Risk Factors for Relapse of Prostate Cancer after Radical Prostatectomy in Chinese Population

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Purpose: To analyze the risk factors for the relapse of prostate cancer (PC) after radical prostatectomy (RP) and build a nomogram as a predictive model.

Materials and Methods: The patients who underwent PR from March 2019 to February 2022 were retrospectively enrolled in our hospital's case system. During the follow-up process, two consecutive prostate-specific antigens (PSA) ≥ 0.2 µg/L were performed. And needle biopsy was performed to further determine whether the patient had prostate cancer recurrence. According to the follow-up results, the patients were divided into non-relapsed and relapsed groups. The related parameters of the two groups were collected. Independent risk factors for postoperative recurrence were determined using a Cox proportional hazards regression model. Statistical software, R, was used to build nomograms. R software was used to construct a nomogram, and the prediction effect of the nomogram was evaluated by the calibration curve and the area under the ROC curve (AUC).

Results: Among the 367 patients who underwent RP, 112 (30.52%) had, and 255 (69.48%) did not have relapses after surgery. Cox multivariable regression analysis revealed that preoperative Gleason score, preoperative PSA, pathological staging, positive margin, and seminal vesicle invasion, were the risk factors for postoperative recurrence after RP (all $P < 0.05$). Verification of the predictive model by ROC curve demonstrated that the AUC of the ROC curves for patients' relapses 3 and 5 years after RP was 0.986 (95%CI0.975-0.998) and 0.974 (95%CI0.961-0.987), respectively. This model validation showed that the results of the predictive model were basically consistent with the actual results, suggesting that the nomogram was able to accurately predict a patient's relapse.

Conclusion: The nomogram of this study was a good predictor of postoperative recurrence of PC after RP, which will help doctors provide personalized treatment and follow-up strategies for patients.

Keywords: prostate cancer; radical prostatectomy; relapse; nomogram

INTRODUCTION

PC is a common malignancy of the male genitourinary system, accounting for 26% of all tumor incidence worldwide. It is also the second leading cause of male tumor death across the globe, second only to lung cancer[1]. In recent years, the incidence of PC in our country has increased dramatically. RP, as the preferred method for treating localized PC, can remove the ejaculatory ducts, ductus deferens, and seminal vesicles in and around the prostate with proven clinical efficacy[2]. However due to focal residues, distant micrometastases, and other biological characteristics, some patients (27% to 53%) will experience biochemical recurrence (BCR) after RP, which is an important reason for the high mortality rate[3,4]. With the popularization of PSA, the rate of early detection of tumors has increased, and the rate of postoperative BCR has decreased. Therefore, to improve the postoperative efficacy of RP and the prognosis of patients, the search for risk factors for postoperative recurrence of PC after RP has become a hot topic. According to previous foreign studies, preoperative Gleason score, capsular invasion, preoperative PSA, positive surgical margin, etc. are risk factors for postoperative BCR after RP[5,6]. There are many postoperative nomograms to predict the likelihood of disease recurrence in patients who underwent radical prostatectomy for prostate cancer. The nomogram of Kattan et al. showed promising accuracy and discrimination in predicting recurrence-free probability, with a 73% rate over 7 years in the studied cohort[7]. Another nomogram predicted outcomes up to 10 years post-surgery and allowed adjustments based on the disease-free interval after surgery[8]. Different predictive models have used different variables. The Kattan and CaPSURE/CPDR scores, which consider PSA value, Gleason score, tumor stage, and other patient data, were used in Zeigler-Johnson et al. study[9]. Despite the availability of postoperative nomograms in predicting disease recurrence after radical prostatectomy for prostate cancer, there is a lack of similar studies evaluating the impact of obesity on prognostic tools in China. To date, studies in China have not extensively explored how obesity may influence the predictive abilities of these nomograms.

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Table 1. Comparison of clinically relevant factors between two groups

Factors	Recurrence Group (n=112)	Non- recurrence Group (n=255)	t/χ²	*P*
Age (years old)	60.57 ± 6.24	59.78 ± 5.97	1.147	0.252
Preoperative PSA levels (μg/L)	50.88 ± 12.20	22.01 ± 7.12	28.393	< 0.001
Preoperative Gleason score (points)	7.25 ± 1.15	6.43 ± 1.01	6.868	< 0.001
Postoperative prostate volume (cm3)	35.10 ± 9.94	34.88 ± 9.65	0.592	0.554
Pathological staging			20.770	< 0.001
T2	34	111		
T3	33	100		
T4	45	44		
Seminal vesicle invasion	25	7	37.471	< 0.001
Positive surgical margin	16	10	12.699	< 0.001
Duration of Surgery (min)	173.78 ± 30.25	175.05 ± 30.18		-0.371
0.711				

In China, there are fewer studies on long-term follow-up after RP and influencing factors for relapse of PC. Based on this, we analyzed the risk factors affecting the postoperative recurrence of PC after RP, and constructed a relevant predictive model, to provide a reference for the prediction of prognosis and early administration of personalized treatment in clinical practice.

MATERIALS AND METHODS

Study subjects

The patients who underwent PR from March 2019 to February 2022 were retrospectively enrolled in our hospital's case system. Inclusion criteria:(1) Patients diagnosed with PC by prostate biopsy before surgery, with postoperative diagnostic results provided by the pathological center of our hospital consistent with preoperative diagnostic results.(2) Patients who did not receive any adjuvant therapy (such as endocrine therapy or chemotherapy) before and after surgery.(3) No lymph node metastasis or distant metastasis was detected by imaging examination. (4) Patients with complete follow-up materials. Exclusion criteria: (1) Patients who died due to other diseases during follow-up. (2) Patients with other malignancies. (3) Patients with respiratory diseases, cardiovascular diseases, and organ failure.
Based on previous studies that have demonstrated a substantial and clinically meaningful association between the identified risk factors (e.g., preoperative Gleason score, preoperative PSA, pathological staging, positive margin, seminal vesicle invasion) and postoperative recurrence6-9, a moderate to large effect size was considered. out one specific risk factor is expected to have a medium effect size (Cohen's f = 0.25)assuming a medium effect size (f = 0.25), power of 80%, a significance level of 0.05, 5 potential covariates, and an expected dropout rate of 10%, the sample size estimation might indicate a need for approximately 400 participants.

Methods

We logged in to our hospital's medical record management system to collect the patients' general materials and surgery-related materials. General materials: age, preoperative total PSA levels, testosterone levels, and preoperative Gleason score. Vein blood samples were collected from patients after an overnight fast before the prostate biopsy in the early morning. Serum testosterone levels were measured by chemiluminescence, and total PSA levels were measured by enzyme-activated luminescence. Surgery-related materials: pathological staging, seminal vesicle invasion, positive surgical margin, postoperative Gleason score, and duration of surgery.

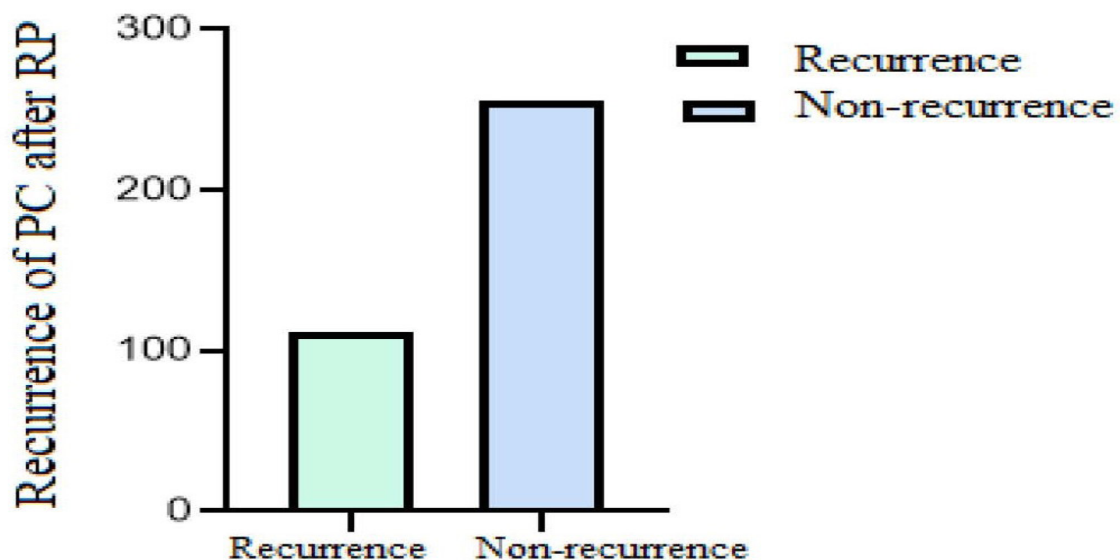

Figure 1. Recurrence of PC after RP.

Table 2. Assignment of values to valuables

Independent valuables	Valuable type	Assignment of values
Preoperative PSA	Continuous variable	Original value
Preoperative Gleason score	Continuous variable	Original value
Pathological staging	Categorical variable	T2=1, T3=2, T4=3
Seminal vesicle invasion	Categorical variable	Yes =1, No =0
Positive surgical margin	Categorical variable	Yes =1, No =0

Table 3. Cox multivariable regression analysis.

Variables	HR	95%CI	*P*
Preoperative PSA	1.074	1.061-1.087	< 0.001
Preoperative Gleason score	1.233	1.053-1.444	0.009
Pathological staging	1.318	1.021-1.703	0.034
Seminal vesicle invasion	1.814	1.020-3.228	0.043
Positive surgical margin	1.901	1.127-3.207	0.016

Assessment of recurrence of PC after RP

Patients were reexamined on the third day after surgery to ensure that the tumor had been removed. Total PSA ≥ 0.2μg/L for two consecutive times was regarded as a sign of recurrence. Then patients needed to do a needle biopsy of the prostate to determine if they had a relapse. A positive biopsy of the prostatic bed was essential to confirm the recurrence.

According to the results of the follow-up, they were divided into non-relapsed and relapsed groups.

Statistical analysis

Statistical analysis (SPSS24.0 software) was used for data analysis. Quantitative data were tested by the Shapiro-Wilk test along with the Q-Q plot visualization, used to mean ± standard deviation ($\overline{x} \pm s$) to describe normal distribution data. An Independent t-test was used to compare differences in means between the two groups after ensuring homogeneity of variance and normality of data. Qualitative data were expressed as frequency and percentage (n%) and tested by chi-square test or Fisher exact test in cases where the chi-square assumption was not met.

Time-to-event analysis was performed based on the start time of surgery and the end of follow-up was when a relapse was confirmed. Independent risk factors for postoperative recurrence were determined using a Cox proportional hazards regression model. Cox regression was performed after confirming that the hazard ratio between two groups remains constant over time and the relationship between a quantitative predictor and the log hazard is linear. A straightforward approach was used in Cox regression by including all the candidate variables in the initial model and then evaluating their significance through hypothesis testing (p-values) to determine which variables are significantly associated with the outcome (recurrence after RP). Statistical software, R, was used to build nomograms. To use calibration curve and ROC curve AUC to verify and evaluate the prediction effect of the nomogram. $P < 0.05$ stands for a statistically significant difference.

RESULTS

Recurrence of PC after RP

They were followed up for 13 to 58 months (IQR= 10.52 to 51.52 months), with an average duration of follow-up of (31.52±10.50) months. During this period, patients came to the hospital regularly for examination. However, 17 patients were lost to follow-up at different time points during the study, and their last known follow-up time ranged from 1 to 2 years. Moreover, 8 patients passed away during the study duration.

According to Figure 1, among the 367 patients who underwent RP, 112 (30.52%) and 255 (69.48%) did not have relapses after surgery. 5-year recurrence-free survival rate was 69.48% (95%CI: 66.12% to 73.15%).

Comparison of clinically relevant factors between two groups

According to **Table 1**, no significant difference was found in age, postoperative prostate volume, and duration of operation between the two groups (P> 0.05). preoperative Gleason score, preoperative PSA, Pathological staging, seminal vesicle invasion, and positive resection margin between two groups (all $P < 0.05$).

Cox multivariable regression analysis

The above-mentioned indicators with $P < 0.05$ (preoperative Gleason score, preoperative PSA, postoperative Gleason score, preoperative prostate volume, pathological staging, seminal vesicle invasion and positive surgical margin) were taken as the independent variables. Recurrence after RP in prostate cancer patients was taken as the factor variation (2= recurrence, 1= non-recurrence). The assignment of values to valuables is displayed in Table 2. According to Table 3, Cox multivariable regression analysis revealed that preoperative

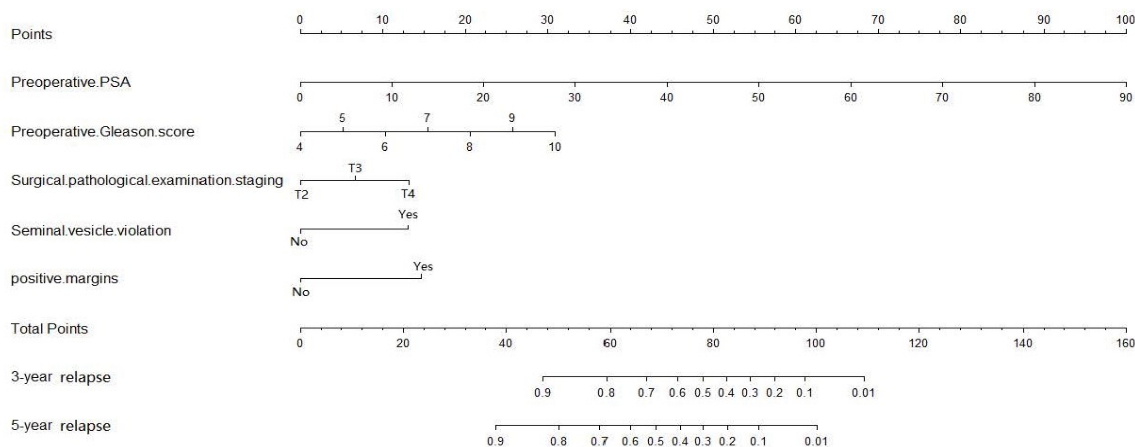

Figure 2. Nomogram as a predictive model of the relapse rate of patients 3 and 5 years after RP.

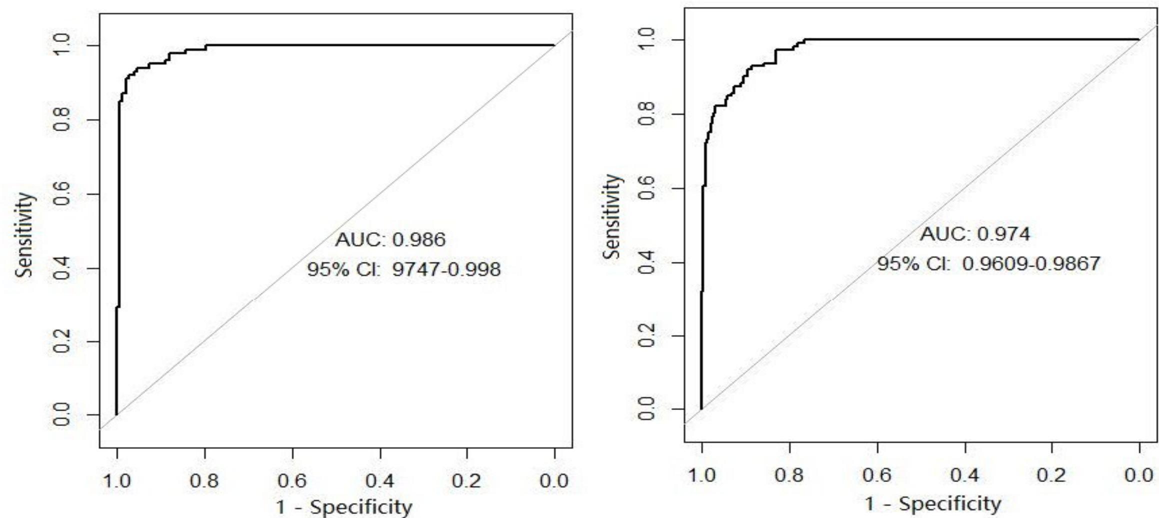

Figure 3. ROC curves of nomogran as a predictive model of recurrence of PC in patients 3 and 5 years after RP.

Gleason score, preoperative PSA, pathological staging, positive margin, and seminal vesicle invasion, were the risk factors for postoperative recurrence after RP (all $P < 0.05$).

Construction of a nomogram as a predictive model

Based on the results of Cox analysis, five predictable indicators (preoperative PSA level, preoperative Gleason score, pathological staging, seminal vesicle invasion, and positive surgical margin) were combined to construct a nomogram as a predictive model of recurrence of PC in patients 3 years and 5 years after RP.

Verification of predictive model

(1) Discrimination: The above model was verified using Bootstrap sampling and we resampled 500 times. ROC curve was used to verify the nomogram, and the results shown in Figure 3 demonstrated that the AUC of the ROC curves for patients' relapses 3 and 5 years after RP was 0.986 (95%CI0.975-0.998) and 0.974 (95%CI0.961-0.987), respectively, illustrating that the discrimination ability of the predictive model was good. (2) Calibration: Calibration curves of the nomogram are shown in **Figure 4**, which showed that the results of the predictive model were basically consistent with the actual results, suggesting that the nomogram was able to accurately predict a patient's relapse.

DISCUSSION

PC is a malignant tumor with a high degree of hetero-

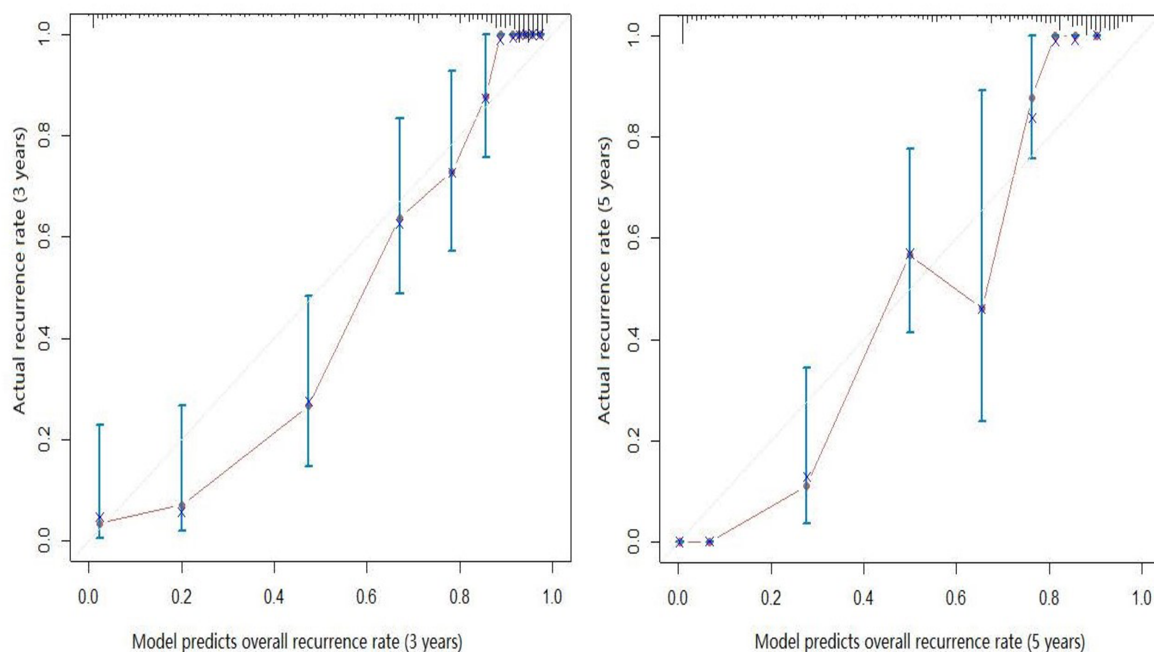

Figure 4. Calibration curves of nomogran as a predictive model of recurrence of PC in patients 3 and 5 years after RP.

geneity. RP is the preferred treatment method for PC because of its ideal tumor control probability and reduced short-term mortality rate, but there is still a risk of recurrence after surgery[10,11]. The mechanism of postoperative recurrence after RP has not been clearly defined, which may be related to incomplete tumor removal, tumor nature, failure to detect micro-metastases, and the patient's constitution[12]. Therefore, PC patients are at risk of tumor recurrence within 10 years after RP, which may further increase the medical burden on patients and long-term mortality. Studies have shown that 27%-53% of patients had experienced BCR within 10 years after RP[13,14]. Fakhrejahani and other scholars have found that the incidence of BCR within 3 years after RP is about 30%, but this does not mean that the patient will experience clinical recurrence[15]. As BCR often occurs before clinical occurrence, it can be regarded as a precursor to clinical recurrence and an important indicator of postoperative follow-ups. The results of this study showed that among the 367 patients who underwent RP, 112 (30.52%) and 255 (69.48%) did not have relapses after surgery. Therefore, to further assess the risk of postoperative recurrence, it is necessary to formulate targeted treatment plans and effectively predict the risk of BCR after surgery.

Our developed nomogram demonstrated outstanding accuracy and discrimination in predicting patient relapses 3 and 5 years after radical prostatectomy (RP) with impressive AUC values of 0.986 (95% CI 0.975-0.998) and 0.974 (95% CI 0.961-0.987), respectively. These results outperform the predictive capabilities of previously studied nomograms. For instance, the nomogram by Kattan et al. showed a 73% rate for recurrence-free probability over 7 years in the studied cohort7, while another nomogram predicted outcomes up to 10 years post-surgery with adjustments based on disease-free intervals8. Our nomogram's high AUC values indicate its potential clinical value in predicting patient relapses after RP and may offer improved accuracy and prognostic ability compared to previously published models.

Cox multivariable regression analysis in this study revealed that preoperative Gleason score, preoperative PSA, pathological staging, positive margin, seminal vesicle invasion, were risk factors for postoperative recurrence after RP, which may increase the recurrence of PC after surgery. Serum PSA is currently clinically recognized as one of the most sensitive tumor markers for PC. Kang and other scholars conducted univariate analysis on 203 patients who underwent RP from 2006 to 2012 and found that preoperative PSA was associated with biochemical recurrence after RP in univariate analysis ($P < 0.05$)[16]. Hashimoto and other scholars analyzed 1762 patients with localized PC who underwent RP between 2006 and 2016 and found that preoperative PSA is a risk factor for BCR after surgery and that the timing of preoperative PSA detection is also an important predictor of BCR, indicating that early detection of PSA is very important for early diagnosis and treatment of PC[17]. At present, the Gleason score has become a reference for deciding specific clinical treatments for PC patients and has been widely used in risk stratification for PC patients[18]. Song and other foreign scholars retrospectively analyzed 795 patients with pT3a receiving PR and found that Gleason grading is the only independent predictor of biochemical recurrence risk stratification[19]. That is, the Gleason score is proportional to the postoperative recurrence rate. The pathological stage has been found to be an important predictor of BCR after RP, that is, the pathological stage is directly proportional to the risk of postoperative recurrence in patients. Seminal vesicle invasion is one of the manifestations of PC breaking through the connective tissue that covers prostate, which may be related to tumor aggressiveness. For patients with seminal vesicle infiltration, the incidence of BCR after RP is higher, so it can be considered a risk factor for recurrence[20].Whether positive margins are associated with biochemical recurrence after RP remains unclear. Studies have shown that positive surgical margin is not a risk factor for BCR after RP and is not related to prognosis[21]. However, there is also a study believing that a positive surgical margin is a risk factor for BCR, and it should be avoided as much as possible[22]. Preisser and other scholars analyzed the data of 8770 patients who underwent RP, and the results showed that patients with positive margins had a higher incidence of biochemical recurrence[23].

Nomogram is a model based on multivariable regression analysis that predicts clinical outcomes or the probability of certain types of events and is presented in a visual and graphical form to help clinicians make decisions based on the prognosis predicted by the model. At present, there are many studies based on nomograms in other fields, such as the nomogram of the specific survival of tumor patients, and the nomogram of radiotherapy combined with clinical features to diagnose the risk of postoperative recurrence of lymph node metastases peritoneal metastases, and malignant tumors[24-31]. But there are fewer studies on the nomogram model for the postoperative recurrence of PC after RP. According to the results of multivariableCox analysis, selected indicators were obtained to construct nomogram for predicting recurrence in patients after RP within 3 and 5 years. The model was verified using Bootstrap sampling with repeated sampling of 500 times. Verification of the predictive model by ROC curve demonstrated that the AUC of the ROC curves for patients' relapses 3 and 5 years after RP was 0.986 (95%CI0.975-0.998) and 0.974 (95%CI0.961-0.987), respectively, suggesting that the predictive model has good predictive differentiation. Calibration curves of nomogran were drawn, which showed that the results of the predictive model were basically consistent with the actual results, suggesting that the nomogram was able to accurately predict a patient's relapse. The nomogram predictive model in this study visualized complex and abstract regression equations so that clinical caregivers can more intuitively conduct personalized assessments for patients.

CONCLUSIONS

In summary, the nomogram of this study was a good predictor of postoperative recurrence of PC after RP, which will help doctors provide personalized treatment and follow-up strategies for patients.

The limitations of this study, the limitation of this study is that it is a single-center retrospective study, and some information, such as body mass index (BMI) and underlying diseases, were not collected. so there may be a certain degree of selection bias. In addition, due to the limitation of the number of patients included, the nomogram predictive model has not been externally

validated. Therefore, larger, multicenter and prospective studies are needed to further confirm the findings.

CONFLICT ON INTEREST

None declared by the authors.

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