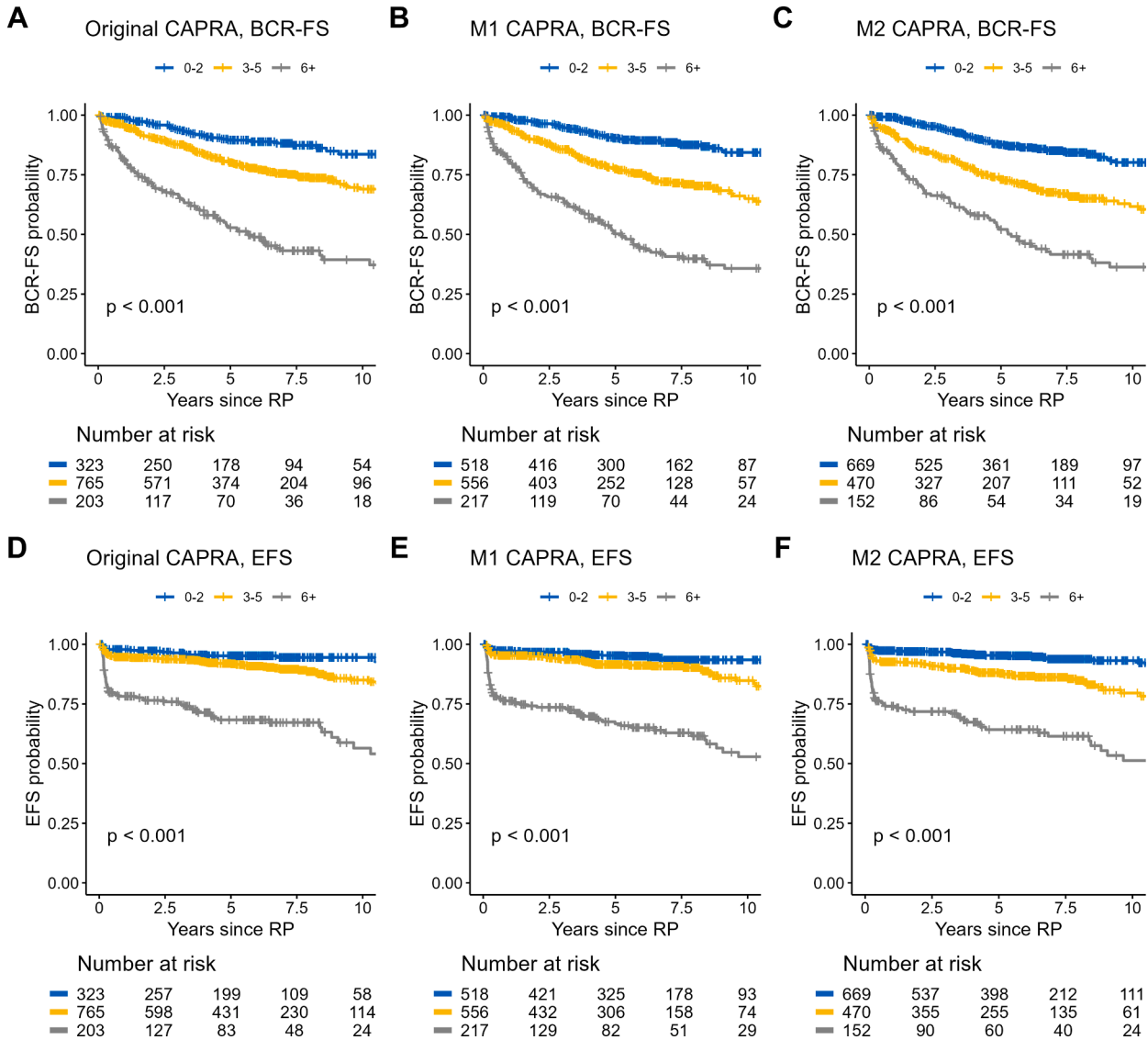


Figure 2.

Kaplan-Meier curves for BCR-FS and EFS in the systematic biopsy cohort. (A-C) Five-year BCR-FS probabilities in the systematic biopsy cohort using the original CAPRA, M1 CAPRA, and M2 CAPRA, respectively. (D-F) Five-year EFS probabilities in the systematic biopsy cohort using the original CAPRA, M1 CAPRA, and M2 CAPRA, respectively. BCR-FS, biochemical recurrence-free survival; CAPRA, Cancer of the Prostate Risk Assessment; EFS, event-free survival; M1 CAPRA, modified 1 CAPRA; M2 CAPRA, modified 2 CAPRA; RP, radical prostatectomy.

The DCA for BCR-FS and EFS in the systematic biopsy cohort is depicted in Figure 4. Regarding BCR-FS, M1 CAPRA yielded the greatest net clinical benefit at all threshold probabilities. M2 CAPRA had increased net clinical benefit for BCR-FS compared with the original CAPRA at threshold probabilities ranging from 0.14 to 0.24. With regard to EFS, M1 CAPRA had overall the greatest net clinical benefit. Compared with the original CAPRA, M2 CAPRA had higher net clinical benefit for EFS for all threshold probabilities.

Across all classification systems, the proportion of patients with adverse pathology at radical prostatectomy increased from the low-risk to high-risk groups, both in the MRI-targeted biopsy cohort and the systematic biopsy cohort (Supplementary Fig. S1).

Discussion

The CAPRA tool is an effective, straightforward 3-tiered classification system for predicting clinical outcome in prostate

cancer.^{1,21} Zelic et al²¹ demonstrated CAPRA (C-index = 0.80) to be comparable with the Memorial Sloan Kettering Cancer Center nomogram (C-index = 0.81) and Cambridge Prognostic Groups system (C-index = 0.78) and superior to D'Amico-derived tools including the NCCN classification. Previous studies published by our group confirmed CAPRA to be superior to the NCCN with respect to model performance.^{14,15}

CC and IDC at biopsy are independently associated with adverse outcomes including high stage at radical prostatectomy, early BCR, nodal disease, distant metastasis, and cancer-specific death.⁹⁻¹³ Previously, we demonstrated that the addition of CC/IDC presence into CAPRA and NCCN pretreatment tools further stratified the CAPRA/NCCN risk groups ($P < .001$) and improved the net clinical benefit in 4 systematic biopsy cohorts.^{14,15} This was also observed in a subset of grade group 2 biopsies.¹⁵ Hence, we believe CC/IDC status should be incorporated in contemporary risk stratification tools with point attribution so that

Table 4

BCR-FS and EFS probabilities across risk groups and Harrell C-indices

Cohort, survival outcome	Risk classification system	Probabilities ^a (95% CI)			Model performance	
		Low-risk group (scores 0-2)	Intermediate-risk group (scores 3-5)	High-risk group (scores 6+)	Harrell C-index	P
MRI-targeted biopsy cohort, 4-y BCR-FS	Original CAPRA	0.84 (0.70-1.00)	0.81 (0.75-0.87)	0.68 (0.54-0.85)	0.574	N/A
	CAPRA-T	0.88 (0.76-1.00)	0.80 (0.74-0.87)	0.66 (0.51-0.84)	0.592	.019 ^a
	M1 CAPRA	0.91 (0.84-0.98)	0.77 (0.70-0.85)	0.66 (0.52-0.83)	0.635	.045 ^a
	M2 CAPRA	0.90 (0.83-0.96)	0.71 (0.63-0.81)	0.70 (0.54-0.91)	0.641	.045 ^a
MRI-targeted biopsy cohort, 4-y EFS	Original CAPRA	0.93 (0.82-1.00)	0.95 (0.92-0.98)	0.89 (0.80-1.00)	0.584	N/A
	CAPRA-T	0.94 (0.84-1.00)	0.95 (0.92-0.98)	0.89 (0.79-1.00)	0.601	.010 ^a
	M1 CAPRA	0.98 (0.94-1.00)	0.94 (0.89-0.98)	0.89 (0.79-0.99)	0.675	.096
	M2 CAPRA	0.99 (0.96-1.00)	0.92 (0.86-0.97)	0.86 (0.74-1.00)	0.731	.003 ^a
Systematic biopsy cohort, 5-y BCR-FS	Original CAPRA	0.89 (0.86-0.93)	0.80 (0.77-0.83)	0.53 (0.46-0.61)	0.655	N/A
	M1 CAPRA	0.90 (0.88-0.93)	0.77 (0.74-0.81)	0.50 (0.43-0.58)	0.696	<.001 ^a
	M2 CAPRA	0.88 (0.85-0.91)	0.73 (0.69-0.78)	0.52 (0.44-0.62)	0.674	.147
Systematic biopsy cohort, 5-y EFS	Original CAPRA	0.95 (0.93-0.98)	0.92 (0.90-0.94)	0.68 (0.62-0.76)	0.679	N/A
	M1 CAPRA	0.95 (0.93-0.97)	0.92 (0.89-0.94)	0.67 (0.60-0.74)	0.709	.096
	M2 CAPRA	0.95 (0.94-0.97)	0.88 (0.85-0.91)	0.64 (0.57-0.73)	0.705	.099

BCR-FS, biochemical recurrence-free survival; CAPRA, Cancer of the Prostate Risk Assessment; CAPRA-T, CAPRA MRI-targeted; EFS, event-free survival; MRI, magnetic resonance imaging; M1 CAPRA, modified 1 CAPRA; M2 CAPRA, modified 2 CAPRA; N/A, not applicable.

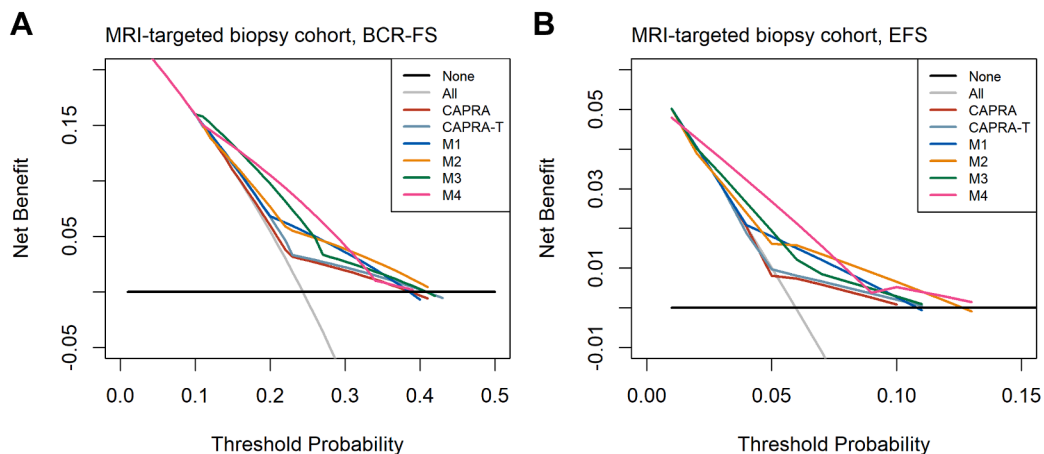
^a Significant P value.

clinicians can readily take into consideration this variable when evaluating the risk of prostate recurrence and making disease management decisions. Considering the widespread adoption of mpMRI and considering CC/IDC presence is an independent predictor of adverse clinicopathological outcomes,⁹⁻¹³ we developed MAPCaRT that consists of a modified CAPRA score incorporating CC/IDC presence and using, in the context of MRI-targeted biopsies, radiological stage and PPB cores based on the aggregate core count method for MRI-targeted lesions. This modified CAPRA tool is meant to be used by clinicians in a real-world setting for MRI-targeted biopsy and/or systematic biopsy.

The high frequency of CC/IDC presence at biopsy (24% in this study) underscores its utility in prognostication. This is even more evident in MRI-targeted biopsies, with 32% being positive for CC/IDC in our cohort. Our MRI-targeted biopsy cohort also

comprised a larger proportion of biopsies with grade group 2 cancer and fewer grade group 1 cancer on biopsy compared with the systematic biopsy cohort. These results are in line with previously published studies showing MRI-targeted biopsies to be associated with higher Gleason scores and increased detection of CC/IDC.^{3,22,23}

To develop MAPCaRT, we first compared the model performance of the original CAPRA in the MRI-targeted biopsy cohort (using the tumor stage based on mpMRI) with that in the systematic-only biopsy cohort (using clinical tumor stage based on DRE). The original CAPRA discriminated well for BCR-FS in both cohorts, suggesting both methods for determining tumor stage at biopsy are reliable. Our results align with a recent paper, which demonstrated that substitution of DRE-based clinical tumor stage by mpMRI-based tumor stage in the original CAPRA

**Figure 3.**

DCA using the original CAPRA, CAPRA-T, M1 CAPRA, and M2 CAPRA in the magnetic resonance imaging-targeted biopsy cohort. (A) DCA for BCR-FS. (B) DCA for EFS. BCR-FS, biochemical recurrence-free survival; CAPRA, Cancer of the Prostate Risk Assessment; CAPRA-T, CAPRA magnetic resonance imaging targeted; DCA, decision curve analysis; EFS, event-free survival; M1 CAPRA, modified 1 CAPRA; M2 CAPRA, modified 2 CAPRA.

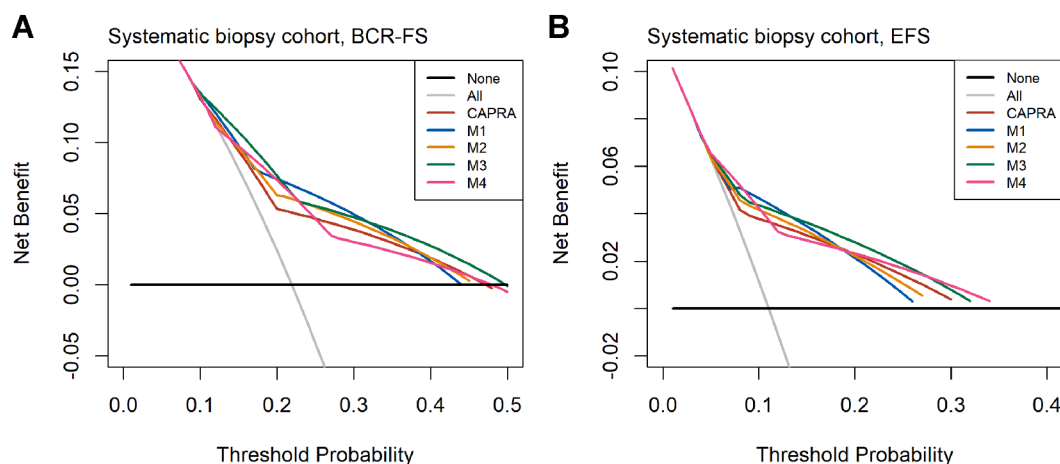


Figure 4.

DCA using the original CAPRA, M1 CAPRA, and M2 CAPRA in the systematic biopsy cohort. (A) DCA for BCR-FS. (B) DCA for EFS. BCR-FS, biochemical recurrence-free survival; CAPRA, Cancer of the Prostate Risk Assessment; DCA, decision curve analysis; EFS, event-free survival; M1 CAPRA, modified 1 CAPRA; M2 CAPRA, modified 2 CAPRA.

algorithm did not affect its prognostic impact.²⁰ The lack of differentiation between the low-risk and intermediate-risk groups on the Kaplan-Meier curves for EFS in the MRI-targeted biopsy cohort may be explained by the low number of events recorded given the smaller MRI cohort and shorter follow-up time.

Furthermore, we evaluated the prognostic impact of calculating PPB cores using the aggregate core count method for MRI-targeted lesions (CAPRA-T) instead of the individual core count method (original CAPRA). Similar to the original CAPRA, the Kaplan-Meier curves showed that CAPRA-T discriminated well for BCR-FS but lacked discrimination of the low-risk and intermediate-risk groups for EFS. With regard to the Harrell C-indices and the DCA, CAPRA-T significantly improved C-indices and marginally improved the net clinical benefit for both BCR-FS and EFS compared with the original CAPRA. Our findings are concordant with the study by Gordetsky et al,²⁴ which showed the aggregate count method to be more strongly correlated with target lesion volume and extraprostatic extension at radical prostatectomy in a cohort of 55 patients. We believe that CAPRA-T would be even more performant than the original CAPRA, especially with regard to EFS stratification, if the analyzed MRI-targeted biopsy cohort was increased in size, had a longer follow-up time with more events, and included more MRI-targeted-only biopsies.

We then demonstrated that M1 CAPRA, which integrates CC/IDC presence and uses the aggregate core count method for MRI-targeted lesions (such as CAPRA-T), had better model performance than the original CAPRA. In fact, M1 CAPRA improved EFS stratification in the MRI-targeted biopsy cohort and a significantly increased C-index for BCR-FS in both cohorts, while showing marginal improvement of the other model performance metrics. These results confirm the independent prognostic value of CC/IDC presence.

When applied to the MRI-targeted biopsy cohort, M2 CAPRA, which removed PPB cores from M1 CAPRA, exhibited substantial improvement of C-indices and the DCA for BCR-FS and EFS but worse BCR-FS stratification compared with the original CAPRA based on the Kaplan-Meier curves. Based on the other performance metrics, M2 CAPRA was comparable with the original CAPRA. In comparison with M1 CAPRA, M2 CAPRA had a significantly higher C-index for EFS and greater net clinical benefit for BCR-FS and EFS in the MRI-targeted biopsy cohort, but it had a significantly lower C-index for BCR-FS in the systematic biopsy

cohort. Our findings suggest that PPB core remains an important prognosticator in systematic biopsies. Its prognostic value in MRI-targeted biopsy is still uncertain because the advantages and disadvantages compared with M1 CAPRA are variable using the Kaplan-Meier method versus the Harrell C-indices and DCA. The discrepancies may be because of the small cohort size, the low number of observations, and the heterogeneity of our MRI-targeted biopsy cohort, which comprised mainly combined biopsies and only few MRI-targeted-only biopsies. Overall, M2 CAPRA still proved to be superior to the original CAPRA in terms of model performance, which highlights once again the independent prognostic significance of CC/IDC presence.

Modified CAPRA scores classified more patients in the low-risk group and less patients in the intermediate-risk group than the original CAPRA and CAPRA-T. Thus, the modified CAPRA scores have the potential of identifying more candidates for which deferred management strategies would be the most beneficial. However, all patients included in our study had radical prostatectomy, which likely contributed to decrease the risk of BCR and metastasis. That said, in both cohorts, the incidence of adverse pathology on radical prostatectomy appropriately increased across risk groups (from low to high) using any risk stratification model, which suggests that our new tools can also reliably predict pathological outcomes. A prospective study in which patients categorized as low risk are managed with active surveillance instead of radical prostatectomy would validate the clinical significance of the M1/M2 CAPRA low-risk group.

While both M1 CAPRA and M2 CAPRA had overall improved model performance compared with the original CAPRA and CAPRA-T, M1 CAPRA demonstrated more advantages and was thus selected to build MAPCaRT (prostatecancercalculator.IMP.utoronto.ca). We did not consider the models' performance for predicting EFS in MRI-targeted biopsies in the selection process, and the MAPCaRT calculator for MRI-targeted biopsies does not output EFS probabilities. We recognize that the number of events ($n = 15$) in the MRI-targeted biopsy cohort may be insufficient to support definitive conclusions.

The main limitations of our study were the small size and limited follow-up time of our MRI-targeted biopsy cohort given mpMRI and MRI-targeted biopsies remain relatively new clinical practice. A larger MRI-targeted biopsy cohort with a longer follow-up would strengthen BCR-FS and EFS analysis. Having an MRI-targeted biopsy cohort from institutions in different

geographical areas would also allow to take into consideration the interinstitutional variation in grading Prostate Imaging Reporting and Data System and performing MRI-targeted biopsy. Moreover, our cohorts, which comprised consecutive biopsies with matched radical prostatectomy, had very few GG4 and GG5 patients, suggesting the models may be more applicable to lower grade cancer. Additional limitations were the retrospective design, the lack of an external validation cohort, and the cohort selection based on radical prostatectomy treatment. Further systematic and MRI-targeted cohorts are required to validate the findings of this novel approach and perform a subanalysis of GG4 and GG5 prostate cancer patients.

Although a few studies have shown cribriform morphology area ratio in radical prostatectomy to be associated with improved BCR predictions,^{25,26} it has not yet been validated in biopsy specimens. MAPCaRT offers the advantage of being simple and is in line with current practice guidelines, with CC/IDC assessed as a dichotomous variable (present vs not identified). An area for improvement is the sensitivity of prostate biopsy for detecting CC/IDC, which currently ranges between 42% and 47%.^{27–30} Methods to increase its sensitivity may raise the clinical impact of CC/IDC presence at biopsy. It may also be useful to develop a postsurgical risk stratification tool incorporating CC/IDC presence.¹⁶

In summary, based on a multi-institutional prostate biopsy cohort, we developed MAPCaRT, a modified and improved version of CAPRA that can be used for MRI-targeted or systematic biopsies. It classifies men in the low-risk (scores 0–2), intermediate-risk (scores 3–5), or high-risk (scores 6+) group using easily accessible clinicopathological variables: patient age, serum PSA level at biopsy, Gleason primary and secondary patterns, CC/IDC presence, radiological/clinical stage, and PPB core, which uses the aggregate core count method for MRI-targeted lesions (prostatecancercalculator.IMP.utoronto.ca). We demonstrated its overall superior model performance for predicting BCR-FS and EFS compared with the original CAPRA in MRI-targeted biopsies and systematic-only biopsies. Our findings strengthen the importance of reporting CC/IDC presence in prostate cancer for informed management decisions.

Author Contributions

M.R.D. and T.H.v.d.K. performed study concept and supervision; M.R.D., T.H.v.d.K., and N.-N.J.N. designed the study; N.-N.J.N., K.Liu, R.B., L.B.Y., L.J.K., E.H., G.J.L.H.v.L., K.A.I., T.H.v.d.K., and M.R.D. provided acquisition of data; N.-N.J.N., T.H.v.d.K., and M.R.D. analyzed and interpreted the data; N.-N.J.N. drafted the manuscript; K.Lajkosz performed the statistical analysis. All authors provided critical revision of the manuscript for important intellectual content and approved the final paper.

Data Availability

The data generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Declaration of Competing Interest

The authors report no relevant conflicts of interest.

Ethics Approval/Consent to Participate

Ethical approval for this study was obtained from the Research Ethics Board of Sunnybrook Health Sciences Centre (REB 395-2017), the Research Ethics Board of the University Health Network (CAPCR17-5727), the Institutional Review Board of Medical College of Wisconsin (IRB PRO16747), and the Medical Ethics Review Committee of Erasmus University Medical Centre (MEC-2018-1614).

Supplementary Material

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