Original Study

Addition of Cribriform and Intraductal Carcinoma Presence to Prostate Biopsy Reporting Strengthens Pretreatment Risk Stratification Using CAPRA and NCCN Tools

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Abstract

Cribriform Gleason pattern 4 and intraductal carcinoma of the prostate are adverse pathologic features. We retrospectively assessed their impact when added to CAPRA and NCCN pretreatment tools in 3 patient cohorts (Toronto, Wisconsin and Rotterdam) and show improved patient stratification for both biochemical recurrence and development of metastases and death of disease (events) with their inclusion.

Background: Pretreatment stratification tools can help in clinical decision making in prostate cancer. To date, none incorporates well-established routinely reported adverse prognostic pathologic features such as intraductal carcinoma of prostate (IDC) or cribriform pattern 4 (CC). **Objective:** To assess the impact of addition of CC and/or IDC on the Cancer of Prostate Risk Assessment (CAPRA) and National Cancer Comprehensive Network (NCCN) tools for predicting biochemical recurrence free survival (BCR-FS) and event-free survival (EFS) across multiple patient cohorts. **Design, setting, and participants:** Matched prostate biopsies and radical prostatectomies from institutions in Toronto, Wisconsin and Rotterdam. The presence/absence of CC/IDC was recorded on all biopsies. **Outcome measurements and statistical analysis:** Relationship to outcome was assessed using Cox proportional hazard models, ANOVA and Harrell's concordance index. **Results and limitations:** We included 1326 patients (Toronto- 612, Wisconsin- 542, Rotterdam- 172) with median follow up of 4.2 years (IQR 2.9-6.4 years); 306 (23.1%) had CC/IDC on biopsy with 207 (20.9%) BCR and 154 (11.6%) events (metastases/death). Addition of CC/IDC improved stratification in CAPRA scores 3 to 5 for BCR-FS (c-index increase 0.633-0.658, $P < .001$) and scores 6-10 for EFS (c-index increase 0.653-0.697, $P < .001$). For NCCN, all risk groups apart from score 1 to 2 showed improvement in BCR-FS (c-index increase 0.599-0.636, $P < 0.001$) and EFS prediction (c-index increase 0.648-0.697, $P < .001$). Sub-analysis of grade group (GG) 2 biopsies showed similar findings. The retrospective nature and inclusion of cases only reported by genitourinary pathologists are study limitations. **Conclusions:** The clinical benefit of the addition of CC/IDC to both CAPRA and NCCN pretreatment tools was validated in 3 cohorts, including the subset of biopsy GG2 prostate cancer patients. **Patient summary:** Including additional pathologic features to existing pretreatment, clinical decision making tools improves the ability to predict prostate cancer recurrence, cancer spread and death of disease.

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Introduction

Pretreatment stratification tools can inform management decisions in prostate cancer patients. Given the heterogeneity of prostate cancer and the variability of its natural history, these risk stratification tools are used to predict biochemical recurrence (BCR) and/or death from prostate cancer in a given individual. A wide variety of such risk tools are in use, each of which incorporates clinical parameters such as patient age, serum prostate specific antigen (PSA) and the clinical stage of the tumor, along with several pathologic parameters at biopsy, such as the Gleason score, its component grades and the fraction of cores with prostate cancer. A recent cohort study from Sweden compared multiple prestratification tools in over 130,000 prostate cancer patients and concluded that the Memorial Sloan Kettering Cancer Center (MSKCC) nomogram and the Cancer of Prostate Risk Assessment (CAPRA) tool outperformed the D'Amico and D'Amico derived tools such as the National Cancer Comprehensive Network (NCCN) tool in predicting prostate cancer death.[1] CAPRA and NCCN are used clinically and rely on the above described clinical and pathologic parameters to produce a risk score,[2,3] which then informs patient discussion regarding future management. To date, existing pretreatment risk tools have not incorporated morphologic features of intraductal carcinoma of the prostate (IDC) or cribriform pattern 4 carcinoma (CC). These pathologic entities are seen in up to ~25% of prostate biopsies,[4-6] are recognizable on standard hematoxylin and eosin (H&E) sections and now routinely reported.[7] Both are associated with adverse patient outcomes including BCR, metastases and death of disease.[6,8-14] We have previously analyzed the impact of addition of CC and IDC on both the CAPRA and NCCN pretreatment stratification tools[15] and found an improvement of patient stratification for CAPRA score 3 to 5 and NCCN score 4, 5, and 6 in a cohort from Toronto, Canada. In our present work, we assess whether the same results could be validated in 2 additional independent cohorts, 1 North American (Wisconsin) and 1 European (Rotterdam). As a secondary aim, we performed the same analysis within the Grade group (GG) 2 biopsies, recognizing that this category (Gleason score 7/10, 3 + 4) is the most frequently reported biopsy result. To assess the clinical benefit of the findings, a decision curve analysis (DCA) was performed.

Materials and Methods

Cohort Selection

The original Toronto cohort comprised patients from 2 university hospitals (University Health Network and Sunnybrook Health Sciences Centre) identified through retrospective searches of each institution's laboratory information system (LIS). The cohort description has previously been published.[15] In brief, consecutive, treatment naïve prostatic adenocarcinoma patients with matched in-house prostate biopsy and radical prostatectomy (time period 2010-2017) were included (REB 395-2017/CAPCR 17-5727). This original cohort is included for comparison with the 2, new validation cohorts.

Two validation cohorts were accrued, one from North America (Wisconsin, USA, IRB PRO16747) and the second from Europe (Erasmus MC, Rotterdam, The Netherlands, MEC-2018-1614). Similar to the Toronto cases, these cohorts comprised therapy naïve prostate cancer patients with both their prostate biopsy and subsequent prostatectomy available within the respective institutions. The Wisconsin cohort consisted of cases from 2013 to 2018 and the Rotterdam cohort of cases from 2010 to 2017.

Case Review and Clinicopathologic Parameters

As previously described,[15] all hematoxylin and eosin (H&E) slides from standard, systematic biopsies and prostatectomy were reviewed by genitourinary pathologists (Toronto: MRD, TvdK, Wisconsin: KI, KL and Rotterdam: EHO, GvL) to assess for the Grade group and presence of CC/IDC. The consensus recommendations from the ISUP were followed and for this work CC/IDC were combined as one entity[7] with previously published definitions of both IDC[4,11] and CC[16] utilized. The following clinicopathologic parameters were collected for each case: patient age, serum PSA (ng/mL) at biopsy, clinical T-stage (c-T), number of biopsy cores, number of cores with prostatic adenocarcinoma, global biopsy Gleason score and nodal status at prostatectomy (pN). The following data were recorded for clinical outcome analysis: biochemical recurrence (BCR) defined as 2 consecutive postprostatectomy PSA readings >0.2ng/mL, with the interval from prostatectomy (years) used to define time to BCR. Both metastases and/or death from prostate cancer were considered for event-free survival (EFS) with time from biopsy (years) to event defining time to EFS. Cases with no recorded events were censored at the last follow up. Both the CAPRA and NCCN (V1, 2019) scores were tabulated using the relevant parameters listed above as previously described.[15] CAPRA score 0 to 2 was "low," 3 to 5"intermediate" and 6 to 10 "high risk." NCCN score 1-2 was "very low/low," 3 "favorable intermediate" 4 "unfavorable intermediate" and 5-6 "high/very high."

Statistical Analysis

BCR-free survival (BCR-FS) and EFS probabilities were estimated using the Kaplan-Meier method. Positive nodes at radical prostatectomy were considered an event in EFS. Differences in curves by risk groups were assessed using the two-sided log-rank test. To evaluate the discriminatory ability of each risk stratification method, Cox proportional hazards models were fit, and Harrell's concordance index (c-index) was estimated using 1000 bootstrap resamples. ANOVA tests comparing the log-likelihood statistic of models with and without CC or IDC were conducted.

Decision curve analysis assessing the net benefit of CAPRA/NCCN with and without CC or IDC was conducted and visualized. The 5-year event probability was assessed in the analysis. The statistical analysis was completed using R version 4.0.0 (R Core Team, 2020). *P*-values less than .05 were considered significant.

Results

Cohort Characteristics

The clinicopathologic parameters of the 3 cohorts (n = 1326) are presented in Table 1 . The original, control Toronto cohort consisted of 612 cases, the Wisconsin cohort of 542 and the Rotterdam cohort of 172. The median age was 64 years (IQR 58-68 years) with a median PSA was 6.7 ng/mL. Overall, 306 of 1326 biopsies

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Table 1 Clinicopathologic Features of the Original and Two Validation Cohorts (n = 1326)

	Original Cohort		Validation Cohorts		*P*-value
	All (n = 1326)	Toronto (n = 612)	Rotterdam (n = 172)	Wisconsin (n= 542)	
Age (years)					<.001
Mean (SD)	62.9 (6.8)	63.1 (7.0)	65.3 (6.4)	61.9 (6.5)	
Median (Q1,Q3)	63.8 (58, 68)	64 (58, 68)	65.9 (61.3, 70.2)	62 (57, 67)	
Range (min, max)	(39.7, 83)	(41, 79)	(39.7, 76.5)	(40, 83)	
PSA (ng/mL)					<.001
Mean (SD)	9.3 (10.6)	8.6 (8.7)	12.6 (11.1)	8.9 (11.9)	
Median (Q1,Q3)	6.7 (5.0, 10.0)	6.7 (4.8, 9.6)	9.0 (6.4, 15.0)	6.3 (4.9, 9.4)	
Range (min, max)	(0.5, 154.0)	(0.5, 97.0)	(2.6, 84.0)	(0.7, 154.0)	
Biopsy GG					<.001
1	269 (20.4)	91 (14.9)	46 (26.9)	136 (25.1)	
2	679 (51.4)	350 (57.1)	91 (52.6)	239 (44.1)	
3	198 (15.0)	99 (16.2)	10 (5.8)	91 (16.8)	
4	92 (7.0)	42 (6.9)	14 (8.2)	36 (6.7)	
5	81 (6.2)	30 (4.9)	11 (6.4)	40 (7.5)	
CC/IDC					<.001
No	1020 (76.9)	453 (74.0)	119 (69.2)	448 (82.7)	
Yes	306 (23.1)	159 (26.0)	53 (30.8)	94 (17.3)	
CAPRA					.03
0	3 (0.2)	1 (0.2)	0 (0.0)	2 (0.4)	
1	75 (5.7)	28 (4.6)	4 (2.3)	43 (7.9)	
2	239 (18.0)	103 (16.8)	28 (16.3)	108 (19.9)	
3	304 (22.9)	159 (26.0)	33 (19.2)	112 (20.7)	
4	280 (21.1)	135 (22.1)	37 (21.5)	108 (19.9)	
5	205 (15.5)	94 (15.4)	32 (18.6)	79 (14.7)	
6	124 (9.4)	55 (9.0)	21 (12.2)	48 (8.9)	
7	65 (4.9)	26 (4.2)	9 (5.2)	30 (5.6)	
8	18 (1.4)	8 (1.3)	5 (2.9)	5 (0.9)	
9	12 (0.9)	3 (0.5)	2 (1.2)	7 (1.3)	
10	1 (0.1)	0 (0.0)	1 (0.6)	0 (0.0)	
CAPRA Group					.005
0-2	317 (23.9)	132 (21.6)	32 (18.6)	153 (28.2)	
3-5	789 (59.5)	388 (63.4)	102 (59.3)	299 (55.2)	
6-10	220 (16.7)	92 (15.0)	38 (22.1)	90 (16.8)	
CAPRA CC/IDC					<.001
0-2	317 (23.9)	132 (21.6)	32 (18.6)	153 (28.2)	
3-5, No	621 (46.8)	289 (47.2)	71 (41.3)	261 (48.2)	
3-5, Yes	168 (12.7)	99 (16.2)	31 (18.0)	38 (7.0)	
6-10, No	98 (7.4)	35 (5.7)	18 (10.5)	45 (8.4)	
6-10, Yes	122 (9.2)	57 (9.3)	20 (11.6)	45 (8.4)	
NCCN					<.001
1	68 (5.1)	18 (2.9)	6 (3.5)	44 (8.1)	
2	138 (10.4)	52 (8.5)	17 (9.9)	69 (12.8)	
3	439 (33.2)	214 (35.0)	55 (32.0)	170 (31.7)	
4	439 (33.1)	235 (38.4)	35 (20.3)	169 (31.2)	
5	199 (15.1)	82 (13.4)	48 (27.9)	69 (12.8)	
6	43 (3.3)	11 (1.8)	11 (6.4)	21 (3.9)	

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Table 1 (*continued*)

	Original Cohort		Validation Cohorts		*P*-value
	All (n = 1326)	Toronto (n = 612)	Rotterdam (n = 172)	Wisconsin (n= 542)	
NCCN Group					<.001
1-2	206 (15.5)	70 (11.4)	23 (13.4)	113 (20.8)	
3	439 (33.2)	214 (35.0)	55 (32.0)	170 (31.7)	
4	439 (33.1)	235 (38.4)	35 (20.3)	169 (31.1)	
5-6	242 (18.3)	93 (15.2)	59 (34.3)	90 (16.8)	
NCCN CC/IDC					<.001
1-2	206 (15.5)	70 (11.4)	23 (13.4)	113 (20.8)	
3, No	368 (27.9)	177 (28.9)	41 (23.8)	150 (27.9)	
3, Yes	71 (5.4)	37 (6.0)	14 (8.1)	20 (3.7)	
4, No	314 (23.7)	156 (25.5)	23 (13.4)	135 (24.9)	
4, Yes	125 (9.4)	79 (12.9)	12 (7.0)	34 (6.3)	
5-6, No	135 (10.2)	50 (8.2)	34 (19.8)	51 (9.5)	
5-6, Yes	107 (8.1)	43 (7.0)	25 (14.5)	39 (7.3)	
BCR					<.001
No	1049 (79.1)	511 (83.5)	124 (72.1)	414 (76.4)	
Yes	277 (20.9)	101 (16.5)	48 (27.9)	128 (23.6)	
Events					<.001
No	1172 (88.4)	548 (89.5)	132 (76.7)	492 (90.8)	
Yes	154 (11.6)	64 (10.5)	40 (23.3)	50 (9.2)	
Follow Up (Years)					<.001
Mean (SD)	4.7 (2.8)	5.3 (3.0)	4.5 (3.4)	4.1 (2.0)	
Median (Q1,Q3)	4.2 (2.9, 6.4)	4.4 (3.2, 8.4)	4.1 (1.2, 7.0)	4.0 (2.9, 5.7)	
Range (min, max)	(0.0, 12.5)	(0.0, 10.8)	(0.1, 12.5)	(0.1, 8.2)	

BCR = biochemical recurrence; CAPRA = Cancer of Prostate Risk Assessment; CC/IDC = cribriform pattern 4 carcinoma/intraductal carcinoma; GG = grade group; NCCN= National Cancer Comprehensive Network; PSA = prostate specific antigen.

had CC/IDC (23.1%). The median follow-up was 4.2 years (IQR 2.9-6.4 years). BCR was documented in 277 of 1326 (20.9%) of the cohort and 154 events were recorded (11.6%).

Stratification of Patient Outcome Using CAPRA and NCCN Scores

Supplementary Figure 1 shows both the overall and each cohort's individual Kaplan-Meier curves for BCR-FS and EFS using both CAPRA and NCCN scores. The 5-year recurrence free probabilities in the CAPRA 0-2, 3-5, and 6-10 categories were 0.90 (95% CI: 0.86-0.94), 0.77 (95% CI: 0.74-0.81) and 0.55 (95% CI: 0.48-0.64), respectively. The 5-year recurrence probabilities in NCCN 1-2, 3-4, and 5-6 groups were 0.83 (95% CI: 0.77-0.89), 0.84 (95% CI: 0.80-0.88), 0.72 (95% CI: 0.67-0.77) and 0.66 (95% CI: 0.59-0.73), respectively.

The 5-year event free survival probabilities in the CAPRA 0 -2, 3-5, and 6-10 categories were 0.95 (95% CI: 0.93-0.98), 0.91 (95% CI: 0.88-0.93) and 0.72 (95% CI: 0.66-0.79), respectively. The 5 year EFS probabilities in the NCCN 1-2, 3, 4, 5-6 risk scores were, respectively, 0.95 (95% CI: 0.92-0.98), 0.93 (95% CI: 0.91-0.96), 0.87 (95% CI: 0.84-0.91) and 0.78 (95% CI: 0.73-0.84).

Addition of CC/IDC to CAPRA and NCCN

Figure 1 shows the impact of the addition of CC/IDC to CAPRA for both BCR-FS and EFS. In terms of BCR-FS, there is improved prognostication most notable in CAPRA 3-5 (intermediate risk) which is evident across the original cohort and both validation cohorts (Figure 1A1). Taking all cohorts together, the addition of CC/IDC in the CAPRA 3-5 category results in a difference in the 5-year BCR free probability of 0.09: 0.79 in those lacking CC/IDC versus 0.70 in those with CC/IDC (HR of 1.91). In the Rotterdam group, addition of CC/IDC also significantly impacted the 6 to 10 risk score (Figure 1A3). The Harrell's c-index increased in the 3 cohorts combined from 0.633 to 0.658 (ANOVA $P <$ .001) with addition of CC/IDC. For EFS, CC/IDC status significantly impacts both the 3 to 5 and 6 to 10 risk scores (Figure 1B1) with c-index increasing from 0.653 to 0.697 (ANOVA $P <$ .001). Figure 3 shows the impact of CC/IDC on BCR-FS and EFS using the NCCN scores with improved prognostication of NCCN risk scores 3, 4 and 5-6 (Figure 2A1) with the c-index increasing from 0.599 to 0.636 (ANOVA $P <$ .001) for BCR-FS. Similar to the CAPRA 3-5 category, in all cohorts, the NCCN score 4 category shows a difference of 0.16 in 5-year BCR free survival: 0.76 in those lacking CC/IDC and 0.60 in those with CC/IDC. For EFS

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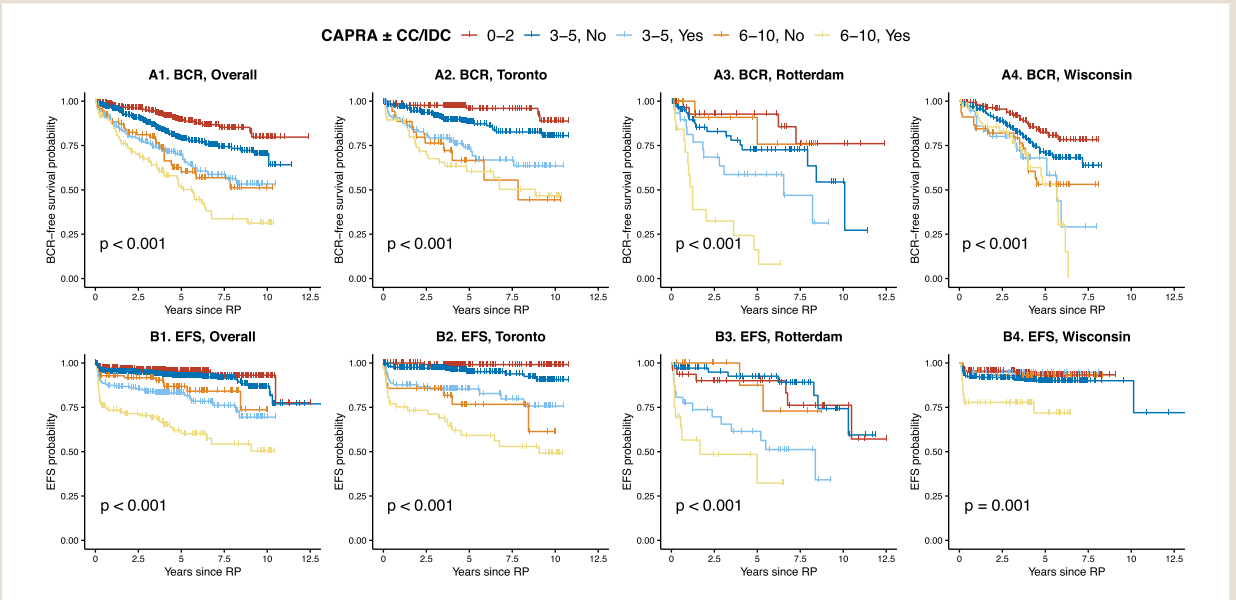
Figure 1 Impact of CC/IDC on CAPRA for both BCR and EFS. Part A demonstrates BCR rates with addition of CC/IDC using CAPRA overall, and in each cohort. Part B demonstrates EFS rates with addition of CC/IDC using CAPRA overall, and in each cohort.



(Figure 2B1), the c-index increased from 0.648 to 0.697 (ANOVA $P < .001$). Supplementary Table 1 shows the Cox proportional hazards models used to model BCR free survival and EFS.

Grade Group 2 Biopsy Sub-Analysis

The entire cohort comprised 680 GG2 biopsies (original Toronto cohort, n = 350, Wisconsin validation cohort, n = 239, Rotterdam validation cohort, n = 91). Supplementary Table 2 shows the clinicopathologic parameters for the GG2 biopsies. Figure 3 shows the KM curves for BCR-FS and EFS using CAPRA and NCCN with the impact of the addition of CC/IDC to each. Similar to the entire cohort, addition of CC/IDC improved BCR-FS (Figure 3A2) prognostication in the CAPRA 3-5 risk score (c-index increased from 0.564 to 0.619, ANOVA $P < .001$) and in all NCCN risk categories (Figure 3B2), most notably for scores 4 and 5-6 (c-index increased from 0.591 to 0.634, ANOVA $P < .001$). For EFS, CAPRA 3-5 and 6-10 scores showed improved prognostication (Figure 3C2) after addition of CC/IDC status (c-index increased from 0.581 to 0.626, ANOVA $P < .001$). For NCCN, again risk category 4, 5-6 showed significant improvement of addition of CC/IDC (Figure 3D2) for EFS prediction (c-index increased from 0.637 to 0.666, ANOVA $P = .043$). The supplementary Figures 2 and 3 display the new risk groups for both CAPRA and NCCN when incorporating CC/IDC.

Decision Curve Analysis

Figure 4 presents the decision curve analysis (DCA) curves for the clinical benefit of the addition of CC/IDC for both CAPRA and NCCN pretreatment classification tools. For BCR-FS at 5 years, the addition of CC/IDC to the NCCN tool (Figure 4B1-B4) showed greater net benefit in identifying patients for adjuvant treatment between threshold probabilities 15% to 30%. For CAPRA this improvement was noted between threshold probabilities 25% to 30% (Figure 4A1-A4). For EFS at 5 years, the addition of CC/IDC improved both the CAPRA (between threshold probabilities 10%-25%) and NCCN (between threshold probabilities 10%-20%) in the cohort (Figure 4, C1-C4 and D1-D4 respectively).

Discussion

We retrospectively analyzed the impact of adding CC/IDC to 2 commonly used pretreatment prostate cancer stratification tools, namely CAPRA and NCCN across 3 separate patient cohorts, including our original, previously published[15] Toronto cohort, and 2 validation cohorts (Wisconsin, USA and Rotterdam, The Netherlands). NCCN is a D'Amico derived risk group system which is used for predicting BCR and was only recently examined[1] in relation to its ability to predict death of prostate cancer. CAPRA is a risk score which has been used to predict BCR-FS[17,18] and also death from prostate cancer.[19,20] Differences in the prognostic performance of these 2 pretreatment tools has been shown[1] with the CAPRA score (c-index 0.80) outperforming NCCN (c-index 0.76) in predicting prostate cancer death at 10 years. In our previous investigation,[15] we analyzed patient series from tertiary care academic health sciences centers in Toronto and found that CAPRA outperformed NCCN in predicting BCR (c-index 0.663 vs. 0.612) while NCCN performed slightly better for EFS, defined as time to metastases and/or death of prostate cancer (c-indexes 0.736 vs. 0.762 respectively). In this current study, CAPRA outperformed NCCN in the 2 validation cohorts for predicting BCR-FS at 5 years and in terms of EFS, CAPRA again outperformed NCCN at 5 years. Our results are

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Figure 2 Impact of CC/IDC on NCCN for both BCR and EFS. Part A demonstrates BCR rates with addition of CC/IDC using NCCN overall, and in each cohort. Part B demonstrates EFS rates with addition of CC/IDC using NCCN overall, and in each cohort.

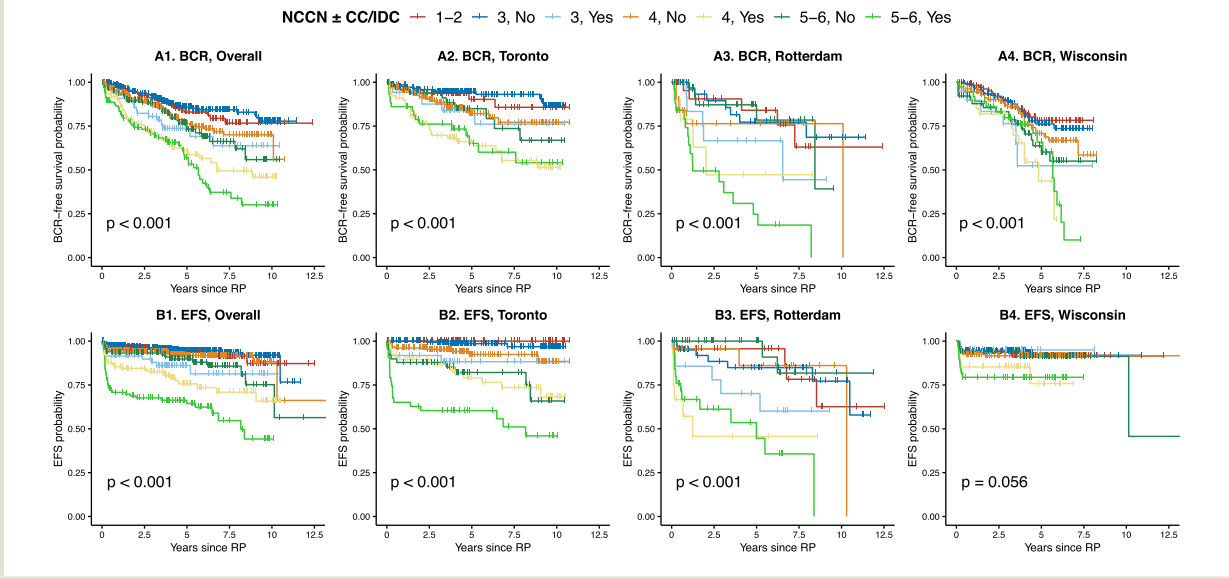
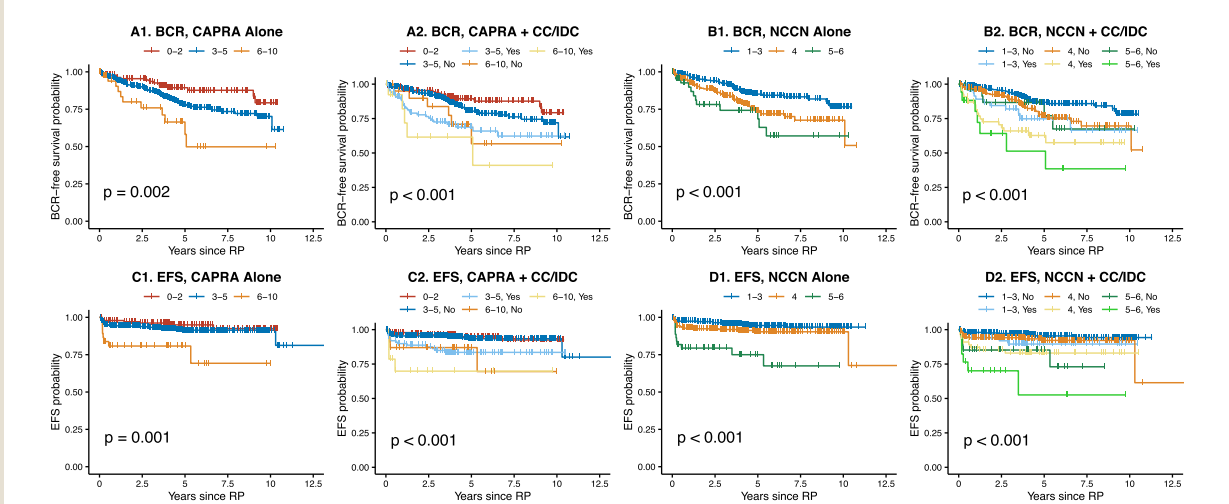


Figure 3 Sub-analysis of all Grade group 2 biopsies. Part A demonstrates BCR rates with addition of CC/IDC to CAPRA. Part B demonstrates BCR rates with addition of CC/IDC to NCCN. Part C demonstrates EFS rates with addition of CC/IDC to CAPRA. Part D demonstrates EFS rates with addition of CC/IDC to NCCN.



in-line with the data from the large retrospective Swedish study[1] however the c-indices in our work are lower. This is largely driven by 100-fold difference in cohort sizes (130,000 vs. 1326).

Both IDC and CC are now recognized as independent, adverse morphologic parameters in prostate cancer and have been shown in multiple studies to associate with increased pathologic stage at prostatectomy,[14] presence of nodal metastases,[6,21] reduced time to BCR-FS,[11,22,23] distant metastases and death of prostate cancer.[5,8,9] IDC/CC status is now recommended pathology reporting element,[7] but despite this, has not been incorporated into existing pretreatment tools. We previously reported on the impact of the inclusion of IDC/CC on both CAPRA and NCCN[15] showing that the c-index of each increased for both BCR-FS and EFS. Herein, we validate those findings in 2 additional cohorts for both BCR-FS and EFS

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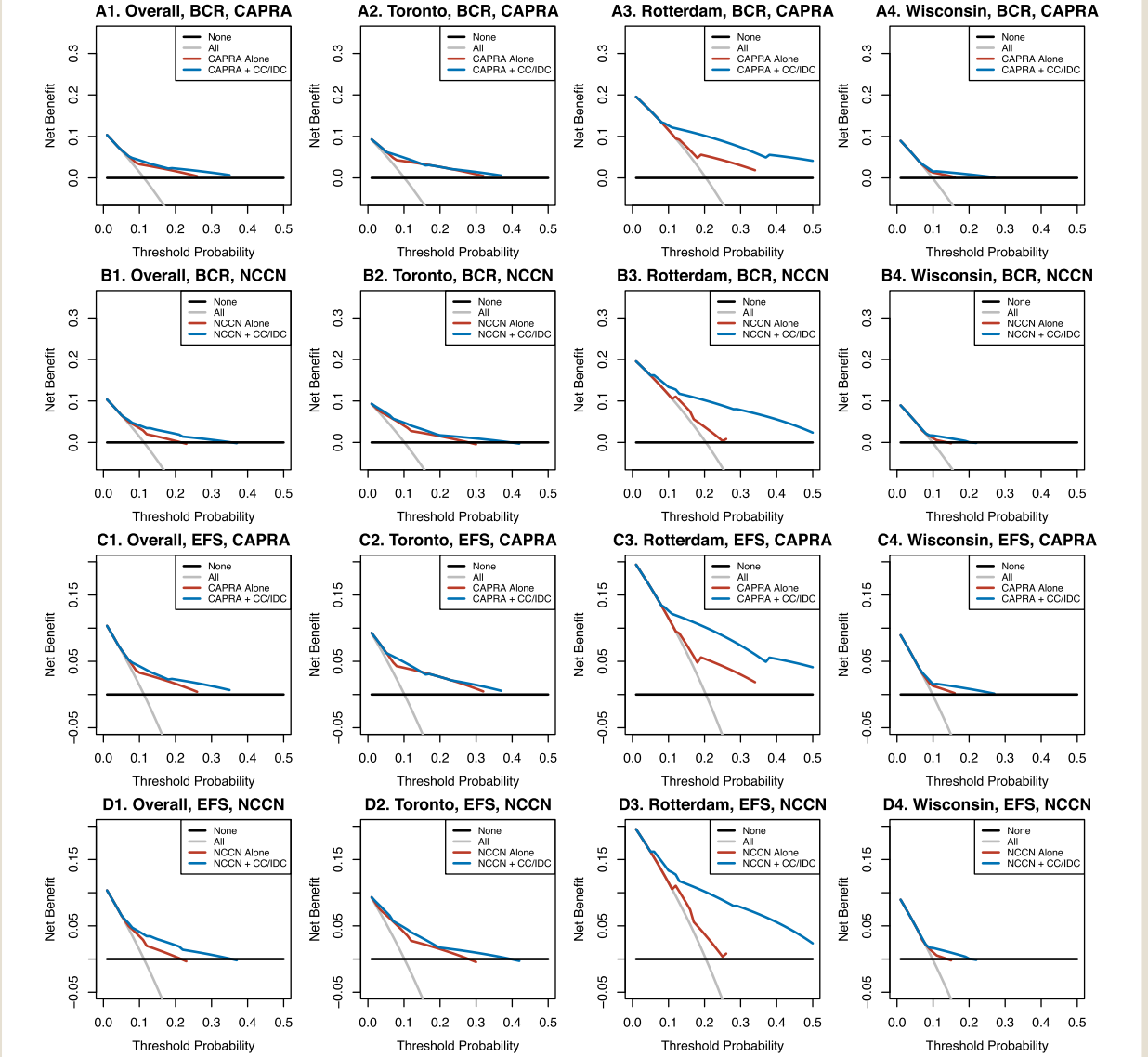
Figure 4 Decision Curve Analysis (DCA). Part A (BCR) and part C (EFS) demonstrates DCA curves using CAPRA alone and with addition of CC/IDC, overall and in each individual cohort. Part B (BCR) and part D (EFS) demonstrates DCA curves using NCCN alone and with addition of CC/IDC, overall and in each individual cohort.



in CAPRA and NCCN. Similar to our prior results, we found that the magnitude of increase in c-index with addition of CC/IDC was greater for NCCN than CAPRA in terms of predicting both BCR-FS and EFS. The impact of addition of CC/IDC was most notable in CAPRA score 3-5 (intermediate scores) for BCR-FS and score 3-5 and 6-10 (high risk) for EFS. In NCCN, improved prognostication was seen in favorable (3) and unfavorable intermediate (4) along the high/very risk (5-6) classes for both BCR-FS and EFS.

GG2 prostate cancer (Gleason score 7/10, 3 + 4) is the most frequent GG reported on prostate biopsy and in this cohort, accounted for 51% of the cases across all 3 cohorts. We performed a sub-analysis limited to GG2 cases to determine if our findings could be replicated within this common patient subset. The c-index for both CAPRA and NCCN was lower in the GG2 subset for both BCR-FS and EFS. The addition of CC/IDC to both CAPRA and NCCN in this subset, showed a larger increase in the c-index for BCR-FS and EFS than noted when all GG cases were examined together. The only exception was a slightly lower increase in c-index for EFS using NCCN. These results suggest that identifying CC and IDC in GG2 biopsy cases is of particular value in predicting patient outcome.

Finally, we used DCA to assess the clinical impact/value of including CC/IDC in both CAPRA and NCCN. A larger magnitude of impact was noted for the NCCN pretreatment tool compared

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with CAPRA. This may be due to the higher c-index of CAPRA as a tool to begin with compared with NCCN, with consequently less room to improve the predictive value by incorporation of additional parameters. Overall, the DCA showed clinical benefit of the addition of CC/IDC status to both pretreatment tools.

The limitations of this study are its retrospective nature, the intermediate length of median cohort follow up, and the inclusion of only a small European cohort in comparison with the number of North American cases. Differences were appreciable between the original Toronto cohort and the Wisconsin cohort, largely related to the widespread use of active surveillance as a management strategy in Toronto (and also in Rotterdam) with a consequently low number of GG1 cases proceeding to radical prostatectomy. Future studies incorporating larger cohorts from other geographic locations will be essential to determine whether our results can be replicated more broadly and in different patient populations. Further, all cases were from academic institutions and were reported by sub-specialty urologic pathologists.

It is notable that standard template prostate biopsies (such as those used in this study) have a low sensitivity for identification of CC/IDC[4,24] which raises the possibility that improved identification and targeting of these lesions may potentially increase the "value" of these sub-pathologies in any pretreatment algorithm. Therefore, current sampling may preferentially identify cases with higher volumes of CC/IDC which have been shown by some authors at prostatectomy to correlate with worse outcome.[11,22,25] A move to "target only" biopsies would also necessitate revisiting the designation of proportion of positive cores in the context of existing pretreatment stratification tools.

Conclusion

In conclusion we have shown a statistical and a clinical benefit for patient stratification by the addition of CC/IDC status to both the CAPRA and NCCN pretreatment tools. The impact of these sub-pathologies on GG2 biopsies is particularly notable and highlights the importance of identifying these and their inclusion in biopsy pathology reports.

Clinical Practice Points

- Cribriform Gleason pattern 4 and intraductal carcinoma of the prostate are adverse pathologic features associated with advanced disease stage, nodal metastases, biochemical recurrence, metastases and death from prostate cancer. Despite this, they are not incorporated into existing prostate pretreatment classification tools.
- Our initial data from a Toronto cohort showed the addition of cribriform pattern 4 and intraductal carcinoma of prostate to the CAPRA and NCCN pretreatment tools improved patient stratification for biochemical recurrence and also development of metastases and death of disease (events).
- Herein these results are replicated in two additional, separate cohorts, one from North America (Wisconsin) and the other from Europe (Rotterdam).
- In a sub-analysis of the combined cohort Grade group 2 biopsies, the most frequent biopsy grade group, the same results were found.
- Further, decision curve analysis demonstrated the clinical net benefit of the addition of cribriform pattern 4 and intraductal carcinoma to both pretreatment classification tools.
- Our results highlight the merit of routinely reporting cribriform pattern 4 and intraductal carcinoma of the prostate and the contribution of these sub-pathologies to determining prostate cancer outcomes.
- It is the first to assess the clinical net benefit of reporting these entities using decision curve analysis methodology.

Author Contributions

Conception and design; MRD, TvdK. Acquisition of data: MRD, YY, KNL, LJK, EH, GJLHvL, KAI, TvdK. Analysis and interpretation of data: MRD, KL, TvdK. Drafting the manuscript: MRD, YY, KNL, LJK, EH, NF, AF, GJLHvL, KAI, TvdK. Critical revision of manuscript for important intellectual content: MRD, YY, KL, KNL, LJK, EH, NF, AF, GJLHvL, KAI, TvdK. Statistical analysis: KL. Supervision: MRD, GJLHvL, KAI, TvdK.

Disclosure

The authors have no conflict of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clgc.2023.07.013.

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