A novel nomogram provides improved accuracy for predicting biochemical recurrence after radical prostatectomy

Haizhui Xia
Peking University Third Hospital https://orcid.org/0000-0001-7609-3096
Hai Bi
Peking University Third Hospital
Ye Yan
Peking University Third Hospital
Bin Yang
Peking University Third Hospital
Ruozhuo Ma
Peking University Third Hospital
Wei He
Peking University Third Hospital
Xuehua Zhu
Peking University Third Hospital
Zhiying Zhang
Peking University Third Hospital
Yuting Zhang
Peking University Third Hospital
Lulin Ma
Peking University Third Hospital
Xiaofei Hou
Peking University Third Hospital
Jian Lu (lujian@bjmu.edu.cn)
https://orcid.org/0000-0002-9144-7486

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Abstract

Background: Various prediction tools have been developed to predict biochemical recurrence (BCR) after radical prostatectomy (RP), however, few of the previous prediction tools used serum prostate specific antigen (PSA) nadir after RP and maximum tumor diameter (MTD) at the same time. In this study, a nomogram incorporating MTD and PSA nadir was developed to predict BCR-free survival.

Methods: 337 patients who underwent RP were retrospectively enrolled in this study. The maximum diameter of the index lesion was measured on magnetic resonance imaging (MRI). Cox regression analysis was performed to evaluate independent predictors of BCR. A nomogram was subsequently developed for the prediction of BCR-free survival at 3 and 5 years after RP. Time-dependent receiver operating characteristic (ROC) curve and decision curve analysis were performed to identify the advantage of the new nomogram in comparison with the CAPRA-S score.

Results: A novel nomogram was developed to predict BCR by including PSA nadir, MTD, Gleason score, surgical margin (SM), and seminal vesicle invasion (SVI), since these variables were significantly associated with BCR in both univariate and multivariate analysis (p <0.05). In addition, a basic model including Gleason score, SM, and SVI was developed and used as a control to assess the incremental predictive power of the new model. The concordance index of our model was slightly higher than CAPRA-S model (0.76 vs. 0.70, p =0.02) and it was significantly higher than that of the basic model (0.76 vs. 0.66, p =0.001). Time-dependent ROC curves and decision curve analyses also demonstrated the advantages of the new nomogram.

Conclusions: PSA nadir after RP and MTD based on MRI before surgery are independent predictors of BCR. By incorporating PSA nadir and MTD into the conventional predictive model, our newly developed nomogram significantly improved the accuracy in predicting BCR-free survival after RP.

Background

Prostate cancer is among the most frequent cancers and the second leading cause of mortality in men. It is estimated that there will be about 191,930 new cases of prostate cancer and 33,330 deaths in the United States in 2020 [1]. Approximately, 20%-30% of the patients experience biochemical recurrence (BCR) after radical prostatectomy (RP) during follow-up[2, 3]. Various prediction tools for BCR have been developed to guide the clinical decision-making for subsequent treatment[4–6]. Most of these tools are developed based on clinical and pathologic parameters such as preoperative serum prostate specific antigen (PSA), Gleason score, tumor stage, surgical margin (SM), extracapsular extension (ECE), seminal vesicle invasion (SVI), and lymph node invasion (LNI). The CAPRA-S score is one of the most commonly used tools with good discriminative accuracy and calibration[6]. However, only few of these tools include tumor diameter and postoperative PSA nadir, simultaneously, although the prognostic value of these two characteristics in predicting BCR has been verified[7, 8].

Measurement of PSA is the cornerstone in postoperative follow-up and serum PSA is expected to be undetectable within six weeks after radical prostatectomy[9] and a detectable PSA in patients after RP is thought to be associated with residual cancer. A persistent (detectable) PSA after RP has been proved to be a poor prognostic indicator of oncologic outcomes[10].

Magnetic resonance imaging (MRI) has been widely used for prostate cancer diagnosis and the prognostic potential of MRI is constantly being explored with the advancement of radiographic technologies [11, 12]. Maximum tumor diameter (MTD) has been demonstrated to be an independent predictor of BCR in patients after RP[13]. However, in most studies, MTD measurement was carried out on the pathological specimens and only few of them measured MTD on MRI[14], while the latter is considered to be more accurate and comparable. To our knowledge, no study addressing on the relationship between MTD measured on MRI and BCR was conducted.

In this study, we aim to assess the prognostic power of MTD from MRI in predicting BCR-free survival (BCRFS) after RP and develop a new nomogram that incorporates MTD, PSA nadir, and other common perioperative variables.

Methods

Patients

This study was approved by the Peking University Third Hospital Medical Science Research Ethics Committee. Data of 542 patients who underwent laparoscopic RP for prostate cancer between Jan 2010 and Mar 2017 were retrospectively analyzed. The exclusive criteria were as follow: 1) patients with neoadjuvant therapy before surgery; 2) patients who had undergone transurethral resection of the prostate (TURP); 3) patients with unidentifiable lesions on MRI; 4) patients whose pathological results were not prostatic adenocarcinoma; 5) incomplete follow-up data. Follow-up was executed every 3 months for the first two years, semi-annually for the third and fourth year, and annually thereafter.

The suspicious tumor lesions were identified according to comprehensive understanding of T2-weighted images, diffusion weighted images, and apparent diffusion coefficient maps of MRI. MTD was defined as the largest tumor diameter of index lesion on axial T2-weighted images. For multifocal cases, Only the largest tumor nodule was measured for analysis. PSA nadir was defined as the lowest level of serum PSA after RP without adjuvant androgen deprivation therapy or radiotherapy. BCR was defined as postoperative PSA value higher than 0.2 ng/mL in two consecutive measurements and the recurrence date was assigned to the day when PSA value > 0.2 ng/mL was measured for the first time. BCRFS was calculated from date of RP to date of documented BCR. Other clinical and pathological data, including age at RP, body mass index (BMI), preoperative PSA, Gleason score, SM, ECE, SVI, and LNI were also collected for each patient.

Statistical Analysis

Means, standard deviation, median, and interquartile ranges (IQR) were reported for continuously variables. Numbers and proportions were reported for categorical variables. BCRFS was estimated using the Kaplan-Meier curves and log-rank test. MTD was categorized into ≤ 2.9 cm and > 2.9 cm. The cutoff value of MTD that best discriminated low and high risk for BCR was estimated by maximally selected test with the “maxstat” package of R software[15]. PSA nadir was categorized into undetectable and detectable PSA. An undetectable PSA was defined as a PSA nadir < 0.01 ng/mL. Univariable and multivariable Cox proportional hazards regression models were used to identify significant predictors of BCR. A nomogram predicting BCRFS at 3 and 5 years after RP was developed based on the multivariable model. For the validation of the nomogram, a bootstrap technique (1000 bootstrap resamples) was used for internal validation to assess the discrimination and calibration. The concordance index (c-index) was used to assess the discrimination. The calibration curve was made to assess the calibration which graphically revealed the relationship between predicted probability of BCR and actual observed events. Additionally, we compared our newly developed nomogram to the CAPRA-S score, and comparison of the two models was performed using the “compareC” package of R software[16]. Time-dependent ROC curves were illustrated using the “survivalROC” package[17]. Decision curve analyses at 3 and 5 years were executed to ascertain the clinical value of the new nomogram. Statistical analyses were performed with R software (version 3.6.2, R Foundation for Statistical Computing, Vienna, Austria) and GraphPad Prism (version 7.00, GraphPad Software, San Diego, California, USA). All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant.

Results

Overall, 337 patients were included in this study and the demographic and clinical characteristics of these patients are shown in Table 1. The median follow-up time was 42 months (IQR, 19–64 months) and 100 patients (29.7%) developed BCR during follow-up. The median age of all patients was 71 years (IQR, 65–75 years) with median BMI of 24.6 kg/m^2 (IQR, 22.8–26.6 kg/m^2), respectively. The median value of preoperative PSA was 10.8 ng/mL (IQR, 7.3–19.1 ng/mL) and was divided into three groups: <10 ng/mL, 10–20 ng/mL, and > 20 ng/mL. The majority of the patients had PSA nadir < 0.01 ng/mL (n = 242, 71.8%), while 95 patients (28.2%) had PSA nadir ≥ 0.01 ng/mL. The median MTD was 3.09 cm (IQR, 2.24–3.91 cm) with 45.1% of MTD ≤ 2.9 cm and 54.9% of MTD > 2.9 cm.

Table 1
Characteristics of patients treated by radical prostatectomy

Characteristics	No.	%
No. of patients	337	100
No. of BCR	100	29.7
Age (yrs)		
Mean (SD)	69.9 (7.11)	
Median (IQR)	71 (65, 75)	
BMI (kg/m^2)		
Mean (SD)	24.7 (3.09)	
Median (IQR)	24.6 (22.8, 26.6)	
Preoperative PSA (ng/mL)		
Mean (SD)	17.6 (22.0)	
Median (IQR)	10.8 (7.3, 19.1)	
Preoperative PSA (ng/mL)		
<10	152	45.1
10–20	106	31.5
>20	79	23.4
PSA nadir (ng/mL)		
Mean (SD)	0.033 (0.185)	
Median (IQR)	0 (0, 0.01)	
PSA nadir (ng/mL)		
< 0.01	242	71.8
≥ 0.01	95	28.2
Gleason score		
≤ 3 + 4	148	43.9
≥ 4 + 3	189	56.1
Pathological tumor stage		
≤ T2a	14	4.2

Characteristics	No.	%
T2b	33	9.8
≥ T2c	290	86.0
SM		
Negative	222	65.9
Positive	115	34.1
ECE		
No	225	66.8
Yes	112	33.2
SVI		
No	295	87.5
Yes	42	12.5
MTD (cm)		
Mean (SD)	3.25 (2.53)	
Median (IQR)	3.09 (2.24–3.91)	
MTD (cm)		
≤ 2.9	152	45.1
> 2.9	185	54.9
Follow-up (months)		
Mean (SD)	37 (28)	
Median (IQR)	42 (19–64)	

BCR, biochemical recurrence; BMI, body mass index; PSA, prostate specific antigen; SM, surgical margin; ECE, extracapsular extension; SVI, Seminal vesicle invasion; MTD, maximum tumor diameter

To identify significant predictors of BCR, we evaluated age, BMI, preoperative PSA, Gleason score, SM, ECE, SVI, PSA nadir, and MTD in a univariable Cox proportional hazards regression model and the results are shown in Table 2. Except for age and BMI, all predictors were statistically significantly associated with BCR after RP (p values < 0.01).

Table 2
Univariable and multivariable Cox regression analyses of BCR-free survival

	Univariable			Multivariable		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Age	0.981	0.954–1.008	0.168			
BMI	1.023	0.963–1.087	0.459			
Preoperative PSA (ng/mL)						
< 10	Reference			Reference		
10–20	1.090	0.654–1.817	0.740	1.071	0.638–1.795	0.921
> 20	2.773	1.759–4.374	< 0.001	1.669	0.995–2.799	0.075
PSA nadir (ng/mL)						
< 0.01	Reference			Reference		
≥ 0.01	3.959	2.663–5.887	< 0.001	4.531	2.993–6.861	< 0.001
Gleason score						
≤ 3 + 4	Reference			Reference		
≥ 4 + 3	2.310	1.496–3.568	< 0.001	2.090	1.277–3.420	0.003
SM						
Negative	Reference			Reference		
Positive	1.966	1.326–2.916	< 0.001	1.675	1.076–2.610	0.007
ECE						
No	Reference			Reference		
Yes	1.720	1.155–2.560	0.008	0.791	0.469–1.336	0.376
SVI						
No	Reference			Reference		

	Univariable			Multivariable		
Yes	2.704	1.649–4.436	< 0.001	1.723	0.897–3.307	0.022
MTD (cm)						
≤ 2.9	Reference			Reference		
> 2.9	2.196	1.425–3.385	< 0.001	1.587	1.006–2.503	0.034

BCR, biochemical recurrence; BMI, body mass index; PSA, prostate specific antigen; SM, surgical margin; ECE, extracapsular extension; SVI, Seminal vesicle invasion; MTD, maximum tumor diameter

As shown in Fig. 1, Kaplan-Meier curves were stratified by (**B**) PSA nadir (< 0.01 vs. ≥ 0.01 ng/mL), (**C**) MTD (≤ 2.9 vs. >2.9 cm), and (**D**) the combination of PSA nadir and MTD (0 risk factor: PSA nadir < 0.01 ng/mL & MTD ≤ 2.9 cm, 1 risk factor: PSA nadir < 0.01 ng/mL & MTD > 2.9 cm or PSA nadir ≥ 0.01 ng/mL & MTD ≤ 2.9 cm, 2 risk factors: PSA nadir ≥ 0.01 ng/mL & MTD > 2.9 cm), and showed that the patients with detectable PSA or/and MTD > 2.9 cm had significantly shorter BCRFS (log-rank $p < 0.001$).

These significant predictors in univariable analyses were then assessed in a multivariable Cox regression model, and preoperative PSA and ECE did not retain their significance and were excluded ($p > 0.05$) (Table 2). Finally, PSA nadir and MTD, as well as Gleason score, SM and SVI, were independent predictors of BCR in multivariable Cox regression analysis ($p < 0.05$). These variables were incorporated in a nomogram predicting BCRFS at 3 and 5 years after RP (Fig. 2), which yielded a c-index of 0.76 (95% confidence interval [CI], 0.71–0.81). The calibration plots of the nomogram are shown in Fig. 3 illustrating how the predicted probability of BCRFS compared with the actual outcomes.

The c-index of the CAPRA-S score was 0.70 (95%CI, 0.64–0.75) in our study cohort, which is slightly lower than that of our nomogram ($p = 0.022$). To further verify the prognostic power of the combination of PSA nadir and MTD, we developed a basic model including Gleason score, SM, and SVI. It yielded a c-index of 0.66 (95%CI, 0.60–0.71), which was significantly lower than the c-index of the new nomogram ($p = 0.001$). The time-dependent ROC curves and decision curve analyses compared the new nomogram, the CAPRA-S score, and the basic model (Fig. 4, 5**)**. Our new nomogram showed an advantage in identifying patients with BCRFS in both time-dependent ROC curves and decision curve analyses.

Discussion

In the present study, comparing to conventional predictive models, we proposed a new nomogram by incorporating MTD and PSA nadir, which showed improved accuracy of BCR prediction for patients after RP.

After RP, PSA is expected to be undetectable within six weeks[9] and it is utmost important parameter that should be monitored postoperatively. Elevated PSA level after RP indicates high risk of local recurrence or metastasis[10]. If the postoperative PSA reaches 0.2 ng/mL, patient is assigned the status of BCR[18], which was a signal of cancer activity at visual undetectable level. The relationship between PSA nadir and BCR after RP has been extensively studied. A retrospective study reported that compared with men with PSA < 0.01 ng/mL after RP, the probability of BCRFS at 5 years dropped from 92.4–56.8% in patients with PSA ≥ 0.01 ng/mL[19]. In a study of 582 patients carried out by Matsumoto et al., PSA persistence after RP was associated with increased BCR and overall mortality[20]. These results are in line with the observations in the present study. In current study, 71.8% patients got an undetectable PSA nadir and 28.2% patients had a detectable nadir during follow-up. PSA nadir after RP was found to be an independent prognostic factor ($P < 0.001$) in predicting BCR in univariable and multivariable analyses. Patients with PSA nadir < 0.01 ng/mL had significantly longer BCRFS in our study cohort (Fig. 1B, log-rank $p < 0.0001$).

According to our clinical experience, tumor burden should be associated with oncological outcomes. Tumor volume and MTD as the common indicators of tumor burden have been studied by the researchers and have proved to be independent prognostic factors of BCR[13, 21]. However, prostate cancer has been recognized as a multifocal disease[22] and the calculation of tumor volume and MTD is complicated. In 2013, Billis et al. found that the tumor extent in a surgical specimen should be estimated with the dominant tumor and not the total tumor extent. They also reported the association of the dominant tumor with BCR prediction[23]. Even so, the calculation of tumor volume is time consuming and difficult. For the above reasons, we chose MTD as the research target and it was defined as the maximum diameter of the dominant tumor. Unlike previous studies, we measured MTD based on MRI instead of pathological specimen. MRI has better repeatability and less deformation, while on pathological specimen, deformation can vary greatly due to shrinking of tissues after soaking in formalin. Lee et al. measured the diameter of the suspicious tumor lesion on diffusion weighted images of MRI and demonstrated that the diameter of tumor could increase the prediction of insignificant prostate cancer in candidates for active surveillance[14]. In the studies of Kozal et al.[24] and Müller et al.[25], MTD was an independent prognostic factor for BCR, even though they measured MTD on pathological specimens. Based on their findings, we hypothesized that the MTD on MRI could be an independent prognostic factor for prostate cancer, however the relationship between MTD measured on MRI and BCR after RP has rarely been explored in their study as well as other previous studies. As expected, the results of the present study showed that MTD on MRI was an independently significant predictor of BCR ($p = 0.034$) and the Kaplan-Meier curve depicted that men with MTD > 2.9 cm had shorter BCRFS (Fig. 1C, log-rank $p = 0.0003$). Interestingly, the median MTD in the present study was larger than that in the previous studies[26]. We attributed this phenomenon to shrinking of tissues after soaking in formalin which might decrease the MTD [27]. Additionally, in our study, pathological tumor stage ≥ T2c was reported in the majority of patients (n = 290, 86%, Table 1) and it might be another reason why we have larger MTD. In the study of Eichelberger et al., MTD was found to be associated with the pathologic stages[28]. With the rapid

development of radiographic technologies and artificial intelligence, the identification and measurements of prostate cancer on MRI are more accurate with high repeatability for prognostic evaluation.

The CAPRA-S score is a postoperative score created by Cooperberg et al.[6], based on preoperative PSA, Gleason score, SM, ECE, SVI, and LNI. The prognostic value of these variables was verified in our study cohort as well. All of them were significantly associated with BCR in the univariable analysis and Gleason score, SM, and SVI were independent predictors of BCR in multivariable analysis. The c-index of our newly developed nomogram was slightly higher than that of the CAPRA-S score in our study cohort. Moreover, our nomogram predictions closely approached the actual outcome both at 3 and 5 years after RP, demonstrating good calibration, as depicted in the calibration plot. Comparing these two models, we found that our new nomogram consisted of two parts. One part was composed of the commonly used variables, namely Gleason score, SM, and SVI and the other part was composed of PSA nadir and MTD measured on MRI. In the current study, we observed that both PSA nadir and MTD were significantly associated with BCR in univariable analysis and they were also independent prognostic factors after adjusting preoperative PSA, Gleason score, SM, ECE, and SVI. Kaplan-Meier curve showed that the patients with these two risk factors simultaneously had the shortest BCRFS and patients with none of these two risk factors had the longest BCRFS (Fig. 1D, log-rank $p < 0.0001$). However, only few of the previous prediction tools used MTD and PSA nadir at the same time. To verify the incremental predictive power of the combination of PSA nadir and MTD, we developed a basic model including Gleason score, SM, and SVI for comparison. The c-index was decreased from 0.76 to 0.66 ($p < 0.001$) when PSA nadir and MTD were removed from our new nomogram. The time-dependent ROC curves illustrated the advantage of our new nomogram at both 3 and 5 years after RP. The decision curve analyses also showed the advantage of our new nomogram, across the various threshold probabilities, and the new nomogram had greater net benefit than both the basic model and the CAPRA-S score in our study cohort. Our new nomogram is a promising tool to predict BCRFS and guide follow-up and decision-making of adjuvant treatment. In addition, PSA nadir and MTD improved the accuracy of our new nomogram in predicting BCR.

Our study has several limitations. First, it was a retrospective study and the population was relatively smaller compared to the previous studies. Second, the present study has not yet been validated externally and the analysis of overall survival was lacked due to the short-term follow-up duration.

Conclusions

The newly developed nomogram, which included PSA nadir, MTD measured on MRI, and several commonly used variables, shows excellent accuracy in predicting BCRFS after RP. This nomogram is a useful tool for risk stratification and follow-up planning. The combination of PSA nadir and MTD can improve the accuracy of BCR prediction.

Abbreviations

BCR: biochemical recurrence; RP: radical prostatectomy; PSA: prostate specific antigen; SM: surgical margin; ECE: extracapsular extension; SVI: seminal vesicle invasion; LNI: lymph node invasion; MRI: Magnetic resonance imaging; MTD: maximum tumor diameter; BCRFS: BCR-free survival; TURP: transurethral resection of the prostate; BMI: body mass index; IQR: interquartile ranges; C-index: concordance index.

Declarations

Ethics approval and consent to participate

This study received institutional board approval at Peking University Third Hospital (S2019326).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

XFH, JL and LLM proposed the protocol. HZX, BY, RZM, WH, XHZ, ZYZ and YTZ were involved in data collection and management. HZX, HB and YY analysed the data. HZX and HB contributed to statistical analysis. HZX contributed to manuscript writing. HB, YY and JL critically revised the manuscript. All authors read and approved the final manuscript.

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Figures

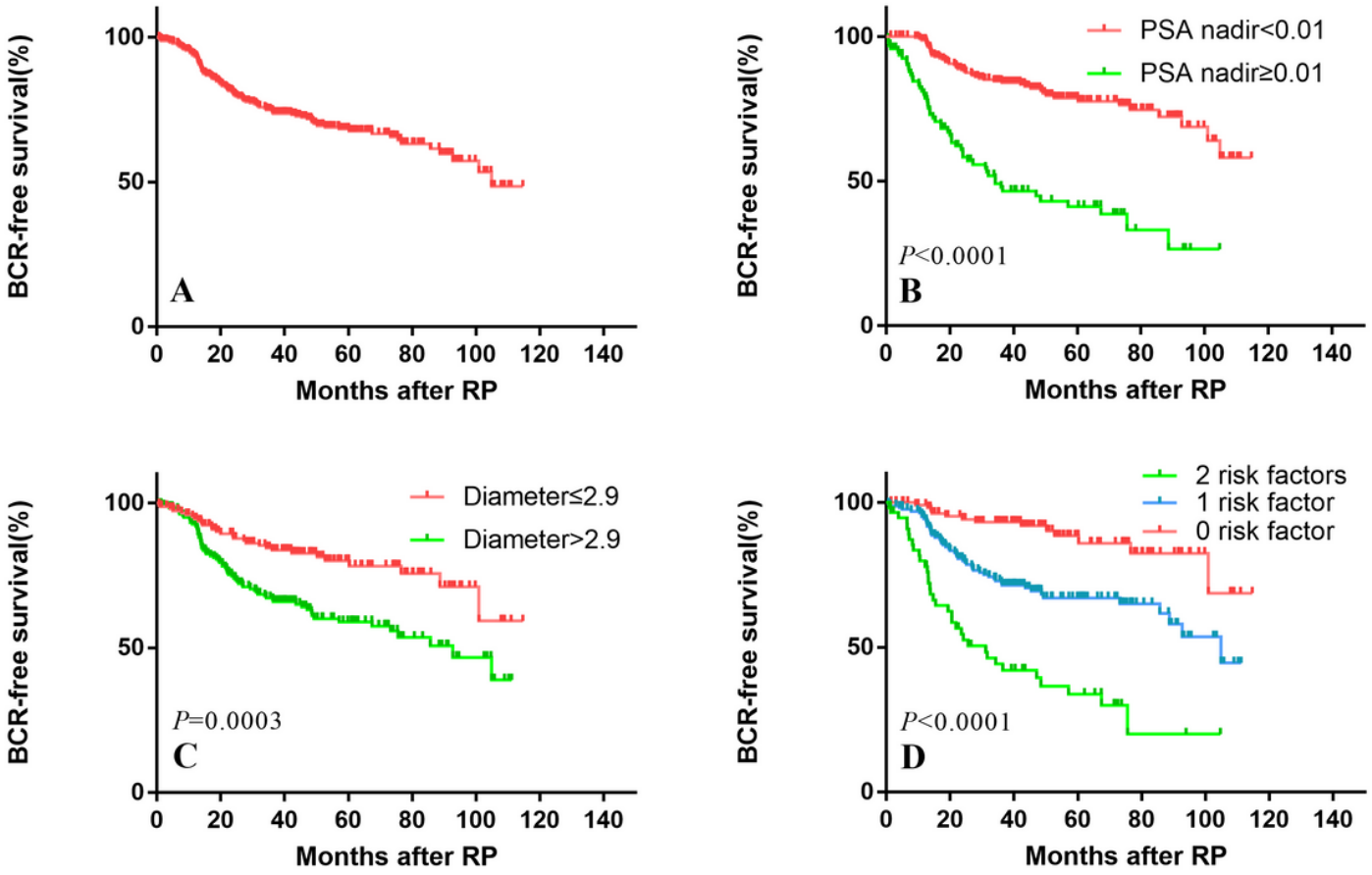

Figure 1

Kaplan-Meier curves of BCR-free survival. (A) The whole patient population. (B) Patients grouped by PSA nadir (< 0.01 vs. ≥ 0.01 ng/mL). (C) Patients grouped by MTD (≤ 2.9 vs. >2.9 cm). (D) Combination of

PSA nadir and MTD. BCR, biochemical recurrence; RP, radical prostatectomy; PSA, prostate specific antigen; MTD, maximum tumor diameter.

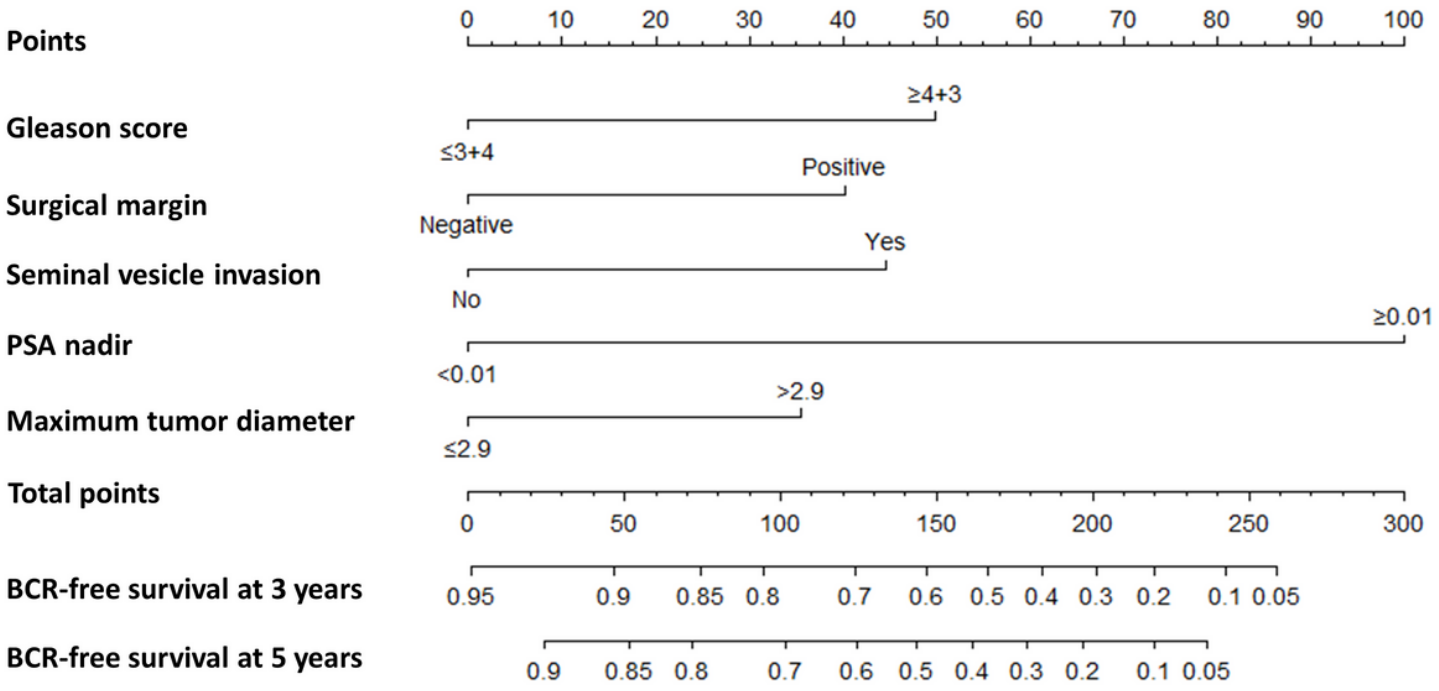

Figure 2

Nomogram predicting BCR-free survival at 3 and 5 years after RP. PSA, prostate specific antigen; BCR, biochemical recurrence; RP, radical prostatectomy

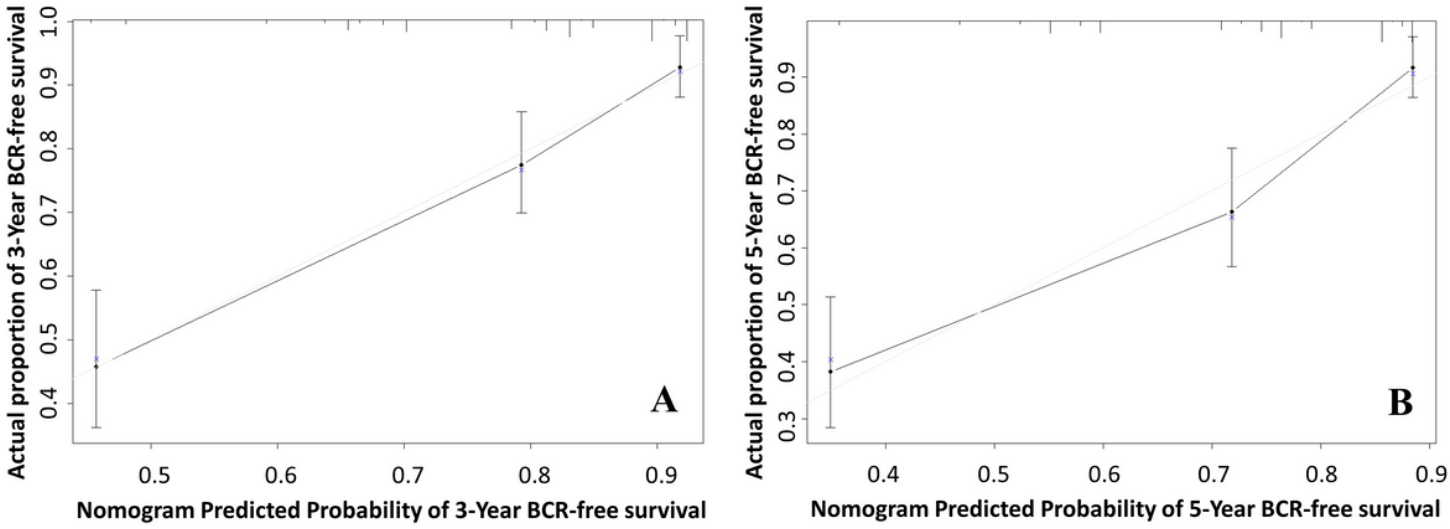

Figure 3

Calibration plots of the new nomogram. (A) 3-Year BCR-free survival. (B) 5-Year BCR-free survival. BCR, biochemical recurrence.

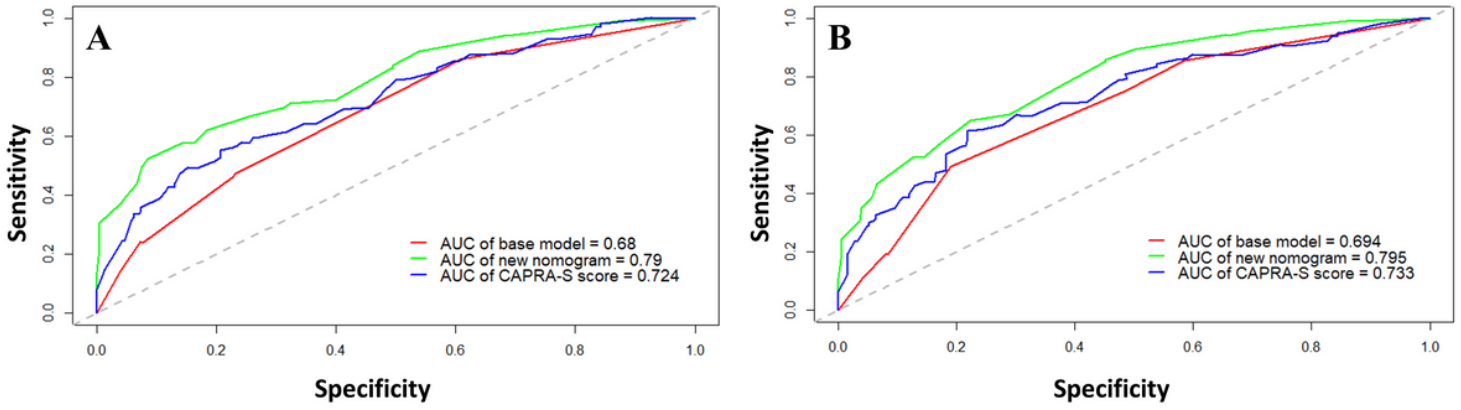

Figure 4

Time-dependent ROC curves. These two ROC curves compared the basic model, the new nomogram and the CAPRA-S score in predicting BCR at 3 (A) and 5 (B) years after RP. BCR, biochemical recurrence; RP, radical prostatectomy.

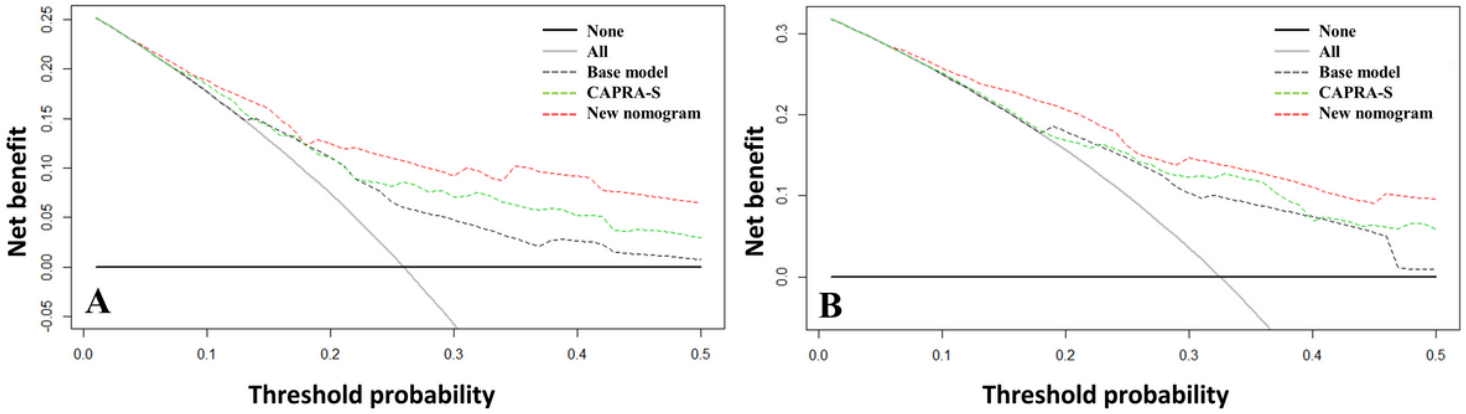

Figure 5

Decision curve analyses. These two curves compared the basic model, the new nomogram and the CAPRA-S score in predicting BCR at 3 (A) and 5 (B) years after RP. BCR, biochemical recurrence; RP, radical prostatectomy.