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

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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 (BCRFS).

Methods: A total of 337 patients who underwent RP between January 2010 and March 2017 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 BCRFS at 3 and 5 years after RP. Time-dependent receiver operating characteristic (ROC) curve and decision curve analyses were performed to identify the advantage of the new nomogram in comparison with the cancer of the prostate risk assessment post-surgical (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), considering these variables were significantly associated with BCR in both univariate and multivariate analyses ($P < 0.05$). 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 curve 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 BCRFS after RP.

Keywords: Nomogram; PSA nadir; Tumor diameter; Magnetic resonance imaging; Biochemical recurrence; Radical prostatectomy

Introduction

Prostate cancer is among the most frequent cancers and the second leading cause of mortality in men. It is estimated that there might be around 191,930 new cases of prostate cancer and 33,330 deaths in the United States in 2020.[1] Approximately, 20% to 30% of the patients experience biochemical recurrence (BCR) after radical prostatectomy (RP) during follow-up.[2-4] Various prediction tools for BCR have been developed to guide the clinical decision-making for subsequent treatment. Most of these tools are developed based on clinical and pathological parameters such as pre-operative serum prostate-specific antigen (PSA), Gleason score, tumor stage, surgical margin (SM), extracapsular extension (ECE), seminal vesicle invasion (SVI), and lymph node invasion (LNI).[5-8] The

cancer of the prostate risk assessment post-surgical (CAPRA-S) score is one of the most commonly used tools with good discriminative accuracy and calibration.[7] However, only few of these tools include tumor diameter and post-operative PSA nadir, simultaneously, although the prognostic value of these two characteristics in predicting BCR has been verified.[9,10]

Measurement of PSA is the cornerstone in post-operative follow-up. Serum PSA is expected to be undetectable within 6 weeks after RP and a detectable PSA in patients after RP is thought to be associated with residual cancer.[11] A persistent (detectable) PSA after RP has been proved to be a poor prognostic indicator of oncologic outcomes.[12]

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.[13,14] Maximum tumor diameter (MTD) has been demonstrated to be an independent predictor of BCR in patients after RP.[15] However, in most studies, MTD measurement was carried out on the pathological specimens and only few of them measured MTD on MRI,[16] while the latter is considered to be more accurate and comparable. To our knowledge, no study addressing 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

Ethics approval

This study was approved by the Peking University Third Hospital Medical Science Research Ethics Committee with a waiver of informed consent and compliant with the principles in the *Declaration of Helsinki* (S2019326).

Patients

Data of 542 patients who underwent laparoscopic RP for prostate cancer between January 2010 and March 2017 were retrospectively analyzed. The exclusion criteria were as follows: (1) patients with neoadjuvant therapy before surgery; (2) patients who had undergone transurethral resection of the prostate; (3) patients with unidentifiable lesions on MRI; (4) patients whose pathological results were not prostatic adenocarcinoma; and (5) incomplete follow-up data. Follow-ups were performed every 3 months for the first 2 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 in the first two follow-ups after RP without adjuvant androgen deprivation therapy or radiotherapy. BCR was defined as post-operative PSA value >0.20 ng/mL in two consecutive measurements, and the recurrence date was assigned to the day when PSA value >0.20 ng/mL was measured for the first time. BCRFS was calculated from date of RP to date of documented BCR or date of last follow-up for those patients who did not experience BCR. Other clinical and pathological data, such as age at RP, body mass index (BMI), pre-operative 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 continuous variables.

Numbers and proportions were reported for categorical variables. The Mann-Whitney U test and Chi-square test were applied for between-group comparison. BCRFS was estimated using the Kaplan-Meier curves and log-rank test. MTD was categorized into ≤2.9 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.[17] 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 with one-shot non-parametric approach, and comparison of the two models was performed using the "compareC" package of R software.[18] Time-dependent ROC curves were illustrated using the "survivalROC" package.[19] Decision curve analyses at 3 and 5 years were performed to ascertain the clinical value of the new nomogram. Statistical analyses were performed with the R software (version 3.6.2, R Foundation for Statistical Computing, Vienna, Austria) and GraphPad Prism (version 7.00, GraphPad Software, San Diego, CA, USA). All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Patients' characteristics

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 (29.7%) patients 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). The median value of pre-operative PSA was 10.8 ng/mL (IQR, 7.3–19.1 ng/mL) and was divided into three groups: <10 ng/mL group, 10 to 20 ng/mL group, and >20 ng/mL group. The majority of the patients had PSA nadir <0.01 ng/mL ($n = 242$, 71.8%), while 95 (28.2%) patients had PSA nadir ≥0.01 ng/mL. Median PSA nadir was 0 (IQR, 0–0.01) 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. Comparison of clinical parameters between patients who experienced BCR or not is shown in Table 2.

Development and evaluation of the novel nomogram

To identify significant predictors of BCR, we evaluated age, BMI, pre-operative PSA, Gleason score, SM, ECE,

Table 1: Characteristics of prostate cancer patients treated by RP (N = 337).

Characteristics	n	%
Pre-operative PSA (ng/mL)		
<10	152	45.1
10–20	106	31.5
>20	79	23.4
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
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)		
≤2.9	152	45.1
>2.9	185	54.9
Follow-up (months), median (IQR)	42 (19–64)	–

BCR: Biochemical recurrence; BMI: Body mass index; ECE: Extracapsular extension; IQR: Interquartile range; MTD: Maximum tumor diameter; PSA: Prostate-specific antigen; RP: Radical prostatectomy; SD: Standard deviation; SM: surgical margin; SVI: Seminal vesicle invasion.

SVI, PSA nadir, and MTD in a univariable Cox proportional hazards regression model and the results are shown in Table 3. Except for age and BMI, all predictors were statistically significantly associated with BCR after RP ($P < 0.01$).

As shown in Figure 1, Kaplan-Meier curves were stratified by PSA nadir (<0.01 *vs*. ≥0.01 ng/mL) [Figure 1B], MTD (≤2.9 *vs*. >2.9 cm) [Figure 1C], and the combination of PSA nadir and MTD (0 risk factor: PSA nadir <0.01 ng/mL and MTD ≤2.9 cm; one risk factor: PSA nadir <0.01 ng/mL and MTD >2.9 cm or PSA nadir ≥0.01 ng/mL and MTD ≤2.9 cm; two risk factors: PSA nadir ≥0.01 ng/mL and MTD >2.9 cm) [Figure 1D] 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 pre-operative PSA and ECE did not retain their significance and were excluded ($P > 0.05$) [Table 3]. 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 [Figure 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 Figure 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,

Table 2: Comparison of clinical parameters between prostate cancer patients with or without BCR.

Parameters	Non-BCR (n = 237)	BCR (n = 100)	Statistics	P
Age (years), median (IQR)	71 (65, 75)	70 (64, 75)	−0.912[*]	0.362
BMI (kg/m²), median (IQR)	24.4 (22.5, 26.4)	25.3 (23.5, 27.3)	−2.403[*]	0.016
Pre-operative PSA (ng/mL), median (IQR)	10.1 (6.7, 16.1)	14.1 (8.2, 28.9)	−3.885[*]	<0.001
PSA nadir (ng/mL), median (IQR)	0 (0, 0.003)	0.010 (0, 0.040)	−5.024[*]	<0.001
Gleason score, n			12.846[†]	<0.001
≤3 + 4	119	29		
≥4 + 3	118	71		
SM, n			8.920[†]	0.003
Negative	168	54		
Positive	69	46		
ECE, n			6.111[†]	0.013
No	168	57		
Yes	69	43		
SVI, n			7.404[†]	0.007
No	215	80		
Yes	22	20		
MTD (cm), median (IQR)	3.09 (2.30, 3.98)	3.02 (2.02, 3.91)	−1.125[*]	0.260

[*]Z values. [†]χ^2 values. BCR: Biochemical recurrence; BMI: Body mass index; ECE: Extracapsular extension; IQR: Interquartile range; MTD: Maximum tumor; PSA: Prostate-specific antigen; SD: Standard deviation; SM: Surgical margin; SVI: Seminal vesicle invasion.

Table 3: Univariable and multivariable Cox regression analyses of BCRFS.

	Univariable		Multivariable	
	HR (95% CI)	P	HR (95% CI)	P
Age	0.981 (0.954–1.008)	0.168	–	–
BMI	1.023 (0.963–1.087)	0.459	–	–
Pre-operative PSA (ng/mL)				
<10	1.000 (reference)		1.000 (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	1.000 (reference)		1.000 (reference)	
≥0.01	3.959 (2.663–5.887)	<0.001	4.531 (2.993–6.861)	<0.001
Gleason score				
≤3 + 4	1.000 (reference)		1.000 (reference)	
≥4 + 3	2.310 (1.496–3.568)	<0.001	2.090 (1.277–3.420)	0.003
SM				
Negative	1.000 (reference)		1.000 (reference)	
Positive	1.966 (1.326–2.916)	<0.001	1.675 (1.076–2.610)	0.007
ECE				
No	1.000 (reference)		1.000 (reference)	
Yes	1.720 (1.155–2.560)	0.008	0.791 (0.469–1.336)	0.376
SVI				
No	1.000 (reference)		1.000 (reference)	
Yes	2.704 (1.649–4.436)	<0.001	1.723 (0.897–3.307)	0.022
MTD (cm)				
≤2.9	1.000 (reference)		1.000 (reference)	
>2.9	2.196 (1.425–3.385)	<0.001	1.587 (1.006–2.503)	0.034

BCRFS: BCR-free survival; BMI: Body mass index; CI: Confidence interval; ECE: Extracapsular extension; HR: Hazard ratio; MTD: Maximum tumor diameter; PSA: Prostate-specific antigen; SM: Surgical margin; SVI: Seminal vesicle invasion.
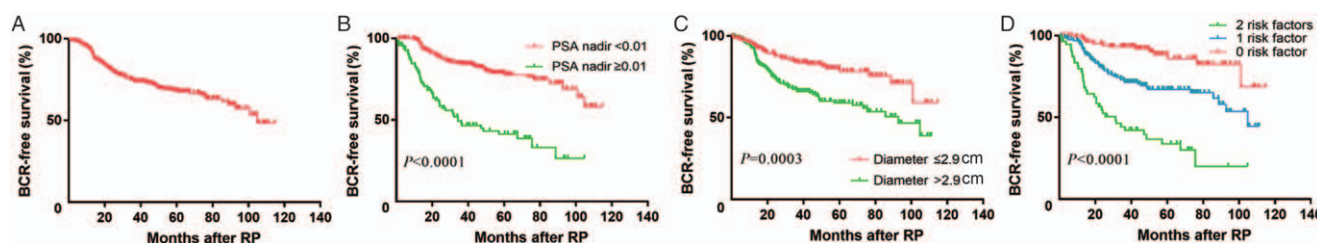

Figure 1: (A) Kaplan-Meier curves of BCRFS for the whole patient population, (B) patients grouped by PSA nadir (<0.01 vs. ≥0.01 ng/mL), (C) MTD (≤2.9 vs. >2.9 cm), and (D) a combination of PSA nadir and MTD. BCR: Biochemical recurrence; BCRFS: BCR-free survival; MTD: Maximum tumor diameter; PSA: Prostate-specific antigen; RP: Radical prostatectomy.

0.60–0.71), which was significantly lower than the c-index of the new nomogram (P = 0.001). The time-dependent ROC curve and decision curve analyses compared the new nomogram, the CAPRA-S score, and the basic model [Figures 4 and 5]. Our new nomogram showed an advantage in identifying patients with BCRFS in both time-dependent ROC curve 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 6 weeks and it is utmost important parameter that should

be monitored post-operatively.[11] Elevated PSA level after RP indicates high risk of local recurrence or metastasis.[12] If the post-operative PSA reaches 0.2 ng/mL, patient is assigned the status of BCR,[20] 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 to men with PSA <0.01 ng/mL after RP, the probability of BCRFS at 5 years dropped from 92.4% to 56.8% in patients with PSA ≥0.01 ng/mL.[21] In a study of 582 patients carried out by Matsumoto et al,[22] PSA persistence after RP was associated with increased BCR and overall mortality. These results are in line with the observations in the present study. In the present study, 71.8% patients had 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
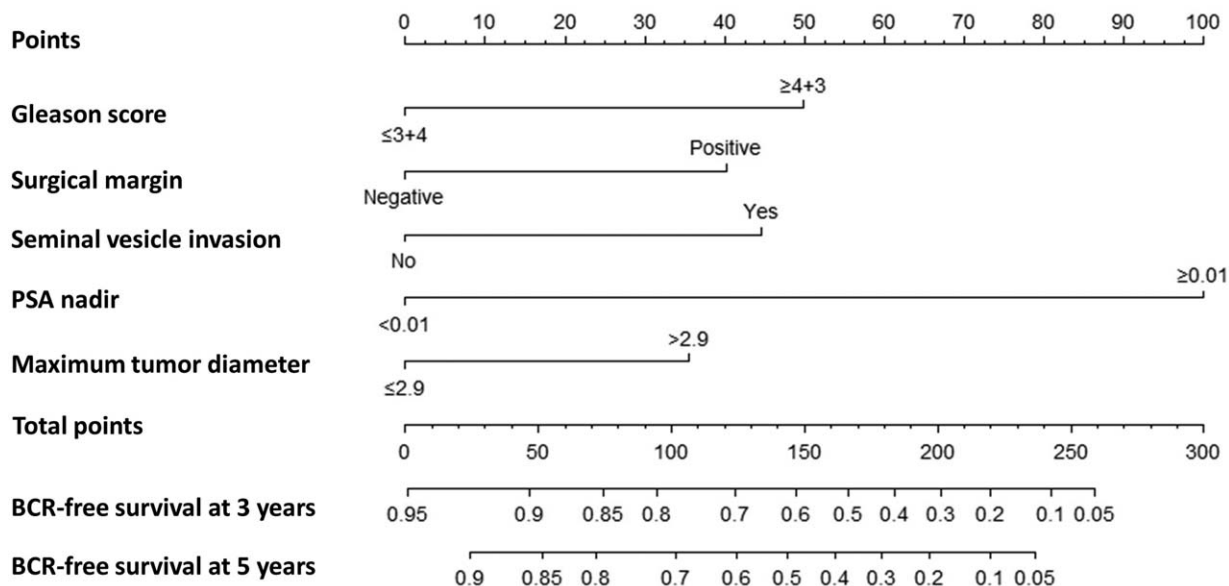
Figure 2: Nomogram predicting BCRFS at 3 and 5 years after RP. BCRFS: BCR-free survival; BCR: Biochemical recurrence; PSA: Prostate-specific antigen; RP: Radical prostatectomy.
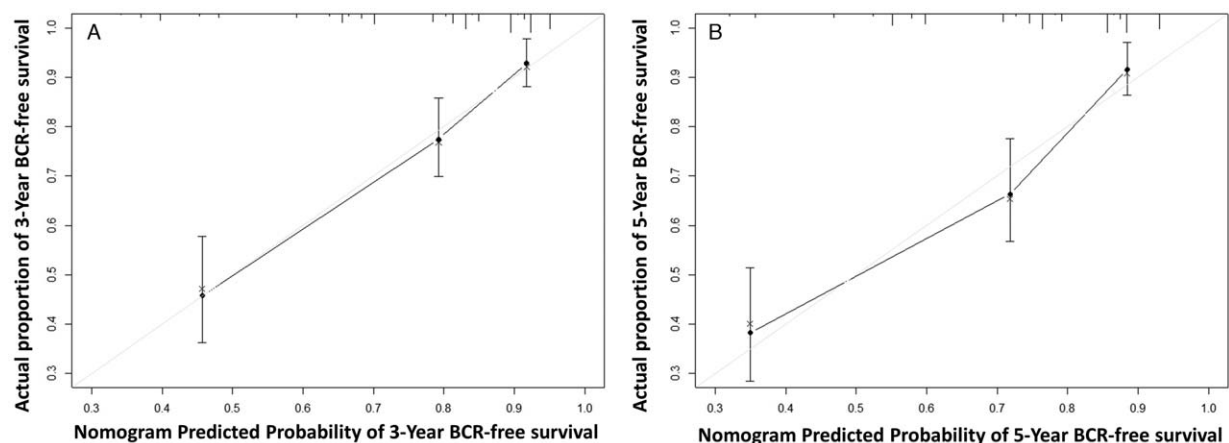

Figure 3: Calibration plot of the nomogram predicting BCRFS at (A) 3 years and (B) 5 years after RP. BCRFS: BCR-free survival; BCR: Biochemical recurrence; RP: Radical prostatectomy.

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 (log-rank $P < 0.0001$) [Figure 1B].

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.[15,23] However, prostate cancer has been recognized as a multifocal disease, and the calculation of tumor volume and MTD are complicated.[24] In 2013, Billis *et al*[25] 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. Nonetheless, 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 because of the shrinking of tissues after soaking in formalin. Lee *et al*[16] 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. In the studies of Kozal *et al*[26] and Müller *et al*,[27] 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
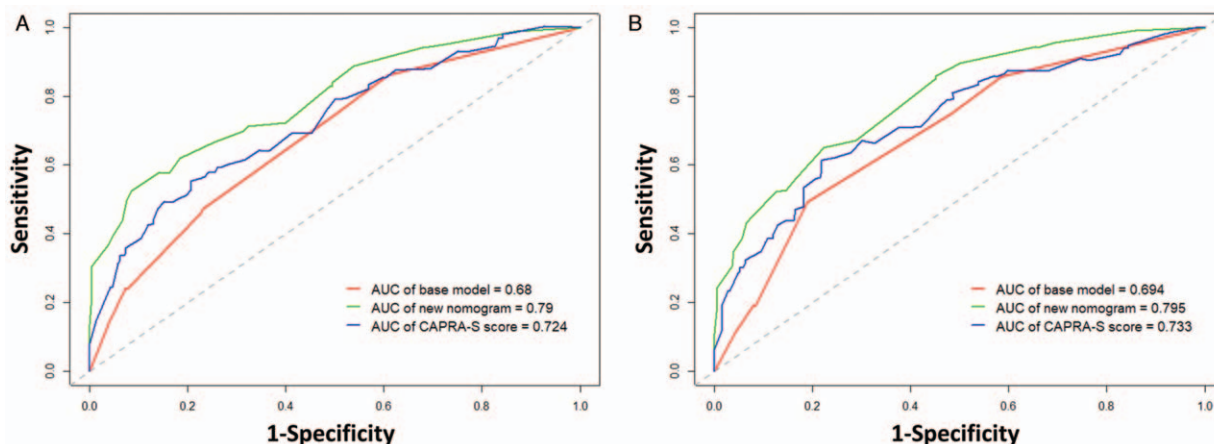
Figure 4: Time-dependent ROC curves comparing the base model, the new nomogram, and the CAPRA-S score in predicting BCR at (A) 3 years and (B) 5 years after RP. BCR: Biochemical recurrence; CAPRA-S: Cancer of the prostate risk assessment post-surgical; ROC: Receiver operating characteristic; RP: Radical prostatectomy.
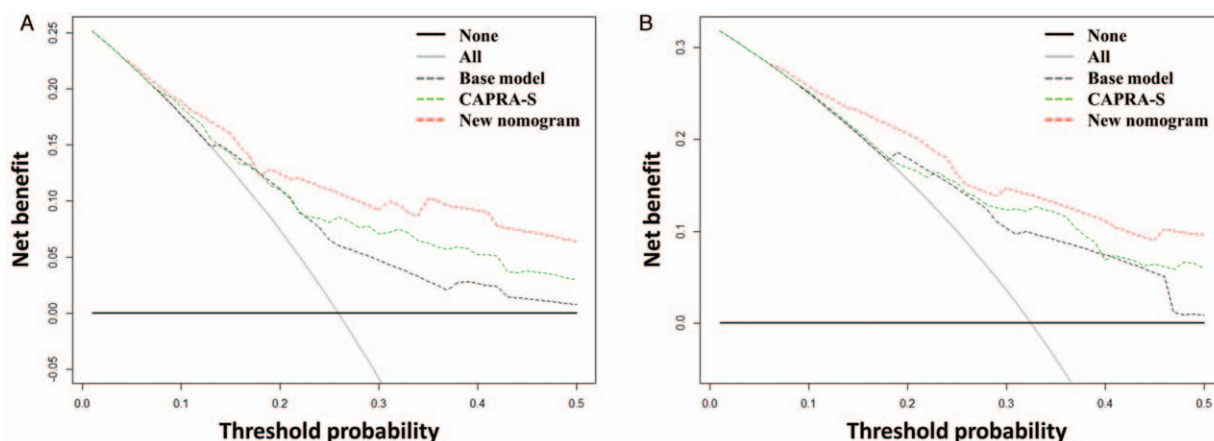

Figure 5: Decision curve analyses comparing the base model, the new nomogram, and the CAPRA-S score in predicting BCR at (A) 3 years and (B) 5 years after RP. BCR: Biochemical recurrence; CAPRA-S: Cancer of the prostate risk assessment post-surgical; RP: Radical prostatectomy.

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 ($P = 0.0340$) and the Kaplan-Meier curve depicted that men with MTD >2.9 cm had shorter BCRFS (log-rank $P = 0.0003$) [Figure 1C]. Interestingly, the median MTD in the present study was larger than that in the previous studies.[28] We attributed this phenomenon to shrinking of tissues after soaking in formalin which might decrease the MTD.[29] Additionally, in the present 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,[30] MTD was found to be associated with the pathological stages. 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 post-operative score created by Cooperberg et al,[7] based on pre-operative 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 present 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 pre-operative 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 (log-rank $P < 0.0001$)

[Figure 1D]. 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.

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

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.

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Conflicts of interest

None.

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