Australian validation of the Cancer of the Prostate Risk Assessment Post-Surgical score to predict biochemical recurrence after radical prostatectomy


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Key words
Cancer of the Prostate Risk Assessment Post-Surgical score, post-operative, prostate neoplasm, radical prostatectomy, risk assessment, validation.

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Abstract

Background: The Cancer of the Prostate Risk Assessment Post-Surgical (CAPRA-S) score is a simple post-operative risk assessment tool predicting disease recurrence after radical prostatectomy, which is easily calculated using available clinical data. To be widely useful, risk tools require multiple external validations. We aimed to validate the CAPRA-S score in an Australian multi-institutional population, including private and public settings and reflecting community practice.

Methods: The study population were all men on the South Australian Prostate Cancer Clinical Outcomes Collaborative Database with localized prostate cancer diagnosed during 1998–2013, who underwent radical prostatectomy without adjuvant therapy (n = 1664). Predictive performance was assessed via Kaplan–Meier and Cox proportional regression analyses, Harrell’s Concordance index, calibration plots and decision curve analysis.

Results: Biochemical recurrence occurred in 342 (21%) cases. Five-year recurrence-free probabilities for CAPRA-S scores indicating low (0–2), intermediate (3–5) and high risk were 95, 79 and 46%, respectively. The hazard ratio for CAPRA-S score increments was 1.56 (95% confidence interval 1.49–1.64). The Concordance index for 5-year recurrence-free survival was 0.77. The calibration plot showed good correlation between predicted and observed recurrence-free survival across scores. Limitations include the retrospective nature and small numbers with higher CAPRA-S scores.

Conclusions: The CAPRA-S score is an accurate predictor of recurrence after radical prostatectomy in our cohort, supporting its utility in the Australian setting. This simple tool can assist in post-surgical selection of patients who would benefit from adjuvant therapy while avoiding morbidity among those less likely to benefit.

Introduction

Prostate cancer (PCA) is the most common cancer among Australian men¹ and second most common male cancer worldwide.² While radical prostatectomy (RP) is an effective treatment for localized PCa, between 20 and 30% of men will experience disease progression following a prostatectomy.³ Accurate identification of men at higher risk of progression is important to ensure appropriate selection for adjuvant therapy to reduce this risk, while sparing men at low risk unnecessary treatment-related morbidity when adjuvant therapy would be of little benefit.⁴ A variety of tools have been developed to assess risk of progression after
prostatectomy, including look-up tables, simple risk stratification, prediction models, nomograms and neural networks. Risk prediction tools have been shown to outperform clinical judgement in predicting patient outcomes. However, not all tools have been validated in different populations or settings other than academic or teaching hospitals. Furthermore, some tools are easier than others to use in the clinical setting due to their simplicity and reliance on measures available to the clinician in routine reports.

The Cancer of the Prostate Risk Assessment Post-Surgical (CAPRA-S) score is a simple post-operative risk assessment tool for predicting disease recurrence. It is easily calculated from pathology outcome data (margin status, extra-capsular extension (ECE), seminal vesicle invasion (SVI), pathological Gleason score and nodal status) along with pre-treatment prostate-specific antigen (PSA) level. Sub-scores are assigned to each of the post-surgical indicators based on severity levels and summed to derive the final CAPRA-S score. Since its development in 2011, the CAPRA-S score has been validated in a multi-institutional cohort in the USA, a large single-institute cohort in Germany and smaller single surgeon/institute series in Korea and Turkey.

Experts suggested that risk assessment tools be assessed within the settings in which they will be used. Previous validation of CAPRA-S undertaken in the USA may not be applicable in the Australian context given the high proportion of African-American men who have more aggressive PCa. Likewise validation in Asian populations may not be applicable to the Australian population. Furthermore, validation studies involving single institutions with specialist uro-pathologist may not be relevant to real-world community practice where specialist pathology is not always available. The aim of this study was to validate the CAPRA-S score in a multi-institutional community setting within Australia, using data from a longitudinal state-based clinical registry.

Methods

Study participants

This study used data from the South Australian Prostate Cancer Clinical Outcome Collaborative (SA-PCCOC) database. This is a state-wide multi-institutional clinical which prospectively collects clinical, treatment and outcome data for men with PCa, independently of the treating physician, from both the public and private sectors. The study population consisted of registry participants who were residing in South Australia and underwent RP as primary treatment for localized PCa diagnosed 1998–2013. Men with clinical stage >cT3a and those who received neoadjuvant or adjuvant therapy, that is, radiotherapy (RT) or androgen deprivation therapy before or within 6 months of RP were excluded. Further cases were excluded from analysis when pre-treatment PSA (8%), or RP Gleason score (1%) was missing. Those with missing data for margin status (1%), ECE (1%), SVI (2%) or nodal status (9%) were included in analysis and assumed to have negative status. Follow-up PSA data (at least two post-treatment measures) were missing for 122 of the eligible cases (6%). The final analytic cohort comprised 1664 cases.

Measures

CAPRA-S scores were calculated according to Cooperberg et al., with missing data for SVI, ECE and margins, and missing or unassessed nodal status scored as 0. Scores of ≥8 were combined due to the small number of cases. The score assigned to specific levels of each characteristic is shown in Table 1.

Biochemical recurrence (BCR) was two consecutive post-surgical PSA values of >0.2 ng/mL at any time post-prostatectomy. Survival time was calculated from date of RP to the date of confirmatory PSA indicating BCR, date of death or the censoring date (June 30, 2016, corresponding to the latest update of PSA data), whichever was earliest.

Analysis

Kaplan–Meier analysis was used to determine biochemical recurrence-free probability (BRFP) at 3 and 5 years after RP and graphed. Cox proportional hazards regression was used to predict the relative likelihood of BCR after RP by CAPRA-S scores and risk categories as per Cooperberg et al. (i.e. low 0–2, intermediate 3–5 and high 6+).

Predictive accuracy of CAPRA-S for BCR was calculated via the Harrell’s Concordance index (C-index), where >0.7 indicates reasonable accuracy and >0.8 strong predictive accuracy. Calibration was visually assessed by plotting the actual probability of BCR (derived from Kaplan–Meier estimates) against the model-predicted probability of BCR at 5 years post-prostatectomy. Decision curve analysis, developed by Vickers et al., is also presented for predicted BCR at 5 years in our cohort. Decision curve analysis provides a visual representation of the net benefit of an intervention (i.e. adjuvant therapy) based on a predictive tool (i.e. CAPRA-S) across a range of risk thresholds, compared with treating none or all of the patient population.

We also undertook sensitivity analysis: (i) using only complete case data, excluding all cases with any unknown surgical pathology; (ii) imputing missing data for all relevant indicators required to calculate CAPRA-S scores including pre-treatment PSA and RP Gleason grade and nodal status, and (iii) excluding cases receiving adjuvant therapy within 12 rather than 6 months of operation.

Ethics approval was obtained from Southern Adelaide Clinical and University of South Australia Human Research Ethics Committees (protocols 307.14 and 3746).

All analyses were in Stata version 12 (StataCorp, College Station, TX, USA).

Results

Table 1 shows clinical and pathological characteristics of our analytic cohort. Characteristics did not vary between the eligible, analytic cohort and imputed datasets. The mean diagnosis age was 62 years. The median follow-up was 79 months for all cases and 80 months for men who did not experience progression.
The distribution of CAPRA-S scores is shown in Table 1, along with 3- and 5-year disease-free probabilities. Forty-seven percent had scores in the low range (0–2), 41% in the intermediate range (3–5) and 12% had scores in the high-risk range (6–10). At both the 3- and 5-year time points, disease-free probabilities decreased incrementally with increasing CAPRA-S score, except for the step between CAPRA-S scores 5 and 6. The 5-year BRFP ranged from 97% (95% confidence interval (CI) 92–99%) for CAPRA-S score = 0, through to 33% (95% CI 23–44%) for cases with scores ≥8. The 5-year BRFP for low risk, intermediate risk and high risk based on CAPRA-S scores were 95% (95% CI 93–96%), 79% (95% CI 76–82%) and 46% (95% CI 39–53%). BCR-free survival curves by CAPRA-S score are shown in Figure S1. The proportions who were free of BCR according to CAPRA-S scores and relevant hazard ratios (HR) relative to CAPRA-S = 0 are shown in Table 2. For CAPRA-S as a continuous variable, the HR was 1.56 (95% CI 1.49–1.64). The HR for intermediate risk (CAPRA-S 3–5) and high risk (CAPRA-S ≥6) was 3.9 (95% CI 2.8–5.3) and 13.3 (95% CI 9.6–18.5), respectively, relative to low risk. Clear increments in HR by CAPRA-S score can be seen, with the exception of the step from score 0 to 1 (Table S1). Harrell’s C-index for CAPRA-S predicting BCR at 5 years was 0.77. Similarly, the C-index for CAPRA-S risk categories predicting 5-year BCR was 0.74.

The calibration plot of predicted versus actual BCR probability at 5 years post-prostatectomy (Fig. 1a) shows a good fit across the range of CAPRA values, though the observed probability is slightly lower than predicted for CAPRA-S = 5. All CIs overlap with the perfect calibration scenario with the exception of CAPRA-S = 5. The decision analysis curve for BCR at 5 years (Fig. 1b) shows that there would be a net benefit in selecting men for adjuvant therapy after RP based on CAPRA-S scores compared with treating all or none.

Sensitivity analyses to address missing data showed very similar results to our main study findings. The C-index for 5-year BRFP was unchanged (0.77) when analyses used imputed data. Extending the exclusion period for adjuvant therapy from 6 months to 1-year post-RP and excluding cases with missing data for margin status, ECE, SVI or nodal status both resulted in a C-index of 0.75.

**Discussion**

This study is the first to validate the CAPRA-S score, a post-operative risk prediction tool for recurrence after RP for treatment of localized PCa, in an Australian cohort. Our findings indicate that the CAPRA-S score accurately predicted risk of BCR at 5 years post-prostatectomy in this population. Our results indicate reasonably good calibration between modelled and actual risk across all scores. The ability for CAPRA-S to discriminate risk of progression was also demonstrated to 10 years post-prostatectomy.
Our findings add to the small but growing literature validating CAPRA-S across different settings. To date validation studies of unmodified CAPRA-S have been undertaken in a multi-institutional cohort from the USA,8 a highly specialized single institution series in Europe9 and single surgeon/institution series in Korea10,11 and Turkey,12 and now a multi-institutional cohort from a large community based PCa registry in Australia (Table S2 summarizes these studies). Each has shown CAPRA-S to have adequate discrimination, with C-index values for 5-year BCRFP ranging from 0.73 to 0.87, and generally good calibration across the range of scores. Our C-index of 0.77 for BCR at 5 years was within the range reported in other studies, and indicates that CAPRA-S is an accurate risk prediction tool within the Australian context.

Our BCR-free probabilities were somewhat higher across CAPRA-S scores than those reported by Punnen et al.8 for the US multi-institutional cohort (Shared Equal Access Regional Cancer Hospital (SEARCH)), and those reported by Cooperberg et al.7 in the original developmental Cancer of the Prostate Risk Assessment Post-Surgical; CI, confidence interval; HR, hazard ratio.

Table 2 Three- and 5-year BCRFP and hazard ratios for BCR by CAPRA-S score

<table>
<thead>
<tr>
<th>CAPRA-S scores</th>
<th>Total No. (%)</th>
<th>No. with BCR† No. (%)</th>
<th>3 years % (95% CI)</th>
<th>5 years % (95% CI)</th>
<th>Risk of BCR HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>154 (9)</td>
<td>8 (5)</td>
<td>98.7 (94.9–99.7)</td>
<td>96.9 (92.0–98.6)</td>
<td>1.0</td>
<td>–</td>
</tr>
<tr>
<td>1</td>
<td>276 (17)</td>
<td>15 (5)</td>
<td>98.2 (95.7–99.2)</td>
<td>95.9 (92.6–97.7)</td>
<td>1.0 (0.4–2.5)</td>
<td>0.92</td>
</tr>
<tr>
<td>2</td>
<td>303 (18)</td>
<td>29 (10)</td>
<td>95.0 (91.9–97.0)</td>
<td>93.5 (90.0–95.8)</td>
<td>1.9 (0.9–4.3)</td>
<td>0.10</td>
</tr>
<tr>
<td>3</td>
<td>318 (19)</td>
<td>51 (16)</td>
<td>90.0 (86.0–92.7)</td>
<td>87.0 (82.7–90.3)</td>
<td>3.5 (1.7–7.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>4</td>
<td>236 (14)</td>
<td>55 (23)</td>
<td>87.6 (82.7–91.2)</td>
<td>80.3 (74.4–85.0)</td>
<td>5.3 (2.5–11.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5</td>
<td>188 (10)</td>
<td>65 (39)</td>
<td>76.2 (68.9–81.9)</td>
<td>62.8 (54.8–69.8)</td>
<td>9.8 (4.7–20.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6</td>
<td>80 (5)</td>
<td>37 (46)</td>
<td>68.7 (67.3–77.6)</td>
<td>57.5 (45.7–67.7)</td>
<td>12.7 (5.9–27.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>7</td>
<td>53 (3)</td>
<td>30 (57)</td>
<td>56.3 (41.9–68.4)</td>
<td>47.9 (33.7–60.7)</td>
<td>17.7 (8.1–38.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>8+</td>
<td>76 (5)</td>
<td>52 (68)</td>
<td>39.3 (28.3–50.0)</td>
<td>33.4 (22.9–44.2)</td>
<td>29.6 (4.0–62.4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CAPRA-S categories

<table>
<thead>
<tr>
<th>CAPRA-S (continuous score)</th>
<th>Total No. (%)</th>
<th>No. with BCR† No. (%)</th>
<th>3 years % (95% CI)</th>
<th>5 years % (95% CI)</th>
<th>Risk of BCR HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (0–2)</td>
<td>733 (44)</td>
<td>52 (7)</td>
<td>97.0 (95.5–98.0)</td>
<td>95.0 (93.2–96.4)</td>
<td>1.0</td>
<td>–</td>
</tr>
<tr>
<td>Intermediate (3–5)</td>
<td>722 (43)</td>
<td>171 (24)</td>
<td>85.9 (83.2–88.3)</td>
<td>79.2 (76.0–82.1)</td>
<td>3.9 (2.8–5.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High (≥6)</td>
<td>209 (13)</td>
<td>119 (57)</td>
<td>54.8 (47.8–61.3)</td>
<td>46.2 (39.2–52.9)</td>
<td>13.3 (9.6–18.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Concordance index for CAPRA-S scores = 0.77. Concordance index for CAPRA-S risk categories = 0.73. †Number with BCR at 5-years post-prostatectomy. BCR, biochemical recurrence; BCRFP, biochemical recurrence-free probability; CAPRA-S, Cancer of the Prostate Risk Assessment Post-Surgical; CI, confidence interval; HR, hazard ratio.

advocated offering adjuvant RT to men with adverse pathological findings after RP, based on increasing evidence of benefits of adjuvant and early RT.24 These recommendations would replace usual practice of delaying the start of secondary therapies (e.g. salvage RT) until there is evidence of BCR. Current European Association of Urology guidelines are less prescriptive and recommend discussing the option of adjuvant RT to reduce the risk of recurrence for pT3N0/M0 patients with undetectable PSA, but also recommend informing patients of the alternative option of salvage RT if PSA increases.25 Being able to accurately classify men according to risk of recurrence is a valuable and useful tool in counselling men and more importantly, is vital to selecting those who could benefit from adjuvant RT while sparing those who are unlikely to benefit unnecessary treatment-related toxicity and might be best served by ongoing surveillance. In addition, considering a combination of factors in selecting candidates for adjuvant therapy can be more discriminatory than selecting all men with any single indicator of adverse surgical outcomes.26 The use of CAPRA-S scores in such a context would be ideal.

Limitations of this study include a high proportion of cases with missing data on components of the CAPRA-S score (12% of cases). In our main analysis, we assumed negative status when data were missing for margin status, ECE, SVI and nodal status. However, sensitivity analyses to address issues of missing data are consistent with findings from the main analyses. Also, we observed low numbers of men in the higher CAPRA-S score ranges (scores 8–10) which limit our ability to assess discrimination at the higher end of the CAPRA-S score scale. The low numbers with high CAPRA-S scores may reflect stricter and possibly more conservative selection for RP within the Australian urological community, resulting in fewer prostatectomies being performed among men with adverse clinical characteristics, and hence, fewer with adverse pathological features. Another contributing factor may be the exclusion of men who received neo/adjuvant therapy within 6 months of RP, who are most likely those with multiple adverse surgical outcomes (i.e. high CAPRA-S scores). Even so, our criteria for determining cases who...
received adjuvant therapy may not have been stringent enough. Further sensitivity analysis excluding those having secondary treatments within 12 months of RP gave similar results. Relatively short follow-up and small number of PCa deaths precluded validation of CAPRA-S for predicting PCa-specific mortality.

Strengths of this study include the relatively large sample size (>1600 men), prospective data collection, and the multi-institutional community and population-based nature of our cohort, with patients from both the private and public health care setting.

Conclusion

The CAPRA-S score is a reasonably accurate predictor of risk of recurrence after RP within an Australian cohort. Our findings support the use of the CAPRA-S score as a post-prostatectomy risk assessment tool within the Australian health care setting, and are an additional powerful validation as it was performed in a prospective, independently collected, longitudinal disease-specific registry. CAPRA-S’ simplicity is a major asset for application within clinical practice at point of care and decision-making. It can be easily calculated without reference to look up tables, visual diagrams or computer-based algorithms (e.g. as in the case of nomograms) and all the component measures that comprise the CAPRA-S score are routinely described in pathology reports and are readily accessible to treating clinicians.

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References


Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:

Figure S1. Biochemical recurrence-free probabilities. (a) By Cancer of the Prostate Risk Assessment Post-Surgical (CAPRA-S) scores. (b) By CAPRA-S risk categories.

Table S1. Hazard ratios for risk of biochemical recurrence by Cancer of the Prostate Risk Assessment Post-Surgical score compared with previous score.

Table S2. Summary of studies which validate the Cancer of the Prostate Risk Assessment Post-Surgical score.