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Prostate Cancer

Multi-institutional Validation of the CAPRA-S Score to Predict Disease Recurrence and Mortality After Radical Prostatectomy

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Abstract

Background: The University of California, San Francisco, Cancer of the Prostate Risk Assessment Postsurgical (CAPRA-S) score uses pathologic data from radical prostatectomy (RP) to predict prostate cancer recurrence and mortality. However, this clinical tool has never been validated externally.
Objective: To validate CAPRA-S in a large, multi-institutional, external database.
Design, setting, and participants: The Shared Equal Access Regional Cancer Hospital (SEARCH) database consists of 2892 men who underwent RP from 2001 to 2011. With a median follow-up of 58 mo, 2670 men (92%) had complete data to calculate a CAPRA-S score.
Intervention: RP.
Outcome measurements and statistical analysis: The main outcome was biochemical recurrence. Performance of CAPRA-S in detecting recurrence was assessed and compared with a validated postoperative nomogram by concordance index (c-index), calibration plots, and decision curve analysis. Prediction of cancer-specific mortality was assessed by Kaplan-Meier analysis and the c-index.
Results and limitations: The mean age was 62 yr (standard deviation: 6.3), and 34.3% of men had recurrence. The 5-yr progression-free probability for those patients with a CAPRA-S score of 0–2, 3–5, and 6–10 (defining low, intermediate, and high risk) was 72%, 39%, and 17%, respectively. The CAPRA-S c-index was 0.73 in this validation set, compared with a c-index of 0.72 for the Stephenson nomogram. Although CAPRA-S was optimistic in predicting the likelihood of being free of recurrence at 5 yr, it outperformed the Stephenson nomogram on both calibration plots and decision curve analysis. The c-index for predicting cancer-specific mortality was 0.85, with the caveat that this number is based on only 61 events.
Conclusions: In this external validation, the CAPRA-S score predicted recurrence and mortality after RP with a c-index >0.70. The score is an effective prognostic tool that may aid in determining the need for adjuvant therapy.

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1. Introduction

With 29 720 estimated deaths, prostate cancer (PCa) is the second most common cancer-related cause of death among men [1]. Although many men have relatively indolent disease amenable to active surveillance or definitive local monotherapy, others have more aggressive disease requiring multimodal treatment. Proper risk assessment to identify men at high risk for cancer recurrence, for whom additional treatment may be beneficial [2], is essential to help direct appropriate individualized management.

Numerous nomograms exist to characterize patients by disease risk to facilitate clinical decision making [3]. Most of these nomograms rely on various pretreatment variables to predict the likelihood of disease recurrence. The University of California, San Francisco, Cancer of the Prostate Risk Assessment (CAPRA) score predicts the risk of cancer recurrence with an accuracy as good as other available prediction instruments, can be calculated easily without the need for paper tables or computer software, and has been extensively validated in predicting recurrence [4–12], metastasis, and mortality across multiple treatment modalities [13].

Pretreatment variables such as clinical T stage, biopsy Gleason grade, and percentage of positive biopsy cores provide only an approximation of cancer severity and may overestimate or underestimate cancer grade or extent [14,15]. An advantage of radical prostatectomy (RP) is that it provides a more accurate assessment of grade and stage that may improve prognostic accuracy.

To reflect these variables, a CAPRA Postsurgical (CAPRA-S) score was devised. CAPRA-S incorporates these variables as well as pretreatment prostate-specific antigen (PSA) to predict the likelihood of PCa recurrence and mortality [6]. CAPRA-S was developed based on 3837 RP patients in the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE), a large, national PCa registry. The CAPRA-S instrument generates a score of 0–12. It had discriminatory accuracy comparable to an existing postoperative nomogram and performed better in both calibration and decision curve analyses [6].

The CAPRA-S score has not yet been validated in an external data set. Therefore, we aimed to validate the ability of CAPRA-S to predict risk of recurrence and PCa-specific mortality (PCSM) in the Shared Equal Access Regional Cancer Hospital (SEARCH) database, a large, multi-institutional cohort of patients treated with RP.

2. Materials and methods

2.1. Patient population

Under institutional review board supervision at each site, data from men who underwent RP between 2001 and 2011 at four US Department of Veterans Affairs medical centers (West Los Angeles and Palo Alto, CA; Durham, NC; and Augusta, GA) were combined into the SEARCH database. Data collected in SEARCH include sociodemographic parameters, clinical tumor characteristics, surgical pathology, and follow-up PSA and clinical outcomes. Details regarding SEARCH methodology were published previously [16].

Table 1 – The Cancer of the Prostate Risk Assessment Postsurgical (CAPRA-S) score

Variable	Level	Points
Serum prostate-specific antigen	0–6	0
	6.01–10	1
	10.01–20	2
	>20	3
Surgical margins	Negative	0
	Positive	2
Seminal vesicle invasion	No	0
	Yes	2
Gleason	2–6	0
	3 + 4	1
	4 + 3	2
	8–10	3
Extracapsular extension	No	0
	Yes	1
Lymph node involvement	No	0
	Yes	1

CAPRA-S scores were calculated as previously described (Table 1) [6]. Points for each variable are added, and a final score is generated. Scores ≥9 were combined because of the small number of men at these levels [6]. In total, 222 men were excluded from this analysis because they were missing data on variables required to calculate the CAPRA-S score. Men were also excluded if they received any neoadjuvant treatment. For 67 men who received *adjuvant treatment*, defined as undetectable PSA at the time of secondary treatment, follow-up was censored at the time of secondary treatment. *Recurrence* was defined as a single PSA >0.2 ng/ml, two PSAs at 0.2 ng/ml, or any secondary treatment of an elevated postoperative PSA. *Metastasis* was based on the findings of imaging performed at the clinician's discretion. *PCa mortality* was defined as a death of any patient with metastases showing PCa progression after androgen-deprivation therapy.

2.2. Statistical analysis

The performance of CAPRA-S in predicting recurrence after prostatectomy was assessed by Cox proportional hazards regression using CAPRA-S as an ordinal variable. Kaplan-Meier analysis determined the progression-free probabilities (PGPs) at 3 yr and 5 yr after RP for each CAPRA-S level. These findings were compared with the PGPs for each level of CAPRA-S in the original CaPSURE data set. In addition, PGPs at 3 yr and 5 yr after surgery were determined for predefined groupings of CAPRA-S scores that correspond to low risk (CAPRA-S 0–2), intermediate risk (CAPRA-S 3–5), and high risk (CAPRA-S 6–10), as previously described [6]. As a comparison, the PGPs at 3 yr and 5 yr after RP were also calculated for each decile of predicted PGP using the postoperative nomogram developed by Stephenson et al. [17]. We chose this nomogram for comparison because it is among the best known and most commonly used validated nomograms using pathologic information from RP, and it was used as a comparator instrument during the original development of CAPRA-S [6]. The Stephenson nomogram also incorporates into the model receipt of adjuvant treatment and year of surgery, which is entered as a continuous variable up to 2004. Surgeries done after 2004 were counted as being done in 2004 based on the methodology of the model.

The concordance index (c-index) was calculated for both CAPRA-S and the Stephenson nomogram in this validation data set [18]. Model calibration at 5 yr was assessed by a plot of Kaplan-Meier estimates in the cross-validated data set compared with the model-predicted estimates for each CAPRA-S score. For comparison, similar calibration plots were made for the Stephenson nomogram deciles. Finally, decision curve analysis [19] was used to compare the Stephenson nomogram

Table 2 – Demographic, clinical, and pathologic information for men in the SEARCH data set

Characteristic	Data
Age, yr, mean (SD)	61.9 (6.4)
Ethnicity, no. (%)	
Caucasian	1550 (58)
African American	970 (36)
Other	149 (6)
Pathologic Gleason score, no. (%)	
2–6	1109 (42)
3 + 4	946 (35)
4 + 3	317 (12)
8–10	298 (11)
PSA at diagnosis, no. (%)	
0–6	1159 (43)
6–10	809 (30)
10–20	506 (19)
>20	196 (7)
Extracapsular extension, no. (%)	
Absent	2100 (79)
Present	570 (21)
Seminal vesicle involvement, no. (%)	
Absent	2406 (90)
Present	246 (10)
Surgical margin status, no. (%)	
Absent	1549 (58)
Present	1121 (42)
Missing	
Lymph node status, no. (%)	
Negative	2628 (98)
Positive	42 (1.6)

SD = standard deviation; PSA = prostate-specific antigen.

Table 3 – Distribution of CAPRA-S scores among men in the SEARCH database

CAPRA-S score	Frequency, no.	Patients, %
0	413	15.5
1	413	15.5
2	440	16.5
3	392	14.7
4	332	12.4
5	232	8.7
6	167	6.3
7	110	4.1
8	63	2.4
≥9	108	4.0

CAPRA-S = Cancer of the Prostate Risk Assessment Postsurgical.

with the CAPRA-S score, based on the probability of being recurrence free at 5 yr within the SEARCH data set. Decision curve analysis is a novel method for evaluating prediction models and comparing the usefulness of two different models by determining which model provides the greatest net benefit, for example, the highest proportion of patients appropriately identified for adjuvant therapy.

Kaplan-Meier analysis was used to determine the association between the CAPRA-S score and the probability of PCSM. The discriminative ability of CAPRA-S to predict metastasis and PCSM was assessed by the c-index [18]. In these analyses, patients who did not have a lymph node dissection were treated as having negative nodes. A sensitivity analysis was performed in which these patients were excluded. Another sensitivity analysis was performed excluding patients with Gleason 2–5 tumors to ensure that contemporary data were represented. All analyses were performed using Stata 11.

3. Results

Among the 2892 men in the SEARCH database, 2670 (92%) had full data available to calculate a CAPRA-S score. Demographic, clinical, and pathologic information for men in SEARCH are given in Table 2. Recurrence occurred in 34.3% of men at a median time of 14 mo (interquartile range [IQR]: 5–28). The median follow-up for men who did not have recurrence was 58 mo (IQR: 28–97). There was a broad distribution of CAPRA-S scores (Table 3), with 16.8% of men having a score ≥6, consistent with high-risk disease.

The 3-yr and 5-yr Kaplan-Meier PGP estimates for each CAPRA-S level, which are shown in Table 4 and illustrated in Figure 1a, display an increased likelihood of recurrence with increasing CAPRA-S scores. Similar estimates from the development data set are shown in Table 4 for comparison. CAPRA-S scores were then grouped into previously defined categories of low, intermediate, and high risk using CAPRA-S scores of 0–2, 3–5, and 6–10, respectively [6]. Kaplan-Meier

Table 4 – Hazard ratios and 3-yr and 5-yr progression-free probabilities for each CAPRA-S level in the SEARCH and CaPSURE data sets

CAPRA-S score	*p* value	HR[a] (95% CI)	SEARCH		CaPSURE	
			3-yr % PGP (95% CI)	5-yr % PGP (95% CI)	3-yr % PGP (95% CI)	5-yr % PGP (95% CI)
0	Ref	1	89.2 (85.2–92.2)	81.8 (74.6–87.2)	96.3 (94.8–97.4)	94.5 (92.3–96.1)
1	0.011	1.9 (1.3–2.8)	75.3 (69.1–80.4)	68.7 (60.4–75.5)	95.3 (93.2–96.7)	91.0 (87.7–93.4)
2	0.004	2.3 (1.6–3.3)	72.3 (66.6–77.1)	64.1 (55.7–71.3)	89.8 (86.9–92.1)	83.3 (79.2–86.6)
3	<0.001	3.7 (2.7–5.3)	60.0 (53.4–65.2)	49.2 (39.8–57.8)	80.7 (76.5–84.3)	73.8 (67.5–77.3)
4	<0.001	5.1 (3.6–7.2)	46.6 (39.5–53.4)	36.6 (27.9–45.3)	74.9 (69.3–79.6)	70.2 (63.9–75.5)
5	<0.001	7.1 (5.0–10.0)	37.8 (30.2–45.3)	27.2 (17.8–37.4)	63.1 (55.5–69.8)	42.5 (33.4–51.3)
6	<0.001	8.4 (5.8–12.0)	33.1 (24.2–42.2)	29.8 (20.0–40.2)	49.2 (38.3–59.2)	25.9 (16.0–36.9)
7	<0.001	12.9 (8.8–18.7)	17.8 (10.0–27.3)	17.8 (10.0–27.3)	50.9 (37.5–62.8)	26.9 (15.5–39.7)
8	<0.001	17.0 (11.3–25.7)	12.3 (4.5–24.3)	0	26.9 (12.8–43.2)	12.3 (2.8–29.4)
≥9	<0.001	24.7 (17.1–35.8)	7.2 (2.6–15.1)	0	7.3 (1.4–19.9)	0

CAPRA-S = Cancer of the Prostate Risk Assessment Postsurgical; HR = hazard ratio; CI = confidence interval; SEARCH = Shared Equal Access Regional Cancer Hospital; CaPSURE = Cancer of the Prostate Strategic Urologic Research Endeavor; PGP = progression-free probability; Ref = reference.

[a] HR for the likelihood of prostate cancer recurrence for each CAPRA-S score compared with a CAPRA-S score of 0.

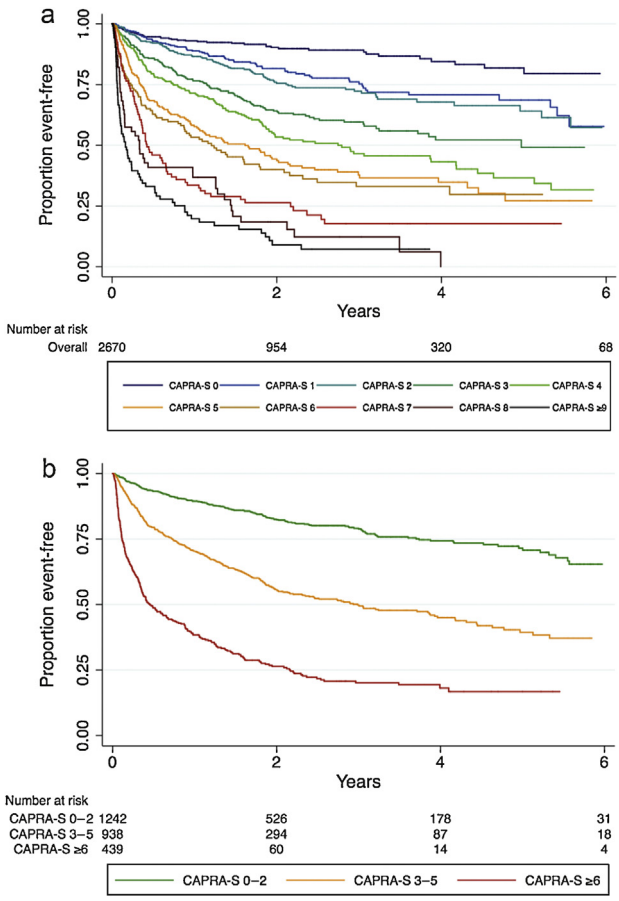

Fig. 1 – (a) Biochemical progression-free probability after radical prostatectomy stratified (a) by Cancer of the Prostate Risk Assessment Postsurgical (CAPRA-S) score and (b) by grouped CAPRA-S score: 0–2 indicates relatively low risk, 3–5 indicates intermediate risk, and >6 indicates high risk.

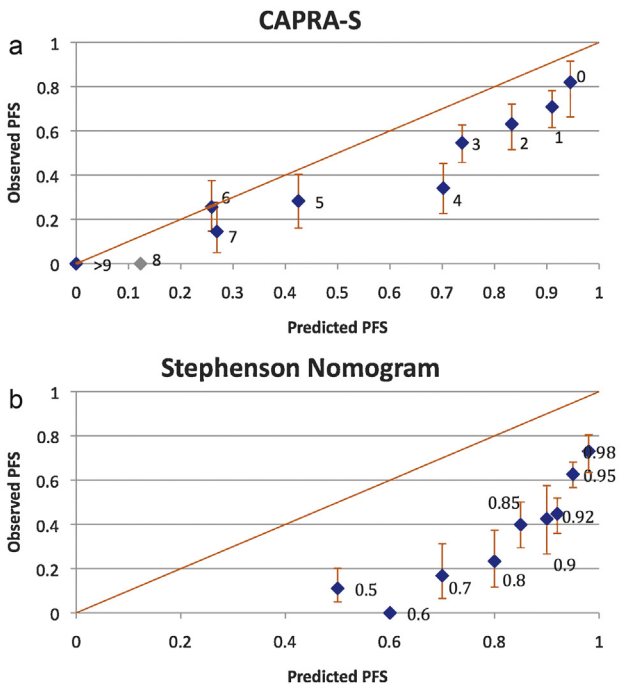

Fig. 2 – Calibration plots of observed compared with predicted recurrence-free probability at 5 yr for (a) Cancer of the Prostate Risk Assessment Postsurgical (CAPRA-S) score and (b) the Stephenson nomogram in the Shared Equal Access Regional Cancer Hospital validation data set. PFS = progression-free survival.

curves illustrate increased progression of disease with increasing risk (Fig. 1b). The 3-yr and 5-yr PGPs dropped from 79% and 72%, respectively, for low-risk tumors (CAPRA-S 0–2); to 50% and 39%, respectively, for intermediate-risk tumors (CAPRA-S 3–5); and to 20% and 17%, respectively, for high-risk tumors (CAPRA-S 6–10).

The c-index for CAPRA-S in SEARCH was 0.73, compared with 0.72 for the Stephenson nomogram. Calibration plots at 5 yr suggest some evidence of a lack of fit, with CAPRA-S scores being overly optimistic in their predictions of PGPs relative to outcomes observed in SEARCH (Fig. 2a). However, the Stephenson nomogram showed an even greater lack of fit and was substantially overoptimistic compared with the CAPRA-S score in this validation cohort (Fig. 2b). Finally, decision curve analysis comparing the CAPRA-S score and the Stephenson nomogram showed a greater net benefit (net increase in the proportion of patients appropriately identified for adjuvant treatment) of the CAPRA-S score over the Stephenson nomogram at all threshold probabilities for intervention (Fig. 3). However, for threshold probabilities <40%, treating all patients appeared to be better than using either model.

Eighty-three men developed metastasis, and 61 men died from PCa. The c-index for CAPRA-S in predicting metastasis was 0.84, and the c-index for predicting mortality was 0.85. Patients with high-risk CAPRA-S scores (≥6) displayed worse PCSM compared with men with low- or intermediate-risk tumors (Fig. 4).

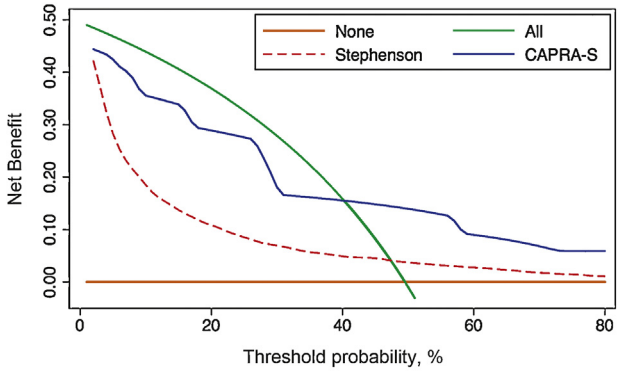

Fig. 3 – Decision curve analysis comparing the Cancer of the Prostate Risk Assessment Postsurgical (CAPRA-S) score with the Stephenson nomogram. The y-axis shows the net increase in the proportion of patients appropriately identified for adjuvant treatment. The solid blue line indicates the CAPRA-S score predictions, and the dashed red line indicates the Stephenson nomogram predictions. The solid green line represents a strategy of treating all men with adjuvant therapy (assuming all will experience recurrence), and the solid orange line represents a strategy of treating no men (assuming none will experience recurrence). Across all threshold probabilities, the CAPRA-S score had a greater net benefit of appropriately identifying patients for adjuvant treatment compared with the Stephenson nomogram.

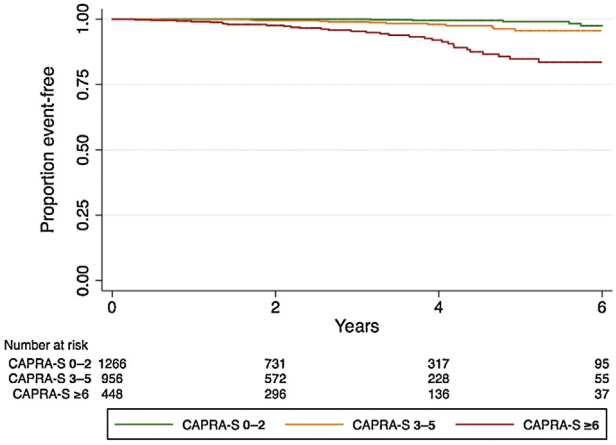

Fig. 4 – Prostate cancer–specific mortality for the following groupings: low-, intermediate-, and high-risk Cancer of the Prostate Risk Assessment Postsurgical (CAPRA-S) scores.

Sensitivity analyses excluding patients who did undergo a lymph node dissection and patients with Gleason 2–5 tumors failed to yield any significant changes to the results.

4. Discussion

The CAPRA-S postsurgical risk assessment tool is a novel instrument that incorporates pathologic information from RP and preoperative PSA to predict the likelihood of cancer recurrence after surgery. Its performance was externally validated in SEARCH, showing an increased risk of recurrence with increasing CAPRA-S scores. The c-index for CAPRA-S was 0.73, compared with 0.72 for the Stephenson nomogram, and the CAPRA-S score performed better than the Stephenson nomogram on both calibration plots and decision curve analysis. The CAPRA-S score also predicted metastasis and mortality with a c-index of 0.84–0.85.

Among the roughly one-third of men with PCa in the United States who undergo RP [20], some will experience a recurrence, of which a proportion will progress and be at risk for death [21]. PSA kinetics can help identify these patients [22] but often involve multiple PSA measurements that can result in a delay of secondary therapy. Risk assessment tools that can accurately predict cancer recurrence and progression would allow a more timely institution of additional treatments that might be beneficial for selected patients [23–25]. Among the 109 published prediction tools [3], only 8 take advantage of pathologic information gained from RP, and very few of these tools have been validated. Among these nomograms, the updated Stephenson postoperative nomogram is well known and commonly referenced and thus was used for comparison with CAPRA-S [17].

CAPRA-S showed good discriminatory accuracy in predicting recurrence in SEARCH, comparable to its performance in the original CaPSURE development data set. There was a wide distribution of CAPRA-S scores among the men in this validation set, and very few men (8%) had to be excluded for inability to calculate their CAPRA-S score. This fact suggests good external applicability for clinical and research purposes.

The PGP at each CAPRA-S level was lower in SEARCH compared with the CaPSURE data set, and calibration plots of CAPRA-S in SEARCH revealed that the CAPRA-S tool was somewhat overoptimistic in predicting progression-free survival. This finding may reflect a higher degree of cancer risk among men in SEARCH compared with men in CaPSURE. For instance, 17% of men in SEARCH were high risk (CAPRA-S $\geq$6), compared with only 6.5% of men in CaPSURE. Thirty-three percent of men in SEARCH experienced a recurrence, compared with only 16% in CaPSURE.

Both CAPRA-S and the Stephenson postoperative nomogram accurately discriminated cases in terms of tumor recurrence, with similar c-indexes. However, on analysis of calibration plots in both CaPSURE [6] and SEARCH, the Stephenson nomogram appeared more optimistic than the CAPRA-S score in predicting PGP. In the original CAPRA-S paper, the validation analysis was internal for CAPRA-S and external for the Stephenson nomogram, which could explain why CAPRA-S was superior in the original development paper [26]. However, verification in the current analysis, which involved external validation of both instruments, suggests rather that the calibration findings for the nomogram may reflect the application of a nomogram based on the results of high-volume academic surgeons to broader-based, multicenter cohorts.

Decision curve analysis showed that the CAPRA-S score had a greater proportion of patients appropriately identified for receiving adjuvant treatment compared with the Stephenson nomogram at all threshold probabilities for recommending adjuvant therapy. However, the analysis showed that for lower threshold probabilities ($<$40%) for administration of adjuvant treatment, it appeared better to treat all men instead of using either predictive model. One would assume that this approach, of treating all men, would put more weight on missing a patient who might benefit from adjuvant treatment compared with giving adjuvant treatment to a man unnecessarily. However, this assumption might not take into account the adverse effects of secondary therapies on recovery of sexual and urinary function and the burden on quality of life that these effects may have. Given the potential adverse effects of secondary radiotherapy on urinary and sexual function, many clinicians may choose not to give adjuvant radiotherapy and rather favor early salvage unless the probability of recurrence is high ($>$40% in this cohort). At these higher threshold probabilities, decision curve analysis suggests that the CAPRA-S score can aid in deciding whether or not to give adjuvant treatment. The actual threshold probability at which using CAPRA-S becomes more beneficial than treating everyone varies by the probability of recurrence in the population. In the development data set, for instance, CAPRA-S had a greater net benefit than treating everyone at a much lower threshold probability of approximately 10%.

This validation study had several strengths, including the use of a large, multi-institutional, and sociodemographically diverse database in which the significant majority of

patients (92%) had complete data available to calculate a CAPRA-S score. In addition, CAPRA-S was also robust for predictions of PCSM, with a high c-index of 0.85.

Several limitations should be noted. First, a quarter of patients in the SEARCH database did not undergo a lymph node dissection. They were deemed to have negative lymph nodes, given that the majority of these patients were low risk and unlikely to have nodal disease. Leaving their lymph node status as *missing* would have required the exclusion of these patients, since we would not be able to attain a CAPRA-S score for them. However, a sensitivity analysis was performed with the exclusion of these patients, and the results did not differ significantly. Second, reporting of pathology in SEARCH is not centralized, and variations may exist between the different medical centers. However, the use of decentralized pathologic assessment may result in greater generalizability of our results compared with single-center academic cohorts in which a single dedicated uropathologist reviewed all cases. Finally, although 448 of the patients in the data set (16.8%) had a CAPRA-S score >6, which is a reasonable proportion of patients with high-risk features for a contemporary surgical cohort, it is possible that this sample size is too small for us to validate the prognostic ability of CAPRA-S in this subset of men.

5. Conclusions

The CAPRA-S score was originally developed and internally validated in the CaPSURE database and has now been externally validated in SEARCH, a large, multi-institutional, and sociodemographically diverse population. The CAPRA-S score displays high discriminatory accuracy in predicting PCa recurrence and mortality following surgery and performed better than an established competing nomogram in appropriately identifying patients most likely to benefit from adjuvant treatment. These results validate the use of CAPRA-S as an effective prognostic tool to stratify men with PCa for risk of recurrence following surgery. Although no nomogram can substitute for individual clinician–patient decision making, the CAPRA-S tool is easy to use and provides an effective method of risk assessment that can facilitate usefulness in both clinical and research settings.

Author contributions: Matthew R. Cooperberg had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Cooperberg, Carroll.
Acquisition of data: Freedland, Cooperberg, Punnen.
Analysis and interpretation of data: Cooperberg, Punnen, Freedland.
Drafting of the manuscript: Punnen, Cooperberg.
Critical revision of the manuscript for important intellectual content: Punnen, Cooperberg, Carroll, Freedland, Presti, Terris, Kane, Amling, Aronson.
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Supervision: Cooperberg, Freedland, Carroll.
Other (specify): None.

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