Published in final edited form as:

Urol Oncol. 2012 September ; 30(5): 584–589. doi:10.1016/j.urolonc.2010.06.007.

External Validation of the Cancer of the Prostate Risk Assessment (CAPRA) Score in a Single-Surgeon Radical Prostatectomy Series

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SUMMARY

Objectives—Prostate cancer clinical staging has significant limitations in the ability to accurately risk-stratify patients for prompt treatment or expectant management. The University of California San Francisco Cancer of the Prostate Risk Assessment (UCSF CAPRA) was recently described as a straightforward staging system that uses clinical variables to generate a score ranging from 0 to 10. Our objective was to perform an external validation of the CAPRA score as a predictor of 5-year progression-free survival (PFS) in a single-surgeon radical retropubic prostatectomy (RRP) series.

Materials and Methods—We examined the performance characteristics of the preoperative CAPRA score (0–10) to predict biochemical progression-free survival (PFS) in 990 men who underwent RRP by a single surgeon from 2003 to 2009.

Results—CAPRA scores were significantly associated with the risk of early biochemical progression in our series. For example, 5-year PFS was markedly different for scores at the extremes of 0 to 1 versus 7 (95% vs. 40%, respectively). The concordance index was 0.764 for the prediction of biochemical progression using CAPRA scores in this cohort, which compares favorably with the concordance index of 0.66 in the original CaPSURE dataset.

Conclusions—Our results validate the UCSF-CAPRA score as a significant predictor of 5-year PFS in a single surgeon series. The CAPRA score is a simple preoperative tool that can be readily applied in clinical practice to help risk-stratify prostate cancer patients.

Keywords

CAPRA; staging; prostate cancer; prostatectomy; biochemical recurrence

INTRODUCTION

Radical prostatectomy has proven to increase cancer-specific and overall survival from prostate cancer compared to watchful waiting in a randomized study.[1] Potential benefits of

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early diagnosis and curative therapy also may be inferred from the reduction in prostate cancer mortality rates observed in the United States for more than a decade.[2] Conversely, some men are diagnosed with very low-risk disease that is unlikely progress during their lifetime.[3] Despite substantial concerns regarding prostate cancer overdiagnosis, the field has been hindered by an inability to accurately distinguish between men with potentially life-threatening disease, curable, and indolent disease at the time of diagnosis.

To this end, many tools have been developed to help risk-stratify prostate cancer patients.[4]:[5] These vary from simple tables considering a few pre-treatment variables, to complex multivariable nomograms and neural networks that rely on sophisticated computational technology for analysis.[6–9] The aim of these risk-stratification tools is improve clinical staging, which is useful in the selection of treatment and prediction of prognosis.[10] Unfortunately, many existing tools are complicated to apply in clinical practice, or define risk groups that have considerable within-group heterogeneity in outcomes.

In 2005, investigators from the University of California San Francisco used data from the CaPSURE registry to develop a novel tool known as the Cancer of the Prostate Risk Assessment (“CAPRA”) score.[11] The CAPRA score incorporates the preoperative prostate-specific antigen (PSA), biopsy Gleason score, T stage, percentage of positive biopsies and age to generate a score ranging from zero to ten points. In the training set, they demonstrated that the CAPRA score predicted 5-year PFS, suggesting that this simple tool could provide meaningful risk stratification. More recently, CAPRA score has also been shown to predict both metastases and death from prostate cancer in men from the CaPSURE registry undergoing various forms of treatment.[12]

Since its initial description, the CAPRA score has been validated in other multi-institutional radical prostatectomy datasets,[13, 14] and in a multiple-surgeon radical prostatectomy series from Johns Hopkins (using a modified 9-point scoring system) to predict biochemical progression.[15] The purpose of our study was to determine whether CAPRA scores predict early biochemical progression after radical prostatectomy in a large, contemporary single-surgeon series.

MATERIAL AND METHODS

From February 2003 to April 2009, a single surgeon (WJC) performed open radical prostatectomy in 1566 men with clinically localized prostate cancer at Northwestern University, of whom 1,383 agreed to enroll in a prospective follow-up study. Clinical stage was assigned based upon digital rectal examination by the same surgeon.

From this population, we excluded 178 men (12.8%) for the following reasons: preoperative PSA less or equal to 2.0 ng/ml (by definition not suitable for analysis with the CAPRA score) (n=71), neoadjuvant or adjuvant treatment prior to biochemical recurrence (n=65), or missing data (preoperative PSA, biopsy Gleason score, clinical T stage, or postoperative PSA) (n=42). An additional 215 men were excluded who did not have data on the percentage of positive biopsies (PPBs), which is necessary to apply the full 10-point CAPRA scoring system. Of note, similar results were obtained in a separate analysis including these 215 men using a modified 9-point CAPRA score (as was previously used in the Johns Hopkins validation study[15]).

Radical prostatectomy and bilateral pelvic lymphadenectomy were performed in a standardized fashion, as previously described.[16] Bilateral or unilateral nerve sparing surgery was attempted in all suitable patients. The surgical specimens were processed as previously reported[16] by our institutional pathology department. The postoperative follow-up protocol consisted of a PSA measurement at approximately four weeks, with

subsequent PSA measurements every six months. Biochemical progression was defined as a postoperative PSA ≥ 0.2 ng/ml verified on a repeat measurement or the initiation of secondary (salvage) radiation or hormonal treatment. For progression-free survival analyses, we included the 726 patients with at least 12 months of follow-up. The study protocol was reviewed and approved by the institutional review board of Northwestern University.

Statistical Analysis

The UCSF-CAPRA score ranges from 0 to 10. The following classification is used to evaluate Gleason grade: primary Gleason pattern 1 to 3 with secondary pattern 1 to 3 = 0 points; primary pattern 1 to 3 with secondary pattern 4 or 5 = 1 point; and primary pattern 4 to 5 with secondary pattern 1 to 5 = 3 points.[11] Preoperative PSA levels of 2.1 to 6, 6.1 to 10, 10.1 to 20, 20.1 to 30, and >30 ng/ml were assigned 0, 1, 2, 3, and 4 points, respectively. Clinical stage T1 or T2 were assigned 0 points, while T3a was assigned 1 point. Age younger than 50 = 0 points, while age 50 years and older = 1 point. Finally, PPB $<34\%$ was assigned 0 points, while $\geq 34\%$ was given 1 point.

Chi-square tests were used to compare the clinical characteristics of the study population from Northwestern to the original CaPSURE dataset. Since the CaPSURE study did not report postoperative pathology data, we compared our postoperative pathologic findings to those of a CAPRA validation study in the Shared Equal Access Regional Cancer Hospitals (SEARCH) database using the chi-square test.[13] The Kaplan-Meier method was used to calculate the 5-year progression-free survival (PFS) rates, stratified by low (0 to 2), intermediate (3 to 5) and high (≥ 6) CAPRA scores. In addition, Cox proportional hazards models were used to examine predictors of biochemical progression. Separate models were performed using the CAPRA variables individually (coded according to their use in the CAPRA score) and in combination as a CAPRA score. Concordance indices were used to examine the predictive accuracy of CAPRA scores for the prediction of biochemical progression in our population. In addition, model calibration was examined using the Hosmer-Lemeshow Goodness-of-Fit test, and by plotting observed versus predicted values using the “val.surv” function in the R statistical package designed for censored data (data not shown).[17] All other statistical analyses were performed with SAS[®] software, version 9.2 (SAS, Cary, NC).

RESULTS

Table 1a shows the clinical characteristics of the overall study population. The mean age was 59.3 years, compared to 62 years in CaPSURE. In both studies, the majority of men were Caucasian (93.5% Northwestern, 88% CaPSURE).

Compared to the original CaPSURE population, our cohort was younger with significantly lower preoperative PSA levels ($p<0.0001$) and a more favorable clinical stage distribution. Also, fewer Northwestern patients had $\geq 34\%$ positive biopsy cores ($p<0.0001$). However, the biopsy Gleason score distribution was significantly more favorable in CaPSURE, compared to the Northwestern population ($p=0.012$).

The pathology features in our cohort also differed from those in the prior external validation from the SEARCH database. Specifically, fewer Northwestern patients had extracapsular tumor extension (15.5% vs. 25%, $p<0.0001$), positive surgical margins (14.1% vs. 32.4%, $p<0.0001$), seminal vesicle invasion (2.6% vs. 7.3%, $p<0.0001$), and lymph node metastases (0.4% vs. 1.4%, $p=0.015$), compared to the SEARCH population.

Table 2 compares the CAPRA score distribution between the Northwestern and CaPSURE datasets. In both series, the vast majority had CAPRA scores between 0 and 4.

At a median follow-up of 34 months, 62 (8.5%) men had biochemical progression. For comparison, in the original CaPSURE dataset, 210 (15%) men progressed at a median time of 21 months.

Next, we performed a Cox proportional hazards model to predict biochemical progression using the CAPRA variables in our population (Table 3). PSA, Gleason score, and PPB were significant predictors of biochemical recurrence, whereas age ≥ 50 years and clinical stage $\geq T2$ were not.

Figure 1 shows the progression-free survival rates in the Northwestern population stratified by CAPRA score. Similar to the results in CaPSURE, the progression-free survival rate continuously decreased with increasing CAPRA score (Table 4). Furthermore, each 1-point increment in CAPRA score led to a significantly increased hazard ratio for biochemical progression in our cohort. The actuarial 5-year PFS rates were 95%, 79%, and 48% for the low (0–2), intermediate (3–5), and high risk (6–10) CAPRA score groups.

Finally, the CAPRA score had a concordance index of 0.764 to predict biochemical progression in the Northwestern population. This compares favorably with the concordance index of 0.66 in the original CaPSURE dataset, and 0.76 in the Johns Hopkins validation study. The model also demonstrated good calibration in our population (Hosmer-Lemeshow $p=0.56$).

COMMENT

Prostate cancer risk stratification tools have become increasingly important and refined over the last two decades.[9, 10] Currently, two of the most common risk assessment tools used to predict biochemical progression are the D'Amico risk groups [18] and the Kattan nomogram[8], although many other predictive tools have been described.[5] The D'Amico stratification performs well in identifying low risk patients, but there is a considerable overlap in outcomes for patients in the intermediate and high risk groups.[19] The Kattan nomogram, although integrating multiple variables, can be difficult to calculate without computational instruments, which are not always available at hand. Additionally, a validation study of the Kattan nomogram in CaPSURE patients suggested that it may overestimate the probability of recurrence-free survival in community-based datasets, especially in men with lower risk cancers. [20]

The UCSF-CAPRA score was more recently proposed to provide to the clinician a simple, yet accurate tool to preoperatively predict 5-year recurrence-free survival in patients with prostate cancer amenable to surgical treatment. [11] It was derived from the large multi-institutional CaPSURE database encompassing 40 community practices across the United States. In their initial report, the authors demonstrated a strong correlation between the CAPRA score with the D'Amico risk groups ($r=0.74$) and Kattan nomogram ($r=0.77$). [11] However, the CAPRA score was superior to D'Amico risk groups for the prediction of 5-year recurrence-free survival. [11] More recently, Cooperberg et al. reported that CAPRA additionally predicted metastases and cancer-specific mortality among men from CaPSURE managed by radical prostatectomy, radiation therapy, hormonal therapy, or watchful waiting.[12]

The same authors also have validated the CAPRA scoring system to predict PFS after radical prostatectomy in another multi-institutional cohort, the Shared Equal Access Regional Cancer Hospital (SEARCH) database. [13] In this population, the CAPRA score also was associated with worse pathologic outcomes. [13] Third-party external validation of the CAPRA scoring system also has been reported by a multicenter German study[14] and in a single-institution, multiple-surgeon study from Johns Hopkins.[15]

To our knowledge, the present report represents the first validation of the CAPRA score in a contemporary single-surgeon radical prostatectomy population. Because our series involved standardized surgical technique, pathologic analysis, and follow-up, we hoped to better evaluate the performance of the model by reducing bias from variability in surgical, pathologic, and follow-up practices compared to a multi-institutional or multiple-surgeon series. Indeed, the CAPRA scoring system demonstrated good calibration and discrimination for the prediction of biochemical progression in our population (c-index=0.76), comparable to the studies from CaPSURE (c-index=0.66) and Johns Hopkins (c-index=0.76).

Another key point is that the CAPRA score was significantly associated with biochemical progression in all datasets studied, despite considerable differences in the populations. For example, the CaPSURE study included patients treated from 1992 to 2001; whereas, our series included cases from February 2003 to April 2009. Moreover, the distribution of clinical and pathological features were significantly different between our study compared to the CaPSURE and SEARCH populations, respectively. Overall, it appears that the CAPRA scoring system has good geographic and temporal transportability.

A limitation of our study is that 215 men did not have biopsy core data from which to calculate the full 10-point CAPRA score, since the presence of more than 34% of positive biopsy cores yields the final point in the original CAPRA description.[11] Nevertheless, we repeated the analysis using the modified 9-point CAPRA score described by Zhao et al.[15] and similarly found it to be a significant predictor of biochemical progression (data not shown). It is encouraging that even without biopsy core data, the 9-point modified CAPRA score maintained its prognostic capability.

A second limitation is that only a single patient in our series had clinical stage T3 prostate cancer, limiting the prognostic utility of this variable. Indeed, neither clinical stage >T2 nor age $\geq$ 50 years (2 components to the CAPRA score) were significant independent predictors of biochemical progression in the multivariable Cox proportional hazards model for our study population. Because our objective was to perform a validation study, we still applied the full 10-point CAPRA scoring system to our population including both variables. Nevertheless, it is possible that an alternate classification scheme might fit our data better. Although head-to-head comparisons between CAPRA and other predictive tools are beyond the scope of this manuscript, we plan to address this issue in a future study.

In addition, we excluded patients who received adjuvant therapy, which may have introduced selection bias. However, the reason for this exclusion was to examine the relationship between preoperative CAPRA score and biochemical progression after radical prostatectomy alone, without the differential influence of adjuvant therapy.

Another limitation of our study is the relatively short follow-up, since our goal was to examine the current utility of CAPRA scores to predict biochemical progression in a contemporary cohort. Additional study is warranted into the relationship between CAPRA scores and long-term treatment outcomes, such as metastasis-free and cancer-specific survival.

CONCLUSIONS

In our single-surgeon radical prostatectomy series, the UCSF-CAPRA score was a significant predictor of actuarial 5-year progression-free survival. The ease of use and its temporal and geographic transportability suggest that the CAPRA score may be useful for prognostication in contemporary patients undergoing prostatectomy.

Acknowledgments

Supported in part by the Urological Research Foundation, Prostate SPORE grant (P50 CA90386-05S2) and the Robert H. Lurie Comprehensive Cancer Center grant (P30 CA60553).

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Figure 1.

5-Year Kaplan-Meier progression-free survival curves in men from Northwestern, according to the (a) full 10-point CAPRA score classification and (b) its simplified categorization into low (CAPRA 0–2), intermediate (CAPRA 3–5) and high (CAPRA 6–10) risk groups, as suggested by Cooperberg et al.[13]

Table 1

Comparison of preoperative characteristics between the Northwestern series and CaPSURE.

Variable	CAPRA Points	Northwestern n (%)	CaPSURE n (%)	P-value
PSA (ng/ml)				
2.1–6	0	690 (69.7)	721 (50.1)	<0.0001
6.1–10	1	222 (22.4)	453 (31.5)	
10.1–20	2	66 (6.7)	209 (14.5)	
20.1–30	3	9 (0.9)	36 (2.5)	
> 30	4	3 (0.3)	20 (1.4)	
Gleason score (Primary/Secondary)				
(1 to 3)/(1 to 3)	0	682 (68.9)	1,068 (74.2)	0.012
(1 to 3)/(4 or 5)	1	190 (19.2)	239 (16.6)	
(4 to 5)/(1 to 5)	3	118 (11.9)	132 (9.2)	
T stage:				
T1/T2	0	989 (99.9)	1,410 (98.0)	<0.0001
T3a	1	1 (0.1)	29 (2.0)	
PPB:				
<34%	0	722 (72.9)	911 (63.3)	<0.0001
34%	1	268 (27.1)	528 (36.7)	
Age:				
<50 years	0	96(9.7)	51 (3.5)	<0.0001
50 years	1	894 (90.3)	1,388 (96.5)	

Table 2

Distribution of CAPRA scores in the Northwestern and CaPSURE populations.

CAPRA Score	Northwestern 0–10 (n;%)	CaPSURE (n;%)
0	45 (4.6)	18 (1.3)
1	396 (40.0)	383 (26.6)
2	263 (26.6)	432 (30)
3	113 (11.4)	296 (20.6)
4	80 (8.1)	155 (10.8)
5	57 (5.8)	84 (5.5)
6	23 (2.3)	43 (3.0)
7	9 (0.9)	21 (1.5)
8	3 (0.3)	4 (0.3)
9	1 (0.1)	3 (0.2)
10	0 (0)	0 (0)

Table 3

Cox proportional hazards model to predict biochemical progression using the CAPRA variables in our radical prostatectomy population.

	Hazard Ratio	95% CI	p-value
Age >50	2.72	0.66 – 11.27	0.17
Clinical stage >T2	0	0	0.99
PSA	1.95	1.47 – 2.60	<0.0001
Biopsy Gleason score	1.78	1.45 – 2.17	<0.0001
PPB >=34%	1.91	1.12 – 3.26	0.017

Results of Cox models and Kaplan-Meier analysis of 3 and 5-year progression-free survival for Northwestern and CaPSURE patients using the CAPRA score.

Table 4

CAPRA (0-10)	Northwestern				CaPSURE			
	HR (95%CI)	P	3-Yr PFS (95%CI)	5-Yr PFS (95%CI)	HR (95%CI)	P	3-Yr PFS (95%CI)	5-Yr PFS (95%CI)
0-1			97 (90-99)	95 (89-98)			91 (85-95)	85 (73-92)
2	1.1 (0.4-3.0)	0.79	99 (96-100)	95 (67-99)	1.3 (0.8-2.1)	0.31	89 (83-94)	81 (69-89)
3	4.1 (1.7-10.0)	0.002	89 (59-97)	84 (57-95)	2.4 (1.5-3.7)	<0.001	81 (73-87)	66 (54-76)
4	5.1 (2.1-12.5)	0.0004	86 (62-96)	80 (54-92)	2.4 (1.4-4.0)	0.001	81 (69-89)	59 (40-74)
5	10.5 (4.4-24.7)	<0.0001	72 (42-89)	67 (36-85)	3.3 (1.9-5.8)	<0.001	69 (51-82)	60 (37-77)
6	12.2 (3.8-38.9)	<0.0001	87 (10-99)	54 (4-89)	7.1 (3.8-13.2)	<0.001	54 (27-75)	34 (12-57)
7-10	47.8 (17.1-133.2)	<0.0001	40 (6-75)	40 (6-75)	17.4 (9.9-30.5)	<0.001	24 (9-43)	8 (0-28)