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RESEARCH ARTICLE

Factors Affecting Biochemical Recurrence After Radical Prostatectomy and Validity of CAPRA Score in Predicting Biochemical Recurrence

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Abstract

Objective: Biochemical recurrence (BCR) after prostate cancer (PCa) treatment is undesirable. It is important to inform a patient about BCR in preoperative evaluation. We aimed to demonstrate the effectiveness of the (The Prostate Cancer Risk Assessment) CAPRA score used to predict this situation in our study.

Material and Methods: The study included 348 patients who underwent Radical Prostatectony (RP) for localized PCa. Demographic, preoperative and postoperative data were collected. CAPRA score based on preoperative total PSA value, Gleason Score, clinical T stage, percentage of positive biopsy cores and age was calculated using these data. BCR was defined as a total PSA value >0.2 ng/dL for two consecutive times after RP. Follow-up periods, recurrence status and time of recurrence were recorded.

Results: BCR positivity was detected in 60 (17.2%) of 348 patients. In univariate analyses, PSA level, lesion volume on MRI, ISUP grade, D'Amico risk classification, Seminal vesicule invasion (SVI) and CAPRA score were statistically significant in the groups. In multivariate analyses, PSA level, Neutrophile Lymphocyte Ratio, lesion dimension, intermediate risk according to D'amico classification, Extraprostatic extension (EPE) showed differences between both groups. The probability of biochemical progression-free in CAPRA risk groups shows a significant decrease in the probability of biochemical progression-free in the long term as risk increases in CAPRA risk groups: 91.4% in the low-risk group, 77.8% in the intermediate-risk group and only 61.7% in the high-risk group at 80-month follow-up.

Conclusion: CAPRA scoring system should be supported by MpMRI findings and a new nomogram should be developed with these findings.

Keywords: CAPRA score, radical prostatectomy, biochemical recurrence, prostate cancer

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INTRODUCTION

Prostate cancer (PCa) remains one of the most common malignancies affecting men worldwide (1). Despite advances in diagnostic and treatment strategies, predicting disease progression, particularly biochemical recurrence (BCR), remains a clinical challenge. BCR of PCa is defined as an increase in prostate-specific antigen (PSA) levels following primary treatment, such as radical prostatectomy (RP) or radiation therapy, indicating potential disease progression (2). Accurate prediction of BCR is crucial for timely intervention and management (3). The Prostate Cancer Risk Assessment (CAPRA) score developed by the University of California, San Francisco (UCSF) has emerged as a crucial tool in stratifying risk and predicting outcomes for patients with PCa (4). Higher scores indicate a higher risk of recurrence and a worse prognosis (4). This article examines the utility of the CAPRA score in predicting BCR after treatment.

MATERIAL AND METHODS

The study included 348 patients who underwent RP between 2015 and 2022 for localized PCa. Local ethics committee approval was obtained and the study was conducted according to the Declaration of Helsinki Declaration of Human Rights. Patients who were diagnosed with localized PCa, underwent RP operation and were followed up regularly for BCR were included in our study. Patients diagnosed with metastatic PCa, patients with pathologic lymph node metastases, patients receiving neo-adjuvant hormonotherapy or radio-chemotherapy, and patients without regular follow-up were excluded. Age, Body Mass Index (BMI), American Society of Anesthesiologists (ASA) score demographic data, preoperative laboratory tests (neutrophils, lymphocytes, platelets, monocytes, AST, ALT) preoperative total PSA value, prostate volume, PSA density data were recorded. Each patient underwent 3.0 Tesla multiparametric magnetic resonance imaging (MpMRI) for local staging. The size of the lesion, Prostate Imaging–Reporting and Data System (PIRADS) score, lesion volume were recorded. Lesion density was calculated by dividing the lesion size by the lesion volume. PCa was diagnosed by transrectal USG-guided and/or MR fusion-guided biopsy. The positive core rate and International Society of Urological Pathology (ISUP) grade were evaluated and patients were classified according to the D'amico classification in terms of risk.

CAPRA Scoring was based on preoperative total PSA value, GS pattern, clinical T stage, percentage of positive biopsy cores and age (5). Patients whose CAPRA score was calculated between 0-10 according to the values in these parameters were defined as low risk between 0- 2 points, intermediate risk between 3-5 points, and high risk with a score of 6 and above (5). The need for lymph node dissection was calculated for each patient according to the Briganti nomogram in the preoperative period and bilateral extended lymph node dissection was performed in addition to RP in patients with >5% according to the nomogram (6). In pathological evaluation, T stage, nodal involvement, tumor percentage, Extraprostatic extension (EPE) status, Seminal vesicule invasion (SVI), ISUP grade data were recorded. Upgrade status was evaluated according to preoperative and postoperative ISUP pathology results. PSA was evaluated 4-6 weeks after RP and total PSA was evaluated every 3 months for the first two years and then every 6 months for up to 5 years. BCR was defined as a total PSA value >0.2 ng/dL for two consecutive times after RP (7). Follow-up periods, recurrence status and time of recurrence were recorded.

Statistical Analysis

Data analyses were performed using IBM SPSS Statistics for Windows version 24.0 (IBM Corp., Armonk, NY,USA). Distribution of continuous variables was assessed by Shapiro- Wilk's test. Continuous variables are presented as mean and standard deviation (*SD*) or median (1st-3rd interquartile ranges (*IQR*)). Categorical variables were presented as number and frequencies. Mann-Whitney *U* tests were used for comparing the continuous variables based on the distribution. *Chi-square* test (Pearson Chi-Square) was used to compare the categorical variables. The performances of the CAPRA score groups and to predict the BCR- free probability were examined by Cox proportional hazards regression (Backward Wald method) and Kaplan-Meier analysis. A significance level of $p< 0.05$ was considered statistically significant.

RESULTS

In our study, BCR positivity was detected in 60 (17.2%) of 348 patients. When BCR (-) and BCR (+) patients were compared, no difference was detected between age, BMI, ASA scores among demographic data. In the preoperative laboratory evaluation, there was no difference in Neutrophil, Lymphocyte, Platelet, Monocyte, AST, ALT values, but PSA value was statistically higher in the BCR (+) group ($p<0.001$). There was no difference between LMR, PLR, De-Ritis ratio in laboratory-based ratios, while NLR was statistically higher

in the BCR (+) group (p:0.006). Demographic and laboratory data of the patients are given in Table 1.

In terms of preoperative MpMRI, PIRADS scores, lesion size and volume were higher in the group with BCR (+) (p<0.001). EPE was 19.4% vs 31.7% (p:0.036) and SVI was 8.3% vs 23.3% (p:0.002) in BCR (-) and (+) groups, respectively. In the biopsy results of the patients, ISUP grade was higher in BCR (+) patients. In the D'Amico classification of the patients according to PSA and biopsy results, high-risk patients were 13.2% in the BCR (-) group and 40% in the BCR (+) group (p<0.001). In postopetative pathology results, EPE, SVI rate and ISUP grade were higher in BCR (+) patients (p<0.001). The MpMRI and pathologic data of the patients are shown in Table2.

In univariate analyses, PSA level, NLR, lesion volume on MpMRI, ISUP grade, D'Amico risk classification, SVI on MpMRI and pathologic specimen and CAPRA score were statistically significant in the group with and without BCR. In multivariate analyses, PSA level, NLR, lesion dimension, intermediate risk according to D'amico classification, EPE on MpMRI and pathology results showed differences between both groups. Univariate and multivariate analysis results are shown in Table 3.

The probability of biochemical progression-free in CAPRA risk groups shows a significant decrease in the probability of biochemical progression-free in the long term as risk increases in CAPRA risk groups: 91.4% in the low-risk group, 77.8% in the intermediate-risk group and only 61.7% in the high-risk group at 80-month follow-up. The data of patients with biochemical progression-free disease according to CAPRA scores and the respective hazard ratios by CAPRA groups are listed in Table 4 and shown as a Kaplan-Meier curve in Figure 1.

Table 1. Demographic and clinical features of the patients

	All patients (n=348)	**BCR (-) (n=288)**	**BCR (+) (n=60)**	**p value**
Age (*year*)	62.29±5.97	62.12±5.93	63.12±6.14	0.187
BMI (kg/m^2)	26.47±2.48	26.49±2.60	26.38±1.87	0.932
ASA (n /%) 1 2 3	 33 (9.5) 299 (85.9) 16 (4.6)	 27 (9.4) 250 (86.8) 11 (3.8)	 6 (10.0) 49 (81.7) 5 (8.3)	0.305
PSA (ng/dL)	10.20±8.54	9.22±6.92	14.94±12.98	**<0.001**
PSAD	0.26±0.24	0.23±0.24	0.36±0.26	**<0.001**
PV (cc)	46.01±19.06	46.45±19.68	43.88±15.73	0.721
Neutrophil (×10^3 per µl)	5.02±4.47	4.84±3.45	5.92±7.66	0.119
Lymphocyte (×10^3 per µl)	2.51±2.13	2.50±1.79	2.58±3.33	0.084
Platelet (×10^3 per µl)	248.36±66.49	251.20±69.31	234.75±49.00	0.103
Monocyte (×10^3 per µl)	0.68±0.38	0.67±0.23	0.71±0.76	0.246
AST (IU/L)	23.46±9.96	23.62±10.15	22.71±9.03	0.296
ALT (IU/L)	24.08±13.34	24.48±13.86	22.14±10.36	0.414
NLR	2.24±1.22	2.14±0.99	2.70±1.91	**0.006**
PLR	115.83±52.09	114.13±46.24	123.95±73.98	0.415
MLR	0.32±0.39	0.30±0.13	0.43±0.90	0.587
De Ritis Ratio	1.11±0.62	1.11±0.66	1.11±0.34	0.416
Percentage of positive correlation in biopsy	0.35±0.21	0.34±0.21	0.40±0.22	0.052

Table 2. Data of MpMRI and Pathology results of the groups

	All patients (n=348)	BCR(-) (n=288)	BCR (+) (n=60)	p value
	n (%)	n (%)	n (%)	
PIRADS Score (n /%)				**<0.001**
2	83 (23.9)	74 (25.7) [a]	9 (15.0) [a]	
3	49 (14.1)	45 (15.6) [a]	4 (6.7) [a]	
4	159 (45.7)	134 (46.5) [a]	25 (41.7) [a]	
5	57 (16.4)	35 (12.2) [a]	22 (36.7) [b]	
Lesion Diameter (mm)	10.08±8.74	9.51±8.59	12.83±9.01	**0.001**
Lesion Volume (mm^3)	440.02±1157.56	323.50±621.55	999.33±2370.02	**<0.001**
Total Lesion Density	11.57±34.69	8.11±17.04	28.17±73.73	**0.001**
EPE on MpMRI (n /%)				
(-)	273 (78.4)	232 (80.6) [a]	41 (68.3) [b]	**0.036**
(+)	75 (21.6)	56 (19.4) [a]	19 (31.7)	
SVI on MpMRI (n /%)				
(-)	310 (89.1)	264 (91.7) [a]	46 (76.7) [b]	**0.002**
(+)	38 (10.9)	24 (8.3) [a]	14 (23.3) [b]	
BX ISUP (n /%)				**<0.001**
1	169 (48.6)	155 (53.8) [a]	14 (23.3) [b]	
2	118 (33.9)	92 (31.9) [a]	26 (43.3) [a]	
3	36 (10.3)	26 (9.0) [a]	10 (16.7) [a]	
4	20 (5.7)	11 (3.8) [a]	9 (15.0) [b]	
5	5 (1.4)	4 (1.4) [a]	1 (1.7) [a]	
D'Amico Risk classification (n /%)				**<0.001**
Low	121 (42.0)	127 (36.5) [b]	6 (10) [b]	
Intermediate	133 (46.2)	167 (48.0) [a]	34 (56.7) [a]	
High	34 (11.8)	54 (15.5) [a]	20 (33.3) [a]	
CAPRA Score (n /%)				**<0.001**
0-2 (Low Risk)	123 (35.3)	118 (41.0) [a]	5 (8.3) [b]	
3-5 (Intermediate Risk)	163 (46.8)	132 (45.8) [a]	31 (51.7) [a]	
≥6 (High Risk)	62 (17.8)	38 (13.2) [a]	24 (40.0) [b]	
Upgrade (n /%)				0.570
(-)	174 (50.0)	142 (49.3)	32 (53.3)	
(+)	174 (50.0)	146 (50.7)	28 (46.7)	
EPE (n /%)				
(-)	260 (74.7)	228 (79.1) [a]	32 (53.3) [b]	**<0.001**
(+)	88 (25.3)	60 (20.9) [a]	28 (46.7)	
SVI (n /%)				
(-)	298 (85.6)	258 (89.5) [a]	40 (66.6) [b b]	**<0.001**
(+)	50 (14.4)	30 (10.5) [a]	20 (33.3) [b]	
Pathology ISUP (n /%)				**<0.001**
1	66 (18.7)	65 (22.3) [a]	1 (1.7) [b]	
2	154 (44.3)	139 (48.3) [a]	15 (25.0) [b]	
3	88 (25.3)	62 (21.5) [a]	26 (43.3) [b]	

4	16 (4.6)	11 (3.8) [a]	5 (8.3) [a]	
5	24 (6.9)	11 (3.8) [a]	13 (21.7) [b]	
Percent tumor involment	22.37±18.88	19.19±15.76	37.67±24.54	**<0.001**

Table 3. Risk factors affecting BCR with univariate and multivariate analysis results

	Univariate		Multivariate	
Variables	**HR (95 % CI)**	**p value**	**HR (95 % CI)**	**p value**
PSA	1.028 (1.005-1.051)	**0.016**	1.051 (1.021-1.083)	**<0.001**
PSAD	1.274 (0.623-2.605)	0.507	---	---
NLR	1.182 (1.055-1.324)	**0.004**	1.158 (1.030-1.302)	**0.014**
Lesion Diameter	1.020 (0.998-1.042)	0.075	1.000 (1.000-1.000)	**0.002**
Lesion Volume	1.000 (1.000-1.000)	**0.005**	---	---
BX ISUP				
1	1 (Ref.)			
2	3.155 (1.644-6.057)	**<0.001**	---	---
3	3.730 (1.653-8.415)	**0.002**		
4	2.607 (1.115-6.093)	**0.027**		
5	1.207 (0.158-9.246)	0.856		
D'Amico Risk classification				
Low	1 (Ref.)		1 (Ref.)	
Intermediate	5.316 (2.225-12.698)	**<0.001**	3.618 (1.480-8.844)	**0.005**
High	3.008 (1.173-7.713)	**0.022**	0.915 (0.287-2.917)	0.881
PIRADS Score				
2	1 (Ref.)	0.078		
3	0.623 (0.192-2.026)	0.431	---	---
4	1.228 (0.572-2.636)	0.599		
5	2.026 (0.922-4.455)	0.079		
SV on MpMRI				
(-)	1 (Ref.)		---	---
(+)	2.251 (1.228-4.127)	**0.009**	---	---
EPE on MpMRI				
(-)	1 (Ref.)		1 (Ref.)	---
(+)	1.231 (0.713-2.127)	0.456	0.279 (0.131-0.592)	**<0.001**
CAPRA Score				
0-2 low	1 (Ref.)			
3-5 intermediate	4.328 (1.680-11.150)	**0.002**	---	---
≥6 high	5.234 (1.977-13.856)	**<0.001**		
SVI				
(-)	1 (Ref.)		---	---
(+)	1.748 (1.428-3.827)	**0.008**	---	---
EPE				
(-)	1 (Ref.)	0.456	1 (Ref.)	---
(+)	1.693 (0.601-3.612)		0.179 (0.091-0.637)	**<0.001**

HR Hazard Ratio, CI Confidence Interval

Table 4. BCR free probabilities for CAPRA score groups

Score/Risk level	HR (95 % CI)	p value	BCR free probability (95% CI)
CAPRA Score			
0-2 low	1 (Ref.)	0.004	91.41 (80.70-100.00)
3-5 intermediate	4.328 (1.680-11.150)	0.002	77.80 (69.81-85.79)
≥6 high	5.234 (1.977-13.856)	<0.001	61.71 (50.43-72.98)

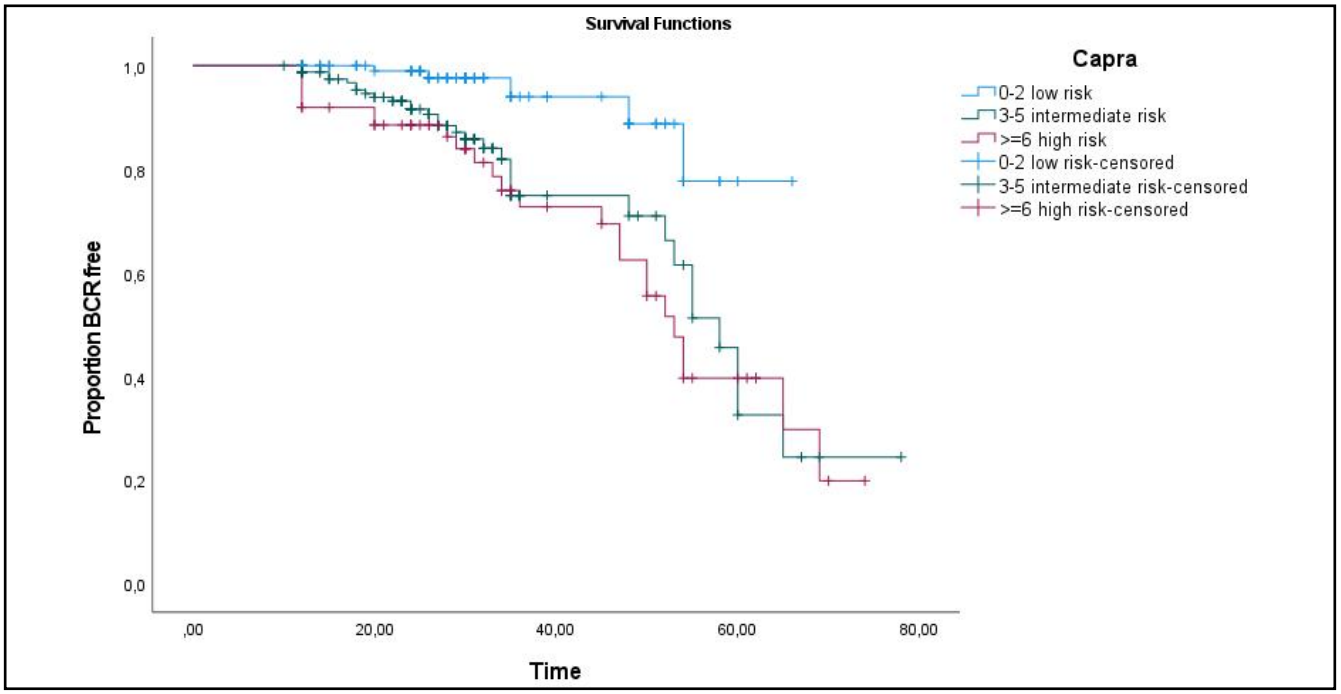

Figure 1. Probability of BCR-free survival of CAPRA risk groups according to Kaplan-Meier survival analysis

DISCUSSION

BCR after RP is the condition that can be encountered in clinical practice due to heterogeneity in prostate cancer. In patients with localized PCa, BCR with post-treatment PSA follow-up is the main predictor of additional treatment (8). Following RP, approximately 20-50% of patients develop BCR within 10 years and BCR is associated with an increased need for secondary treatment, which may negatively affect quality of life (9-10).

BCR depends on many factors such as local staging of the disease on MpMRI, preoperative and postoperative pathology results (11-14). In our study, BCR was determined as PSA, NLR, lesion volume, biopsy ISUP grade, D'amico risk classification, SVI on MpMRI, CAPRA score and SVI on pathologic specimen in univariate analyses while PSA, NLR, Lesion Diameter, being in the intermediate risk class in D'Amico risk classification, EPE on MpMRI and pathology specimen were determined as risk factors in multivariate analyses.

Recently, laboratory-based studies have tried to predict BCR. The most frequently emphasized ratio in these studies is NLR (15). In the study conducted by Minardi et al.(15), NLR>3 was found to be a risk factor for BCR. Similarly, Jang et al. (16) showed in their study that high postoperative NLR was significantly associated with decreased biochemical recurrence-free survival and overall survival. In our study, NLR was found to be one of the factors affecting BCR. We did not set any cut-off value for NLR in our study, but NLR was found to be higher in patients who developed BCR.

Preoperative MpMRI not only provides clinical staging, but also aids in better anatomic control and higher surgical

success (17). Improved strategies for predicting BCR in PCa are increasingly being evaluated in pathologic studies; however, there have been few studies using MRI-based features to noninvasively predict BCR (18-20). Findings such as lesion volume/percentage, EPE and SVI on MpMRI have been identified as risk factors for BCR (12).Manceau et al.(18) emphasized that MpMRI has a very important role in predicting BCR and should be performed peroperatively in every patient. Sademan et al.(19) reported that MpMRI has the ability to predict BCR after RP and a new nomogrom can be developed by adding MR data to the scoring systems. Copogrosso et al (20), on contrary, did not find any correlation between BCR and MpMRI findings. Contradictory findings in the literature on this subject draw attention. In our study, PIRADS score, lesion size and volume were higher in patients with BCR (+) groups among MpMRI findings. In addition, EPE and SVI were more common in patients with BCR (+) groups. In multivariate analysis of these data, lesion size was found to be statistically significant. As in the study of Sademan et al, we suggest that a new nomogram that predicts BCR should be developed using MpMRI data.

Since there are many factors affecting BCR, nomograms have been developed and it has been aimed to predict the BCR rate (21,22). One of these nomograms is CAPRA scoring. In this scoring system, which ranges from 0 to 10 points and risk classification is determined according to the score obtained, Cooperberg et al. found biochemical recurrence-free survival in the low (0-2 points), intermediate (3-5 points) and high (6 points) groups to be approximately 90%, 65% and 25% in 5 years, respectively (4,21). In the cohort of 2670 patients of Punnen et al.(23), the recurrence-free probability at 5 years was 62%, 39% and 17% lower compared to Cooperberg's first study.May et al.(24) evaluated 3- and 5-year recurrence rates in high-risk patients in their study on CAPRA score and found RFS rates of 44% and 31%. Budäus et al. (25) reported 5-year RFS rates of 95.4% in low-risk patients, 82% in intermediate-risk patients and 63.1% in high-risk patients. In our study, CAPRA score was statistically higher in patients with BCR (+) groups. Low risk, intermediate risk and high risk percentages were 8.3%, 51.7% and 40%, respectively, in patients with BCR (+) groups. CAPRA score was also a factor affecting BCR in univariate analyses. In addition, BCR free probabilities were 91.4%, 77.8%, 61.7% in low, intermediate and high risk patients with CAPRA score, respectively.

There are some limitations in our study. The limitations of our study are firstly, the retrospective design, secondly, the shorter follow-up period compared to other studies, and thirdly, the small number of patients.

CONLUSION

The development of BCR after primary treatment in patients with localized PCa necessitates additional treatment. Therefore, factors affecting BCR can be identified and recurrence can be predicted. The CAPRA score is a nomogram developed to predict BCR. We can state that that the CAPRA scoring system should be supported by MpMRI findings (Lesion diameter and volume, EPE) and a new nomogram should be developed with these findings.

Conflict of Interest: No conflict of interest was declared by the authors.

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Consent to participate: For this type of retrospective study, formal consent is not required.

Experimental-Informed Consent: Written informed consent was obtained from patients who participated in this study.
No artificial intelligence program was used in our article.

Inform of publication: The results of the study were not published in full or in part in the form of an abstract.

Authors Contribution: Conception: YA, ED, BAE, Design: YA, MZK, Supervision: DNO,MZK, BE, Data Collection: YA, ED, BEA, Analysis: BE, Literature Review: YA,DNÖ, Writer: YA, ED, Critical Review: MZK, BE, DNÖ

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Health Science Universty Izmir Tepecik Training and Research Hospital Decision No: 2024/07-17 Date: 19/08/2024.

Research involving human participants and/or animals: This article does not contain any studies with animals performed by any of the authors. All procedures performed in studies involving human participants were by the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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