ORIGINAL RESEARCH

Establishment and Validation of a Novel Prediction Model for Early Natural Biochemical Recurrence After Radical Prostatectomy Based on Post-Operative PSA at Sixth Week

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Objective: Based on post-operative PSA at 6th week (PSA_{6w}) after radical prostatectomy to establish an optimal model for predicting natural biochemical recurrence (BCR).

Methods: A total of 742 patients with post-operative PSA_{6w} from PC-follow database, between January 2003 and October 2022, were included. All the patients had not received any hormone therapy and radiotherapy before operation and BCR. Of these patients, 588 cases operated by one surgeon were enrolled for modelling and another 154 cases operated by other surgeons were for external validation. After screened by Cox regression, the post-operative PSA_{6w}, pathological stage, Gleason Grade and positive surgical margins were adopted for modelling. The R software was used to plot the nomogram of the prediction model for BCR. C-index and calibration curve were calculated to evaluate the new model. Finally, integrated discrimination improvement was adopted to evaluate the prediction performances of the new nomogram model and the classical Kattan nomogram.

Results: The C-index of the new model was 0.871 (95% CI: 0.830–0.912). The calibration curve of the new model demonstrated superior consistency between the predicted and actual value. The C-index of the external validation group was 0.850 (95% CI: 0.742–0.958), which demonstrated perfect universality. The integrated discrimination improvement showed a 12.61% improvement in prediction performance over that of the classical Kattan nomogram (P < 0.01). Based on the new nomogram, patients were divided to high and low BCR group with a 3 year BCR-free cutoff probability as 74.72%. Low-risk patients, accounting for 77.89% of the patients, have no need to follow up frequently with a false-negative rate only 5.24%, which will save medical resources to a large extent.

Conclusion: Post-operative PSA6w is a sensitive risk biomarker for early natural BCR. The new nomogram model could predict BCR probability with a higher accuracy and will further simplify the clinical follow-up strategies.

Keywords: prostate cancer, biochemical recurrence, post-operative PSA, prediction model, nomogram

Introduction

Radical prostatectomy (RP) is one of the most important treatment method for prostate cancer (PCa), but approximately 15–45% of patients experience biochemical recurrence (BCR) following the operation.[1] Accurately predicting post-operative BCR time is important for guiding the subsequent treatment. In 1999, based on preoperative PSA levels and pathological Gleason scores (GS), extracapsular extension (ECE), seminal vesicle invasion (SVI), lymph node invasion

(LNI), and positive surgical margins (PSM), Kattan established a nomogram that could predict the BCR rate of patients with PCa following radical prostatectomy, which was later verified at multiple centers in the United States.[2–5] Subsequently, a series of similar prediction models based on the Kattan postoperative nomogram were proposed.[6–8] These models mainly focused on predicting the likelihood of long-term BCR probability; however, nearly two-third of BCR occurred during the first 3 years after RP.[9,10] Thus, a model that can predict the BCR probability in the first 3 years with high precision was even more important than previous models. Otherwise, the predictors included in previous models were limited to the clinical or pathological information obtained during the perioperative period; postoperative short-term PSA levels that were obtained during the follow-up have been always ignored. However, PSA is a serum indicator requiring regular follow-up after radical prostatectomy and the postoperative short-term PSA levels may play an important role in predicting biochemical recurrence based on previous study.[11–13] Theoretically, prostate tumor was removed completely during the prostatectomy, the PSA should decline to an undetectable level after 6 weeks. The persistent PSA after the prostatectomy may indicate that there still remain residual microtumor focus. Therefore, this study attempted to establish a new nomogram prediction model based on the PSA level at week 6 after operation (post-operative PSA_{6w}), which can predict the BCR probability in the first 3 years more accuracy, in an attempt to further simplify the existing clinical follow-up strategies and assist in the early diagnosis of patients with high BCR risk.

Materials and Methods
Study Subjects and Groups
We enrolled 5010 patients from China's largest PCa database (PC-follow database) who underwent radical prostatectomy between January 2003 and October 2022. Of these patients, 1132 who received androgen deprivation therapy (ADT) or radiation therapy before BCR, 3000 patients who were missing the post-operative PSA_{6w} follow-up information and 136 patients' two consecutive PSA levels were higher than 0.2 ng/mL in the first 4–8 weeks post RP, which should be defined as immediately BCR, were excluded, eventually leaving 742 patients in the study. The admitted patients underwent surgery performed by surgeons who experienced a radical prostatectomy. Therein, 588 patients operated by one surgeon from Changhai Hospital were used to establish the new model and the other 154 patients operated by other surgeons were used for the new model's external validation. The flow chart of patient enrollment is shown in Figure 1.

Variable Definition
BCR was the outcome of this study. In this study, BCR was defined as two consecutive PSA elevations after radical prostatectomy, both exceeding 0.2 ng/mL. However, there is no uniform international standard for the threshold value of PSA for BCR after radical prostatectomy. Since the consensus of European urological experts was published in 2004, two
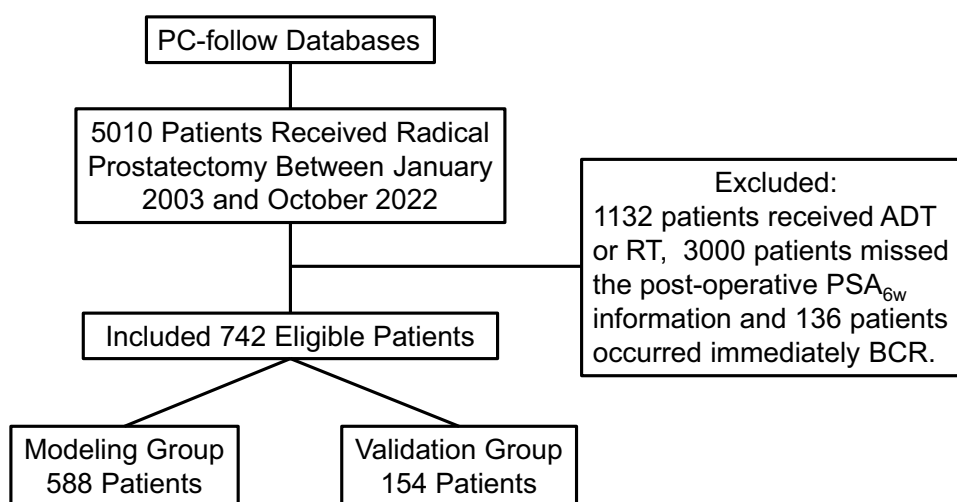

Figure 1 The flow chart of patient enrollment.

consecutive PSA levels above 0.2 ng/mL have been recognized by more researchers.[14] Post-operative PSA_{6w} was one of the important predictors in this study. The PSA level was measured on the 42±3 days after radical prostatectomy within one half-life period. The detection method of PSA was Electrochemiluminescence Immunoassay (ECLIA), the accuracy of which was 0.01ng /mL.

Sample Size Estimation

Since the new prediction model was established through Cox regression model, the estimation of sample size was estimated by EPV (Events Per Variable) rule, which was that each variable should correspond to at least 10 outcome events to prevent overfitting. The BCR rate of all enrollment patients was 14.4%. In the modeling group, all the variables that were related to BCR should be taken into analysis, so pre-operative PSA, LNI, Gleason Grade (GG), PSM, Pathological Stage and post-operative PSA, all the six variables were used for Cox regression analysis. Thus, the multivariable risk model required a sample size of 417=(6*10/14.4%) at least in the modeling group. The sample size in our modeling group was 588, which can ensure the accuracy of modelling.

Statistical Analysis

Using SPSS version 26 (SPSS Pty. Ltd., USA) software, we applied Cox regression to identify the risk factors associated with BCR. Significant variables in univariable regression analysis were included in multivariate analysis. In the multivariable analysis process, backward stepwise regression method was used, and the insignificant variables were excluded. Significant variables were included and then used to establish the nomogram model using the regression modeling strategies (rms) package in R software (Windows version 3.5.1, http://www.r-project.org/). We then calculated the nomogram model's consistency index (C-index) and plotted the calibration curve between the predicted value from the nomogram and the actual value. Internal validation was accomplished via repeated sampling (1000 times) using the Bootstrap method, while external validation was conducted using data from the validation group. Finally, integrated discrimination improvement (IDI) was adopted to compare the prediction accuracy of the new nomogram and the Kattan post-operative nomogram.

Results

New Model Establishment

The clinical and pathological characteristics of patients in the modeling group and the validation group are listed in Table 1. By applying Cox regression to the clinical and pathological information of the modeling group, the independent risk factors associated with BCR were identified (Table 2). Univariable analysis found that all variables were independent risk factors for BCR. Alternatively, when conducting multivariable analysis, only PSM, Gleason Grade, pathological Stage and post-operative PSA_{6w} were considered an independent risk factor. Pre-operative PSA levels and LNI were not collected. Finally, Gleason Grade, PSM, post-operative PSA6w and pathological Stage were included in the establishment of the final model. In order to make the model more convenient for clinical application, nomogram is used to present the model (Figure 2). Nomogram model was essentially a visualization of the regression equation. It set the scoring standard according to the size of the regression coefficient of all independent variables, and gave a score to each value level of each independent variable. For each patient, an overall score could be calculated, and then the probability of the outcome time of each patient could be calculated by the conversion function between the score and the probability of the outcome. The C-index of the new model was 0.871 (95% CI: 0.830–0.912), and additionally calibration on a developed model is always perfect (Figure 3A).

New Model External Validation

Another 154 patients operated by the other surgeons were evaluated for external validation of the new model, which showed that the accuracy of the model, the C-index was 0.850 (95% CI: 0.742–0.958). The calibration of the new model in the validation group also demonstrated good consistency between the predicted and the actual values (Figure 3B).

Table 1 Clinical and Pathological Features of Patients

	All	Modelling Group	Validation Group
No. of patients	742	588	154
Pre-operative PSA(median, IQR), ng/mL	11.024 (7.200–18.734)	10.609 (7.151–18.561)	12.165 (7.813–19.893)
Gleason Grade(n, %)			
1	91 (12.26)	72 (12.24)	19 (12.34)
2	339 (45.69)	264 (44.90)	75 (48.70)
3	172 (23.18)	146 (24.83)	26 (16.88)
4	69 (9.30)	50 (8.50)	19 (12.34)
5	71 (9.57)	56 (9.52)	15 (9.74)
PSM(n, %)	150 (20.22)	101 (17.17)	49 (31.82)
LNI(n, %)	11 (1.48)	7 (1.19)	4 (2.60)
Pathological Stage(n, %)			
T2	572 (77.08)	459 (78.06)	113 (73.38)
T3a	108 (14.56)	82 (13.95)	26 (16.88)
T3b	62 (8.36)	47 (7.99)	15 (9.74)
Post-operative PSA6w(median, IQR), ng/mL	0.010(0.003–0.020)	0.010(0.003–0.020)	0.011(0.005–0.026)
<0.01 (n, %)	342 (46.09)	286 (48.64)	56 (36.36)
0.01~0.02	187 (25.20)	144 (24.49)	43 (27.92)
0.02~0.05	121 (16.31)	89 (15.14)	32 (20.78)
0.05~0.1	42 (5.66)	29 (4.93)	13 (8.44)
≥0.1	50 (6.74)	40 (6.80)	10 (6.49)
Follow-up Time(median, IQR), weeks	67.00 (56.41–77.59)	77.29 (63.13–91.27)	26.86 (15.70–38.02)
BCR Patients(n, %)	107 (14.42)	83 (14.12)	24 (15.58)
<1 year	63 (58.88)	52 (62.65)	11 (45.83)
≥1 year, <3 year	30 (28.04)	22 (26.51)	8 (33.33)
≥3 year	14 (13.08)	9 (10.84)	5 (20.83)

Abbreviations: IQR, inter-quartile range; LNI, lymph node invasion; PSM, positive surgical margins; BCR, biochemical recurrence.

Table 2 Independent Predictors of BCR with Cox Proportional Hazards Model

Covariates	BCR			
	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	P	HR (95% CI)	P
Pre-operative PSA	1.019 (1.012–1.025)	<0.001	N/A	N/A
LNI	4.698 (1.894–11.651)	0.001	N/A	N/A
Pathological Stage	—	<0.001	—	0.021
T_2	1.0	—	1.0	—
T_{3a}	2.853 (1.648–4.940)	<0.001	1.429 (0.770–2.653)	0.258
T_{3b}	8.266 (4.892–13.965)	<0.001	2.392 (1.294–4.424)	0.005
PSM	2.209 (1.365–3.574)	0.001	1.729 (1.023–2.922)	0.041
Gleason Grade	—	<0.001	—	0.003
1	1.0	—	1.0	—
2	3.023 (0.701–13.033)	0.138	2.101 (0.481–9.128)	0.324
3	8.025 (1.895–33.980)	0.005	4.595 (1.059–19.943)	0.042
4	16.600 (3.789–72.727)	<0.001	5.093 (1.088–23.834)	0.039
5	20.805 (4.916–88.056)	<0.001	7.905 (1.600–31.472)	0.010
Post-operative PSA_{6w}	—	<0.001	—	<0.001
<0.01 (ng/mL)	1.0	—	1.0	—
0.01~0.02	1.384 (0.653–2.932)	0.397	1.389 (0.652–2.958)	0.394
0.02~0.05	3.347 (1.653–6.776)	0.001	2.605 (1.274–5.325)	0.009
0.05~0.1	6.550 (2.840–15.108)	<0.001	3.806 (1.591–9.104)	0.003
≥0.1	34.225 (18.874–62.062)	<0.001	21.700 (11.496–40.959)	<0.001

Abbreviations: LNI, lymph node invasion; PSM, positive surgical margins; BCR, biochemical recurrence; HR, hazard rate.
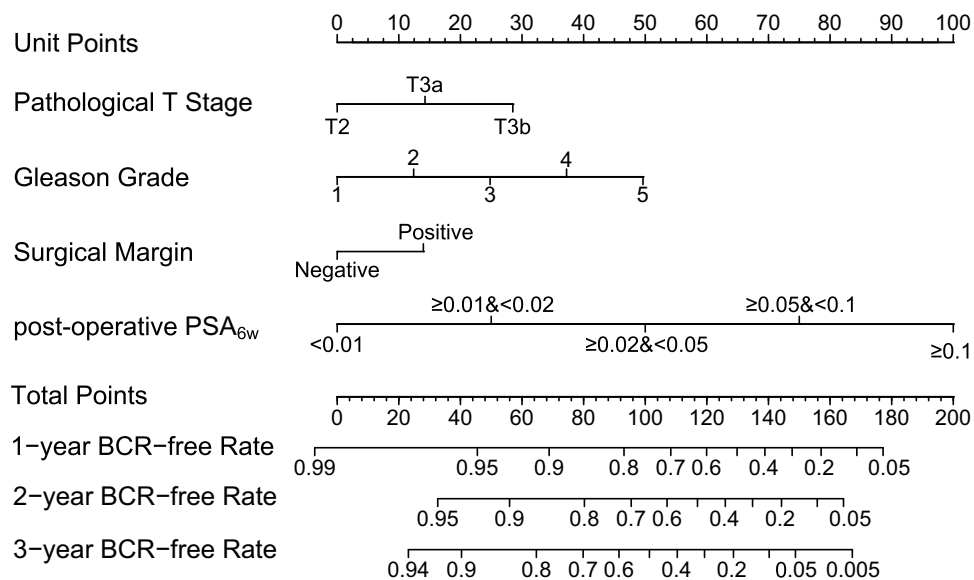
Figure 2 Nomogram predicting 3-year BCR-free probability after radical prostatectomy. A vertical line perpendicular to the horizontal axis is made according to the corresponding state of each predictor, and the intersection point between the vertical line and the upper score line is the score of the predictor. The score of the four predictors was added to obtain the final score of the patient. Then a vertical line was made from the final score, the intersection point between the vertical line and the axis of the 3-year BCR-free rate below the vertical line was the corresponding BCR-free probability of the patient.
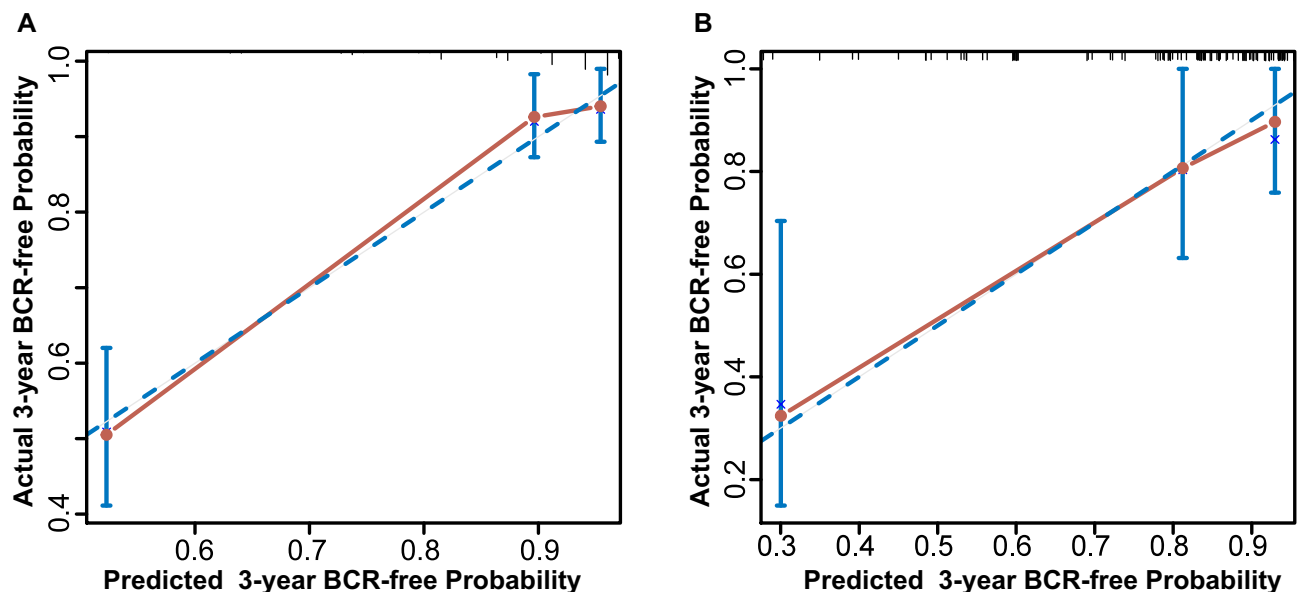
Figure 3 Calibration curve of the new model. The 45 reference line shows where perfect predictions would lie. Closed circles indicate quintiles of patients grouped according to their nomogram predicted probabilities of remaining free of BCR at 3 years after RP. Crosses represent bootstrap-corrected estimates of nomogram performance, vertical bars are 95% CIs. (**A**) Calibration curve of the modelling group. (**B**) Calibration curve of the validation group.

New Model Comparison with Kattan Post-Operative Nomogram

Using the data in the modeling group, we calculated the domestic prediction accuracy of the Kattan postoperative nomogram to be 0.786 (95% CI: 0.736–0.836). Calculation using R software indicated that the IDI of the new model compared to the Kattan post-operative nomogram was 12.61% (P < 0.001) (Figure 4).
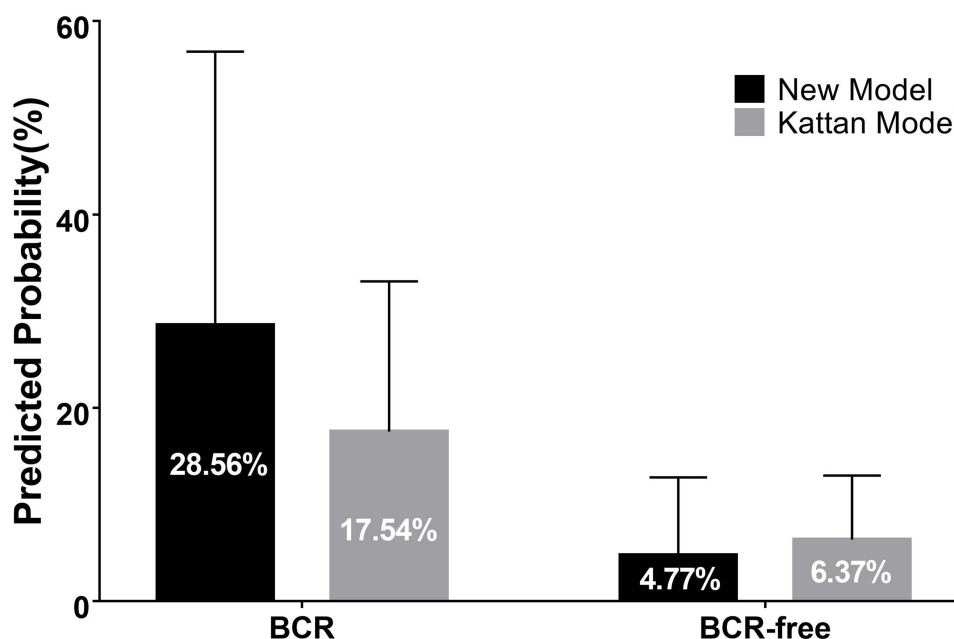
Figure 4 Comparison between the new model and Kattan post-operative nomogram. The dark bars represent the predictive ability of new model. The light bars represent the predictive ability of Kattan post-operative nomogram. The integrated discrimination improvement index was 12.61% (P < 0.001).

Clinical Application of New Model

Every patient's 3-year BCR-free probability was calculated by the modeling nomogram. A receiver operator characteristic (ROC) curve was drawn to identify the cut-off probability to divide the patients to high and low BCR groups. The 3-year BCR-free cut-off probability was 74.72% and area under curve (AUC) was 0.842 (95% CI: 0.810–0.871, Supplementary Figure 1), which mean if a patient's 3-year BCR-free probability was higher than 74.72%, he may not occur BCR in 3 years after operation and was defined as low-risk group, else he may have a high risk to BCR. In the modeling group, 458 (77.89%) patients belonged to the low-risk BCR group, and only 24 patients occurred BCR, the false-negative rate was 5.24%. So based on the nomogram, 77.89% patients have no need to follow up frequently which will save medical resources to a large extent.

Discussion

BCR is an important reference to decide whether a treatment strategy needs to be changed for patients receiving radical prostatectomy. Without further radiotherapy or endocrine therapy, about 34% patients will develop into distant metastasis after BCR.[15] At present, the only method to determine the BCR time in clinical practice is to frequently monitor the postoperative PSA levels. However, studies have reported that the 10-year BCR rate following radical prostatectomy is only 34.3%.[1] Frequent postoperative PSA monitoring not only wastes medical resources but also places a substantial economic burden and psychological pressure on patients. Over the years, researchers have been dedicated to establishing a statistical model that can accurately predict the probability of BCR using patients' clinical and pathological information, the best known of which is the postoperative nomogram proposed by Kattan et al in 1999.[2] This nomogram can relatively accurately predict the patient's BCR probability based on preoperative PSA levels and postoperative Gleason scores, ECE, SVI, LNI, and PSM. Subsequently, a series of prediction models based on the Kattan postoperative nomogram were proposed by different scholars, which introduced additional variables such as surgical experience, race, prostate weight, intraductal carcinoma, and Gleason 4/5 substructure ratio, in an attempt to improve the model's prediction accuracy.[6–8,16] However, the predictors included in previous models were limited to the clinical or pathological information obtained during the perioperative period, and the C-index ranged from 0.73 to 0.83.

As a PCa-specific tumor marker, PSA is one of the most important reference factors for PCa risk stratification and is closely related to prognosis. With the application of electrochemiluminescence immunoassay, the accuracy of PSA detection has been continuously improved, and the accuracy can be as exact as 0.01 ng/mL. Some studies have found that

low PSA level after radical prostatectomy may be closely related to the prognosis of prostate cancer. Doherty et al found that PSA reached an undetectable level after radical prostatectomy (less than 0.01 ng/mL), which may play an important role in determining whether patients will experience BCR.[11] Eisenberg et al found that when the PSA after radical prostatectomy decreased below 0.05ng /mL, the 5-year BCR-free rate was 86%, while the PSA was higher than 0.05ng / mL, the 5-year BCR-free rate was 67% (P < 0.01), which confirmed that the level of early postoperative PSA had important reference significance for BCR.[13] The half-life of PSA is 48–72 hours. Theoretically, for those patients whose tumor is completely removed during surgery, their PSA will decay according to the inherent half-life and will reach undetectable levels at sixth week after surgery.[17] If at this stage PSA is still detected, it may be an external manifestation of residual tumor within the body. Therefore, PSA presents a high reference significance for postoperative BCR.[11,12] In this study, PSA levels were monitored regularly on the sixth week after surgery. Multivariable Cox regression analysis revealed that the post-operative PSA_{6w} was a strong independent risk factor for BCR, which was consequently used to establish a new prediction model. The accuracy of the new model, the C-index, reached 0.871 (95% CI: 0.830–0.912), and additionally the calibration curve showed that the BCR-free rate predicted by the model was in good agreement with the actual rate. Subsequently, the applicability of the model was further validated using external validation data. The model achieved an accurate prediction by using post-operative PSA_{6w}, thereby demonstrating a clinical application value superior to previous models.

As prediction models can combine multiple indicators to predict the occurrence or progression of diseases, they are widely used in various fields of medical research. In 2015, the "TRIPOD" statement was published to standardize the process of prediction model establishment.[18] In 2017, Alba et al specified the standard statistical methods to establish a prediction model.[19] A good prediction model should consist of two parts, discrimination and calibration. Discrimination refers to using an indicator to distinguish the risk of a certain event happening in a group of people, which is usually assessed via the area under the ROC curve (AUC) or the C-index. Calibration, as another important evaluation index of the prediction model, reflects the agreement between the predicted and the actual values. IDI is a statistical method proposed by Pencina et al in 2008 to compare two models.[20] However, according to a report by Wessler et al, only 63% of studies on the prediction model reported discrimination, and 36% reported calibration.[21] In addition, in the field of BCR prediction following radical prostatectomy, almost no studies have used indicators such as net reclassification index (NRI) and IDI for the comparison of two models. On the contrary, the present study not only reported the discrimination and calibration of the model but also adopted IDI to compare the new model with the Kattan postoperative nomogram and found that the new model improved the prediction performance by 12.61% compared to the Kattan post-operative nomogram (P < 0.001). These results indicate that the new model further improves the prediction performance.

According to the European Association of Urology (EAU) guideline, PSA is generally determined every 6 months after prostatectomy until 3 years and yearly thereafter.[22] But the evidence for a specific interval is low, and patients with adverse pathological characteristics, such as PSM, ECE or SVI, may detect PSA every month. Based on the new nomogram, patients were divided to high and low BCR group with a 3 year BCR-free cut-off probability as 74.72%. Low-risk patients, accounting for 77.89% of the patients, have no need to follow up frequently with a false-negative rate only 5.24%, which will save medical resources to a large extent.

In this study, all data used in the study were from the PC-follow database. Therefore, although the patients were divided into the modeling group and the validation group according to the operating surgeon, selection bias could still exist. As a result, additional data from other centers are required for external validation to further determine the model's applicability.

Conclusion

The new nomogram model can intuitively and accurately calculate the probability of BCR-free for each patient within three years, so as to develop individualized follow-up strategies for patients and avoid the waste of medical resources, which has strong clinical practical value and is worth further promotion and application. However, as the data comes from a single center, the data from other centers need to be further validated.

Data Sharing Statement

The original contributions presented in the study are in the article material. Further inquiries can be directed to the corresponding authors Xu Gao.

Ethics Statement

The study was conducted in conformity with the Helsinki Declaration and approved by the Ethics Committee of the Changhai Hospital. Written informed consent was obtained from all study subjects or their legal guardians.

Acknowledgment

The authors thank all the patients who agreed to participate in this study. And thank the PC-follow Database administrator, Ms Yun Zhang for the supplying of the data.

Disclosure

The authors report no conflicts of interest in this work.

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