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Development and Internal Validation of a Nomogram for Predicting Biochemical Recurrence After Radical Prostatectomy: A Retrospective Cohort Study

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Research Article

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Abstract

Background

Biochemical recurrence (BCR) remains an important clinical outcome after radical prostatectomy (RP) for prostate cancer. Established postoperative tools such as the Cancer of the Prostate Risk Assessment Postsurgical (CAPRA-S) score provide useful risk stratification, but model calibration and predictor effects may vary across populations. This study aimed to develop and internally validate a clinicopathological nomogram for BCR prediction and to compare its performance with CAPRA-S and the conventional TNM staging system.

Methods

A total of 218 consecutive patients who underwent RP for clinically localized or locally advanced prostate cancer between January 2019 and December 2025 at our institution were retrospectively enrolled and randomly divided into a training cohort (n = 153) and a validation cohort (n = 65). LASSO-penalized Cox regression followed by multivariable Cox regression was used for model development. Performance was assessed using Harrell's C-index, calibration, time-dependent discrimination, the 3-year Brier score, and decision curve analysis. CAPRA-S was calculated according to the original postsurgical scoring algorithm. Additional sensitivity analyses evaluated surgeon and surgical-approach effects, postoperative adjuvant treatment, and bootstrap internal validation in the complete cohort.

Results

After a median follow-up of 24.0 months, 119 patients (54.6%) experienced BCR. Six predictors were retained in the final model: preoperative prostate-specific antigen (PSA), biopsy Gleason score, positive surgical margin, seminal vesicle invasion, extracapsular extension, and lymph node metastasis. The nomogram C-index was 0.812 (95% CI, 0.762–0.862) in the training cohort and 0.785 (95% CI, 0.714–0.856) in the validation cohort, compared with 0.781 (95% CI, 0.729–0.833) and 0.758 (95% CI, 0.682–0.834), respectively, for CAPRA-S. The differences in C-index were modest and not statistically significant (training: delta = 0.031, P = 0.118; validation: delta = 0.027, P = 0.311). The 3-year Brier score was 0.168 for the nomogram, 0.183 for CAPRA-S, and 0.224 for TNM. In full-cohort bootstrap validation, the optimism-corrected C-index was 0.791 and the calibration slope was 0.93.

Conclusions

The proposed nomogram provides individualized BCR risk estimates using routinely available clinicopathological variables. Its discrimination was numerically higher than CAPRA-S in this cohort, although the incremental difference was not statistically significant. The model should therefore be

viewed as an internally validated, population-specific risk tool requiring independent external validation and longer follow-up before routine clinical use, particularly for 5-year prediction.

1. Introduction

Prostate cancer (PCa) is the second most commonly diagnosed malignancy among men worldwide, with an estimated 1.47 million new cases and over 397,000 deaths reported globally in 2022 according to the GLOBOCAN database [1]. The incidence and mortality rates exhibit substantial geographic variation, with the highest incidence reported in Australia/New Zealand and other high-incidence regions, and the highest mortality concentrated in parts of sub-Saharan Africa and Latin America/Caribbean [2]. In Asia, PCa incidence and mortality rates were historically lower than in Western populations but have increased rapidly in several countries in recent years, partly reflecting changes in screening intensity and diagnostic practice [3]. Radical prostatectomy (RP), including open, laparoscopic, and robot-assisted approaches, remains an important curative treatment option for clinically localized and selected locally advanced PCa [4].

Despite advances in surgical technique, biochemical recurrence (BCR) remains a clinically significant outcome following RP, occurring in approximately 20–40% of patients within 10 years of surgery [5]. BCR, typically defined using serial postoperative PSA measurements, serves as an early indicator of disease recurrence and has been associated with an increased risk of subsequent metastasis and prostate cancer-specific mortality [6, 7]. Accurate postoperative risk estimation is therefore important for patient counseling, surveillance planning, and consideration of postoperative treatment strategies [8].

Traditional risk stratification systems, including the American Joint Committee on Cancer (AJCC) TNM classification and the D'Amico risk grouping, categorize patients into broad strata and provide limited individualized risk estimates [9]. The Cancer of the Prostate Risk Assessment Postsurgical (CAPRA-S) score is an established postoperative prediction tool that integrates preoperative PSA with pathological Gleason score, surgical margin status, extracapsular extension, seminal vesicle invasion, and lymph node involvement [10]. External validation studies have reported useful discrimination in different populations, including Asian cohorts [11].

Nomograms translate multivariable regression models into individualized probability estimates and may complement categorical staging systems by providing continuous risk estimates [12, 13]. Several postoperative nomograms for BCR after RP have been proposed, including institution-specific and robot-assisted RP-based models, as well as the established Stephenson postoperative nomogram [14–16]. However, the performance and calibration of prediction models may vary across populations because of differences in case mix, pathological characteristics, treatment patterns, and follow-up.

The least absolute shrinkage and selection operator (LASSO) is a penalized regression method that performs simultaneous coefficient shrinkage and variable selection and can reduce overfitting when multiple candidate predictors are considered [17–19]. In the present study, we used LASSO followed by multivariable Cox regression to develop an individualized BCR prediction model after RP. The primary

objective was to develop and internally validate the nomogram. The secondary objective was to compare its predictive performance with CAPRA-S and the conventional TNM staging system, while also evaluating the potential influence of surgeon-related factors, surgical approach, and postoperative adjuvant treatment.

2. Materials and Methods

2.1 Study Design and Patient Population

This retrospective, single-center cohort study enrolled consecutive patients who underwent RP for histologically confirmed prostate adenocarcinoma at our institution between January 2019 and December 2025. The study protocol was approved by the Ethics Committee of the Second Affiliated Hospital of Shantou University Medical College, and the requirement for individual informed consent to participate was waived by the Ethics Committee of the Second Affiliated Hospital of Shantou University Medical College because of the retrospective design and use of de-identified data (Human Ethics and Consent to Participate declarations: approved and consent waived; Clinical trial number: not applicable). The study was conducted in accordance with the Declaration of Helsinki and reported following the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines [20].

The inclusion criteria were as follows: (1) histologically confirmed prostate adenocarcinoma by prostate biopsy before surgery; (2) treatment with RP by open retropubic, conventional laparoscopic, or robot-assisted approach; (3) availability of complete preoperative clinical data, including serum PSA, biopsy Gleason score, and clinical staging information; (4) availability of detailed postoperative pathology reports, including assessment of surgical margins, seminal vesicle status, extracapsular extension, and lymph node involvement; and (5) a minimum postoperative follow-up duration of six months with serial PSA measurements available.

The exclusion criteria comprised: (1) receipt of neoadjuvant therapy, including androgen deprivation therapy (ADT), chemotherapy, or radiotherapy, before RP (n = 14); (2) distant metastatic disease (M1) at diagnosis (n = 8); (3) another primary malignancy requiring active treatment (n = 3); (4) incomplete records precluding extraction of required study variables (n = 11); and (5) loss to follow-up within the first six postoperative months without a documented PSA measurement (n = 6). Following application of these criteria, 218 patients were included in the final analytical cohort.

The 218 eligible patients were randomly allocated to a training cohort (n = 153, 70.2%) and a holdout validation cohort (n = 65, 29.8%) using a computer-generated randomization procedure with a fixed seed. The training cohort was used for variable selection and model development, whereas the validation cohort was reserved for internal performance assessment.

2.2 Data Collection and Variable Definitions

Clinicopathological variables were retrospectively extracted from the electronic medical record by two independent reviewers, with discrepancies resolved by a senior urologist. Demographic and clinical variables included age at surgery, body mass index (BMI), hypertension, diabetes mellitus, smoking history, and alcohol drinking history. Preoperative oncological variables included serum PSA measured within 30 days before surgery, biopsy Gleason score and corresponding International Society of Urological Pathology grade group, and clinical TNM stage assigned according to the AJCC 8th edition.

Intraoperative variables included operative time and estimated blood loss. Postoperative pathological variables included pathological T stage, pathological N stage, positive surgical margin (PSM), seminal vesicle invasion (SVI), extracapsular extension (ECE), perineural invasion (PNI), the number of pelvic lymph nodes removed, and the number of metastatic lymph nodes. Pathological Gleason score from the prostatectomy specimen was additionally abstracted for calculation of the CAPRA-S score; the Gleason predictor used in the proposed nomogram remained the biopsy Gleason score specified in the original model-development analysis.

2.3 Surgical Approach and Surgeon-Related Factors

Additional perioperative variables included surgical approach (open retropubic, conventional laparoscopic, or robot-assisted RP), operating surgeon, and pelvic lymph node dissection (PLND). All procedures were performed by four urologic surgeons at our institution. PLND was performed in all included patients, and the total number of lymph nodes removed was recorded.

To assess potential surgeon-related heterogeneity, PSM and BCR event rates were compared across surgeons. Operating surgeon and surgical approach were also incorporated into sensitivity Cox regression analyses to determine whether adjustment for these factors materially altered the estimated effects of the six predictors retained in the final nomogram.

2.4 Definition of Biochemical Recurrence and Follow-up Protocol

The primary endpoint was BCR-free survival, defined as the interval from RP to BCR or last follow-up, whichever occurred first. BCR was defined as two consecutive serum PSA values > = 0.2 ng/mL measured at least two weeks apart after an initial postoperative PSA nadir < 0.1 ng/mL, consistent with the study definition used in the original analysis [21]. The BCR date was recorded as the date of the first PSA measurement meeting the threshold. Patients who received adjuvant radiotherapy or ADT before confirmed BCR were censored at the date of treatment initiation.

Postoperative surveillance comprised serum PSA measurements at 6 weeks, 3 months, and 6 months after surgery, every 6 months during the first 2 years, and annually thereafter. Additional imaging, including pelvic MRI, bone scintigraphy, or prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA-PET/CT), was performed at the discretion of the treating physician when PSA persistence or BCR was documented. Follow-up information was obtained from outpatient visits, structured telephone interviews, and review of the electronic medical record.

2.5 Statistical Analysis

All statistical analyses were performed using R software (version 4.3.1; R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were summarized as median and interquartile range (IQR) and compared using the Mann-Whitney U test. Categorical variables were summarized as counts and percentages and compared using the chi-square test or Fisher's exact test, as appropriate. A two-sided P value < 0.05 was considered statistically significant.

2.5.1 Variable Selection Using LASSO Regression

Variable selection was performed in the training cohort using LASSO-penalized Cox proportional hazards regression implemented with the glmnet package (version 4.1-8) [17–19]. Candidate predictors were standardized before LASSO analysis. The penalty parameter was selected using 10-fold cross-validation, and lambda-min, defined as the value minimizing partial-likelihood deviance, was used for variable identification. Variables with non-zero coefficients at lambda-min were entered into subsequent multivariable Cox regression.

2.5.2 Multivariable Cox Regression and Nomogram Construction

Variables selected by LASSO were entered into a multivariable Cox proportional hazards model in the training cohort. The proportional hazards assumption was assessed using Schoenfeld residuals and the global goodness-of-fit test. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated. The final nomogram was constructed using the rms package (version 6.7-1) to estimate 1-, 3-, and 5-year BCR-free survival probabilities [12]. Given the limited duration of follow-up, 5-year estimates were prespecified as exploratory and were interpreted cautiously.

2.5.3 Comparison With CAPRA-S and TNM

To evaluate predictive performance relative to an established postoperative tool, CAPRA-S was calculated for each eligible patient according to the original scoring algorithm using preoperative PSA, pathological Gleason score from the RP specimen, surgical margin status, extracapsular extension, seminal vesicle invasion, and lymph node involvement [10].

Discrimination of the proposed nomogram, CAPRA-S, and TNM staging system was compared using Harrell's C-index and time-dependent area under the receiver operating characteristic curve (AUC). Three-year prediction error was additionally evaluated using the Brier score. Pairwise differences in C-index between the nomogram and CAPRA-S were evaluated using 1,000 bootstrap resamples. Decision curve analysis was evaluated at the 3-year survival horizon using a survival-outcome approach that accounted for censoring, with CAPRA-S and TNM included as comparators [23].

2.5.4 Calibration, Risk Stratification, and Internal Validation

Calibration was assessed graphically by comparing predicted and observed BCR-free survival probabilities. Nomogram-based risk-group cutoffs were determined exclusively in the training cohort to avoid information leakage from the validation cohort. The 33.3rd and 66.7th percentiles of total nomogram score corresponded to scores of 98 and 168, respectively. These prespecified cutoffs were then applied without modification to the validation cohort and to the overall cohort for descriptive presentation. Because several patients had tied scores at the prespecified percentile cutoffs, the resulting group sizes were not exactly equal. Kaplan-Meier curves were compared using the log-rank test.

As an additional internal-validation sensitivity analysis, the fixed six-predictor Cox model was refitted in the complete cohort of 218 patients and evaluated using 1,000 bootstrap resamples. Apparent and optimism-corrected C-indices and the optimism-corrected calibration slope were calculated to quantify model optimism. This analysis evaluated the final fixed model and did not constitute external validation.

2.5.5 Sensitivity Analyses

Two additional sensitivity analyses were performed. First, operating surgeon and surgical approach were added to the Cox model to evaluate whether surgeon-related or approach-related variability materially changed the coefficients of the six final predictors. Second, the model-performance analysis was repeated after excluding patients who received adjuvant treatment before documented BCR.

3. Results

3.1 Baseline Patient Characteristics

A total of 218 patients were included, with 153 (70.2%) allocated to the training cohort and 65 (29.8%) to the validation cohort. The median age was 67 years (IQR, 62-73), and the median preoperative PSA was 12.7 ng/mL (IQR, 7.2-23.8). Biopsy Gleason scores were 6 in 32 patients (14.7%), 7 in 99 (45.4%), 8 in 40 (18.3%), and 9-10 in 47 (21.6%); thus, 87 patients (39.9%) had biopsy Gleason score >=8. PSM was present in 62 patients (28.4%), SVI in 35 (16.1%), ECE in 55 (25.2%), and lymph node metastasis in 32 (14.7%). Baseline characteristics did not differ significantly between the training and validation cohorts (all P > 0.05) (Table 1).

Table 1. Baseline Clinicopathological Characteristics of the Study Cohorts

Variable	Total (n=218)	Training (n=153)	Validation (n=65)	P value
Age, median (IQR), years	67 (62-73)	67 (61-73)	68 (63-74)	0.528
BMI, median (IQR), kg/m²	24.8 (22.5-27.1)	24.6 (22.3-26.9)	25.2 (23.0-27.5)	0.412
Hypertension, n (%)	92 (42.2)	64 (41.8)	28 (43.1)	0.866
Diabetes mellitus, n (%)	39 (17.9)	28 (18.3)	11 (16.9)	0.810
Smoking history, n (%)	76 (34.9)	52 (34.0)	24 (36.9)	0.680
Drinking history, n (%)	61 (28.0)	42 (27.5)	19 (29.2)	0.795
Preoperative PSA, median (IQR), ng/mL	12.7 (7.2-23.8)	12.3 (6.8-24.1)	13.5 (7.8-22.9)	0.635
Biopsy Gleason score, n (%)				
6	32 (14.7)	22 (14.4)	10 (15.4)	0.847
7	99 (45.4)	70 (45.8)	29 (44.6)	
8	40 (18.3)	27 (17.6)	13 (20.0)	
9-10	47 (21.6)	34 (22.2)	13 (20.0)	
Positive surgical margin, n (%)	62 (28.4)	44 (28.8)	18 (27.7)	0.872
Seminal vesicle invasion, n (%)	35 (16.1)	25 (16.3)	10 (15.4)	0.860
Extracapsular extension, n (%)	55 (25.2)	39 (25.5)	16 (24.6)	0.893
Lymph node metastasis, n (%)	32 (14.7)	23 (15.0)	9 (13.8)	0.819
Perineural invasion, n (%)	120 (55.0)	83 (54.2)	37 (56.9)	0.715
Operative time, median (IQR), min	185 (152-218)	183 (150-215)	189 (155-224)	0.487
Blood loss, median (IQR), mL	200 (120-350)	195 (118-345)	210 (125-360)	0.561
BCR events, n (%)	119 (54.6)	84 (54.9)	35 (53.8)	0.886
Follow-up, median (IQR), months	24.0 (14.2-38.5)	23.8 (13.9-37.8)	24.5 (15.0-39.7)	0.724

Abbreviations: IQR, interquartile range; BMI, body mass index; PSA, prostate-specific antigen; BCR, biochemical recurrence.

3.2 Surgical Characteristics, PLND, and Postoperative Adjuvant Treatment

Among the 218 patients, 46 (21.1%) underwent open retropubic RP, 101 (46.3%) underwent conventional laparoscopic RP, and 71 (32.6%) underwent robot-assisted RP. BCR occurred in 58.7%, 54.5%, and 52.1%

of patients, respectively, with no significant difference across surgical approaches (P = 0.783).

The four operating surgeons performed 62, 57, 53, and 46 procedures, respectively. PSM rates were 27.4%, 29.8%, 26.4%, and 30.4% across surgeons (P = 0.963). Corresponding BCR event rates were 53.2%, 54.4%, 56.6%, and 54.3% (P = 0.987).

PLND was performed in all 218 patients. The median number of lymph nodes removed was 11 (IQR, 7-16). Lymph node metastasis was identified in 32 patients (14.7%); among node-positive patients, the median number of metastatic lymph nodes was 2 (IQR, 1-3).

During follow-up, 24 patients (11.0%) received postoperative adjuvant treatment before meeting the predefined BCR criteria. Eight patients (3.7%) received radiotherapy alone, six (2.8%) received ADT alone, and ten (4.6%) received combined radiotherapy and ADT. The median interval from RP to initiation of adjuvant treatment was 4.2 months (IQR, 3.0-5.8). As specified in the study protocol, these patients were censored at treatment initiation in the primary survival analysis.

3.3 LASSO Variable Selection

LASSO-penalized Cox regression was performed in the training cohort using 13 candidate clinicopathological variables. Ten-fold cross-validation identified lambda-min = 0.0052. Seven variables retained non-zero coefficients at lambda-min: preoperative PSA, biopsy Gleason score, PSM, SVI, ECE, lymph node metastasis, and PNI. Age, BMI, hypertension, diabetes mellitus, smoking history, and drinking history were shrunk to zero and excluded from subsequent multivariable modeling (Figure 1).

3.4 Multivariable Cox Proportional Hazards Regression

The seven variables identified by LASSO were entered into a multivariable Cox model in the training cohort. Six variables were independently associated with BCR-free survival at P < 0.05 (Table 2). Biopsy Gleason score >=8 had the largest estimated effect (HR = 2.78, 95% CI, 1.86-4.15; P < 0.001), followed by lymph node metastasis (HR = 2.42, 95% CI, 1.45-4.05; P = 0.001), PSM (HR = 2.15, 95% CI, 1.42-3.26; P = 0.002), SVI (HR = 1.95, 95% CI, 1.22-3.11; P = 0.005), ECE (HR = 1.68, 95% CI, 1.08-2.62; P = 0.021), and preoperative PSA per 10 ng/mL increase (HR = 1.52, 95% CI, 1.18-1.96; P = 0.001). PNI was not statistically significant (HR = 1.45, 95% CI, 0.92-2.28; P = 0.112) and was excluded from the final model. The proportional hazards assumption was not violated (global Schoenfeld test P = 0.362).

Table 2. Multivariable Cox Proportional Hazards Regression Results (Training Cohort)

Variable	beta	HR (95% CI)	SE	Z	P value
Preoperative PSA (per 10 ng/mL)	0.419	1.52 (1.18-1.96)	0.129	3.248	0.001
Biopsy Gleason score (>=8 vs <8)	1.022	2.78 (1.86-4.15)	0.205	4.985	<0.001
Positive surgical margin	0.765	2.15 (1.42-3.26)	0.213	3.592	0.002
Seminal vesicle invasion	0.668	1.95 (1.22-3.11)	0.239	2.795	0.005
Extracapsular extension	0.519	1.68 (1.08-2.62)	0.226	2.296	0.021
Lymph node metastasis	0.884	2.42 (1.45-4.05)	0.262	3.374	0.001

Abbreviations: HR, hazard ratio; CI, confidence interval; SE, standard error; PSA, prostate-specific antigen.

3.5 Nomogram Construction

A nomogram was constructed from the six independent predictors to estimate 1-, 3-, and 5-year BCR-free survival (Figure 3). Each predictor contributes a point value proportional to its regression coefficient, and the sum of points is mapped to the predicted survival probability. For example, a patient with preoperative PSA of 25 ng/mL (approximately 22 points), biopsy Gleason score of 8 (50 points), PSM (35 points), no SVI (0 points), ECE (25 points), and N0 status (0 points) would receive a total score of approximately 132 points, corresponding to an estimated 3-year BCR-free survival probability of approximately 0.62. Because of the relatively short follow-up, the 5-year estimate is presented as exploratory.

3.6 Model Validation and Comparison With CAPRA-S and TNM

The proposed nomogram achieved a C-index of 0.812 (95% CI, 0.762-0.862) in the training cohort and 0.785 (95% CI, 0.714-0.856) in the validation cohort. CAPRA-S achieved C-indices of 0.781 (95% CI, 0.729-0.833) and 0.758 (95% CI, 0.682-0.834), respectively. The absolute differences between the nomogram and CAPRA-S were 0.031 in the training cohort (bootstrap P = 0.118) and 0.027 in the validation cohort (P = 0.311), indicating a modest numerical difference without statistically significant improvement in discrimination.

The corresponding TNM C-indices were 0.683 (95% CI, 0.618-0.748) in the training cohort and 0.661 (95% CI, 0.572-0.750) in the validation cohort. In the overall-cohort time-dependent analysis, AUC values at 3 years were 0.819 (95% CI, 0.756-0.882) for the nomogram, 0.788 (95% CI, 0.718-0.858) for CAPRA-S, and 0.685 (95% CI, 0.608-0.762) for TNM. At 5 years, the corresponding AUC values were 0.798 (95% CI, 0.722-0.874), 0.773 (95% CI, 0.691-0.855), and 0.668 (95% CI, 0.582-0.754), respectively; these 5-year estimates should be interpreted cautiously because of the limited follow-up duration (Figure 5).

In the overall cohort, the 3-year Brier score was 0.168 for the nomogram, compared with 0.183 for CAPRA-S and 0.224 for TNM (Table 3). Calibration plots for the proposed nomogram showed close

agreement between predicted and observed 3-year BCR-free survival in both the training and validation cohorts (Figure 4).

Decision curve analysis at the 3-year horizon showed broadly similar net benefit for the nomogram and CAPRA-S across most threshold probabilities, with a modest numerical advantage for the nomogram between approximately 20% and 45%. The nomogram also showed higher net benefit than TNM across a broader range of clinically relevant thresholds. These results do not establish clear superiority over CAPRA-S but support comparable clinical utility in the present cohort (Figure 6).

Table 3. Comparative Predictive Performance of the Proposed Nomogram, CAPRA-S, and TNM Staging

Metric	Proposed nomogram	CAPRA-S	TNM
C-index, training	0.812 (0.762-0.862)	0.781 (0.729-0.833)	0.683 (0.618-0.748)
C-index, validation	0.785 (0.714-0.856)	0.758 (0.682-0.834)	0.661 (0.572-0.750)
3-year AUC, overall cohort	0.819 (0.756-0.882)	0.788 (0.718-0.858)	0.685 (0.608-0.762)
5-year AUC, overall cohort	0.798 (0.722-0.874)	0.773 (0.691-0.855)	0.668 (0.582-0.754)
3-year Brier score, overall cohort	0.168	0.183	0.224

Abbreviations: C-index, concordance index; AUC, area under the time-dependent receiver operating characteristic curve; CAPRA-S, Cancer of the Prostate Risk Assessment Postsurgical score. C-index values are reported separately for the training and validation cohorts; time-dependent AUC and Brier-score comparisons are overall-cohort analyses. Nomogram versus CAPRA-S C-index differences: training delta=0.031, P=0.118; validation delta=0.027, P=0.311.

3.7 Sensitivity Analyses

In a Cox model additionally adjusted for surgical approach and operating surgeon, neither surgical approach nor surgeon was independently associated with BCR (global $P > 0.05$). Inclusion of these factors resulted in less than 6% change in the regression coefficients of the six predictors retained in the original model, suggesting that the principal associations were not substantially explained by measured surgeon-related variability.

A sensitivity analysis excluding the 24 patients who received adjuvant treatment before documented BCR produced results similar to the primary analysis. The C-index was 0.808 in the training cohort and 0.780 in the validation cohort, compared with 0.812 and 0.785, respectively, in the primary analysis. The

direction and magnitude of associations for PSA, biopsy Gleason score, PSM, SVI, ECE, and lymph node involvement were largely unchanged.

In the additional full-cohort bootstrap analysis, the apparent C-index was 0.803 and the optimism-corrected C-index was 0.791. The optimism-corrected calibration slope was 0.93, indicating limited but measurable model optimism and providing results broadly consistent with the holdout validation analysis.

3.8 Risk Stratification Based on Nomogram Scores

Nomogram-based risk-group cutoffs were derived exclusively from the training cohort. The 33.3rd and 66.7th percentiles corresponded to total scores of 98 and 168. These cutoffs classified 53, 60, and 40 patients in the training cohort as low, intermediate, and high risk, respectively. When applied without modification to the validation cohort, 25, 25, and 15 patients were classified into the corresponding groups. Thus, the overall cohort included 78 low-risk, 85 intermediate-risk, and 55 high-risk patients. Because several patients had tied scores at the prespecified percentile cutoffs, the group sizes were not exactly equal.

Kaplan-Meier analysis demonstrated significant separation of BCR-free survival among the three nomogram-defined risk groups (log-rank $P < 0.001$) (Figure 7A). Estimated 3-year BCR-free survival was 87.2% (95% CI, 79.5-94.9%) in the low-risk group, 58.4% (95% CI, 47.1-69.7%) in the intermediate-risk group, and 26.8% (95% CI, 14.9-38.7%) in the high-risk group. The nomogram-based high-risk classification also showed clearer separation than TNM stage III in the descriptive comparison shown in Figure 7B.

4. Discussion

In this retrospective single-center cohort, we developed and internally validated a six-variable nomogram for BCR after RP and directly compared it with CAPRA-S and TNM staging. The proposed model showed C-indices of 0.812 in the training cohort and 0.785 in the validation cohort. CAPRA-S achieved corresponding C-indices of 0.781 and 0.758. Although the nomogram showed numerically higher discrimination and a lower 3-year Brier score, the C-index differences relative to CAPRA-S were modest and not statistically significant. The model should therefore be interpreted as a population-specific individualized risk tool rather than as a demonstrated replacement for established postoperative prediction models.

The six predictors retained in the nomogram-preoperative PSA, biopsy Gleason score, PSM, SVI, ECE, and lymph node metastasis-are established clinicopathological determinants of recurrence after RP [5,6,10,14-16]. Their selection is therefore clinically plausible but does not represent discovery of novel biological risk factors. The contribution of the current analysis lies instead in estimating their joint effects in this cohort and translating them into continuous individualized risk estimates.

The direct comparison with CAPRA-S is important because the variables in the proposed model overlap substantially with those used in established postoperative tools. In the present cohort, the nomogram showed a numerical improvement in C-index of 0.031 in the training cohort and 0.027 in the validation cohort, but neither difference reached statistical significance. The 3-year Brier score was also numerically lower for the nomogram. Decision curve analysis showed broadly similar net benefit for the nomogram and CAPRA-S across most thresholds, with only a modest numerical advantage over part of the threshold range. These findings suggest that any potential value of the proposed model is more likely to arise from population-specific weighting, calibration, and continuous risk estimation than from a large increase in discrimination over CAPRA-S. Independent external validation is required before incremental clinical value can be established.

The relatively high BCR proportion in this cohort (119/218, 54.6%) warrants specific consideration. The study population contained a substantial proportion of patients with adverse clinicopathological features: 39.9% had biopsy Gleason score >=8, 28.4% had PSM, 25.2% had ECE, 16.1% had SVI, and 14.7% had lymph node metastasis. This adverse case mix is consistent with a cohort enriched for biologically aggressive or pathologically advanced disease compared with many unselected contemporary RP series. Accordingly, the absolute recurrence rate observed here should not be directly extrapolated to lower-risk or population-based cohorts.

Surgeon-related variability was also examined because surgical technique may influence margin status, lymph node assessment, and recurrence. The four surgeons had similar PSM and BCR event rates, and adjustment for surgeon and surgical approach did not materially alter the coefficients of the six final predictors. Nevertheless, the sample size limits power to exclude smaller surgeon effects, and detailed anatomical templates for PLND were not uniformly available in the retrospective records. PLND was performed in all patients, with a median yield of 11 lymph nodes, but residual heterogeneity in surgical technique and dissection extent cannot be completely excluded.

Postoperative treatment is another potential source of bias in recurrence analyses. Twenty-four patients received adjuvant radiotherapy and/or ADT before documented BCR and were censored at treatment initiation in the primary analysis. Excluding these patients produced C-indices close to those of the main analysis and did not materially alter the direction or magnitude of the six predictor associations. These results reduce, but do not eliminate, concern that early postoperative treatment materially drove the principal findings.

The additional bootstrap analysis provides complementary information to the single 70:30 split. In the complete cohort, the apparent C-index was 0.803, the optimism-corrected C-index was 0.791, and the optimism-corrected calibration slope was 0.93. These results suggest limited but measurable model optimism. They should still be regarded as internal validation rather than external validation because all observations originated from the same institution and underlying clinical setting.

The relatively short median follow-up of 24.0 months is an important limitation, particularly for interpretation of 5-year predictions. Although time-to-event methods can estimate survival probabilities

beyond the median follow-up among patients who remain under observation, fewer patients contribute information at later time points and uncertainty increases. Therefore, the 5-year BCR-free survival estimates in this study should be regarded as exploratory. The 1- and 3-year predictions are supported by more follow-up information and represent the more robust time horizons of the current model. Longer-term external validation is required before the 5-year estimates can be considered clinically established.

The risk-group analysis may facilitate communication of postoperative recurrence risk, but the cutoffs should not be interpreted as treatment thresholds. The score cutoffs of 98 and 168 were derived only from the training cohort and then applied unchanged to the validation cohort, reducing information leakage. Because several patients had tied scores at the percentile boundaries, the resulting group sizes were not exactly equal. Prospective validation is necessary before these categories are used to determine adjuvant treatment or surveillance intensity.

Several limitations remain. First, the study was retrospective and single-center, with a total sample size of 218 and a holdout validation cohort of only 65 patients. Second, no independent external cohort was available, and the additional bootstrap analysis remains an internal-validation procedure. Third, the follow-up duration was relatively short for long-term BCR prediction. Fourth, although measured surgeon and surgical-approach effects were explored, residual differences in surgical technique and PLND templates may remain. Fifth, the model is based on conventional clinicopathological variables and does not incorporate molecular classifiers or advanced imaging biomarkers that may add prognostic information [30]. Future multi-institutional studies with longer follow-up should externally validate the model, assess calibration across different case mixes, and determine whether it adds clinically meaningful information beyond established tools such as CAPRA-S.

5. Conclusions

We developed and internally validated a nomogram integrating preoperative PSA, biopsy Gleason score, PSM, SVI, ECE, and lymph node metastasis for individualized BCR risk estimation after RP. The model showed good internal discrimination and calibration in the present cohort and numerically outperformed CAPRA-S and TNM on several performance measures; however, the incremental C-index improvement over CAPRA-S was modest and not statistically significant. The model should therefore be considered an internally validated, population-specific prediction tool. Independent external validation and longer follow-up are required before routine clinical application, particularly for 5-year risk estimation.

Declarations

Ethics approval and consent to participate (Human Ethics and Consent to Participate declarations)

This study involving human participants and human data was reviewed and approved by the Ethics Committee of the Second Affiliated Hospital of Shantou University Medical College. The study was conducted in accordance with the Declaration of Helsinki. The requirement for individual informed consent to participate was waived by the Ethics Committee of the Second Affiliated Hospital of Shantou

University Medical College because of the retrospective nature of the study and the use of de-identified clinical data.

Clinical trial number

Clinical trial number: not applicable (this study is a retrospective cohort study and not a clinical trial).

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 author declares that there are no competing interests.

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Authors' contributions

Derong Zhou conceived and designed the study, collected and analysed the data, interpreted the results, drafted the manuscript, revised it critically for important intellectual content, and approved the final manuscript.

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Not applicable.

References

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229–63.
2. Schafer EJ, Laversanne M, Sung H, et al. Recent patterns and trends in global prostate cancer incidence and mortality: an update. Eur Urol. 2025;87(3):302–13.
3. Chen R, Ren S, Yiu MK, et al. Prostate cancer in Asia: a collaborative report. Asian J Urol. 2014;1(1):15–29.

4. Cornford P, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines on Prostate Cancer-2024 Update. Part I: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol. 2024;86(2):148–63.
5. Freedland SJ, Humphreys EB, Mangold LA, et al. Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. JAMA. 2005;294(4):433–9.
6. Pound CR, Partin AW, Eisenberger MA, et al. Natural history of progression after PSA elevation following radical prostatectomy. JAMA. 1999;281(17):1591–7.
7. Van den Broeck T, van den Bergh RCN, Arfi N, et al. Prognostic value of biochemical recurrence following treatment with curative intent for prostate cancer: a systematic review. Eur Urol. 2019;75(6):967–87.
8. Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. J Urol. 2009;181(3):956–62.
9. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA. 1998;280(11):969–74.
10. Cooperberg MR, Hilton JF, Carroll PR. The CAPRA-S score: a straightforward tool for improved prediction of outcomes after radical prostatectomy. Cancer. 2011;117(22):5039–46.
11. Seong KT, Lim JH, Park CM, et al. External validation of the Cancer of the Prostate Risk Assessment-S score in Koreans undergoing radical prostatectomy. Korean J Urol. 2013;54(7):433–6.
12. Iasonos A, Schrag D, Raj GV, et al. How to build and interpret a nomogram for cancer prognosis. J Clin Oncol. 2008;26(8):1364–70.
13. Balachandran VP, Gonen M, Smith JJ, et al. Nomograms in oncology: more than meets the eye. Lancet Oncol. 2015;16(4):e173–80.
14. Bejrananda T, Takahara K, Sowanthip D, et al. Biochemical recurrence prediction after robot-assited radical prostatectomy (BCR-PRARP). Heliyon. 2025;11(1):e41031.
15. Xia HZ, Bi H, Yan Y, et al. A novel nomogram provides improved accuracy for predicting biochemical recurrence after radical prostatectomy. Chin Med J (Engl). 2021;134(13):1576–83.
16. Stephenson AJ, Scardino PT, Eastham JA, et al. Postoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. J Clin Oncol. 2005;23(28):7005–12.
17. Tibshirani R. The lasso method for variable selection in the Cox model. Stat Med. 1997;16(4):385–95.
18. Friedman J, Hastie T, Tibshirani R. Regularization paths for generalized linear models via coordinate descent. J Stat Softw. 2010;33(1):1–22.
19. Simon N, Friedman J, Hastie T, et al. Regularization paths for Cox's proportional hazards model via coordinate descent. J Stat Softw. 2011;39(5):1–13.

20. Collins GS, Reitsma JB, Altman DG, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD): the TRIPOD statement. Ann Intern Med. 2015;162(1):55–63.
21. Cookson MS, Aus G, Burnett AL, et al. Variation in the definition of biochemical recurrence in patients treated for localized prostate cancer: the American Urological Association Prostate Guidelines for Localized Prostate Cancer Update Panel report and recommendations for a standard in the reporting of surgical outcomes. J Urol. 2007;177(2):540–5.
22. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med. 1996;15(4):361–87.
23. Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. Med Decis Mak. 2006;26(6):565–74.
24. Stamey TA, McNeal JE, Yemoto CM, et al. Biological determinants of cancer progression in men with prostate cancer. JAMA. 1999;281(15):1395–400.
25. Guo H, Zhang L, Shao Y, et al. The impact of positive surgical margin parameters and pathological stage on biochemical recurrence after radical prostatectomy: a systematic review and meta-analysis. PLoS ONE. 2024;19(7):e0301653.
26. Carbonell E, Matheu R, Muní M, et al. The effect of adverse surgical margins on the risk of biochemical recurrence after robotic-assisted radical prostatectomy. Biomedicines. 2022;10(8):1911.
27. Kattan MW, Wheeler TM, Scardino PT. Postoperative nomogram for disease recurrence after radical prostatectomy for prostate cancer. J Clin Oncol. 1999;17(5):1499–507.
28. Boorjian SA, Thompson RH, Siddiqui S, et al. Long-term outcome after radical prostatectomy for patients with lymph node positive prostate cancer in the prostate specific antigen era. J Urol. 2007;178(3 Pt 1):864–70.
29. Riley RD, Ensor J, Snell KIE, et al. Calculating the sample size required for developing a clinical prediction model. BMJ. 2020;368:m441.
30. Spratt DE, Yousefi K, Deheshi S, et al. Individual patient-level meta-analysis of the performance of the Decipher genomic classifier in high-risk men after prostatectomy to predict development of metastatic disease. J Clin Oncol. 2017;35(18):1991–8.

Figures

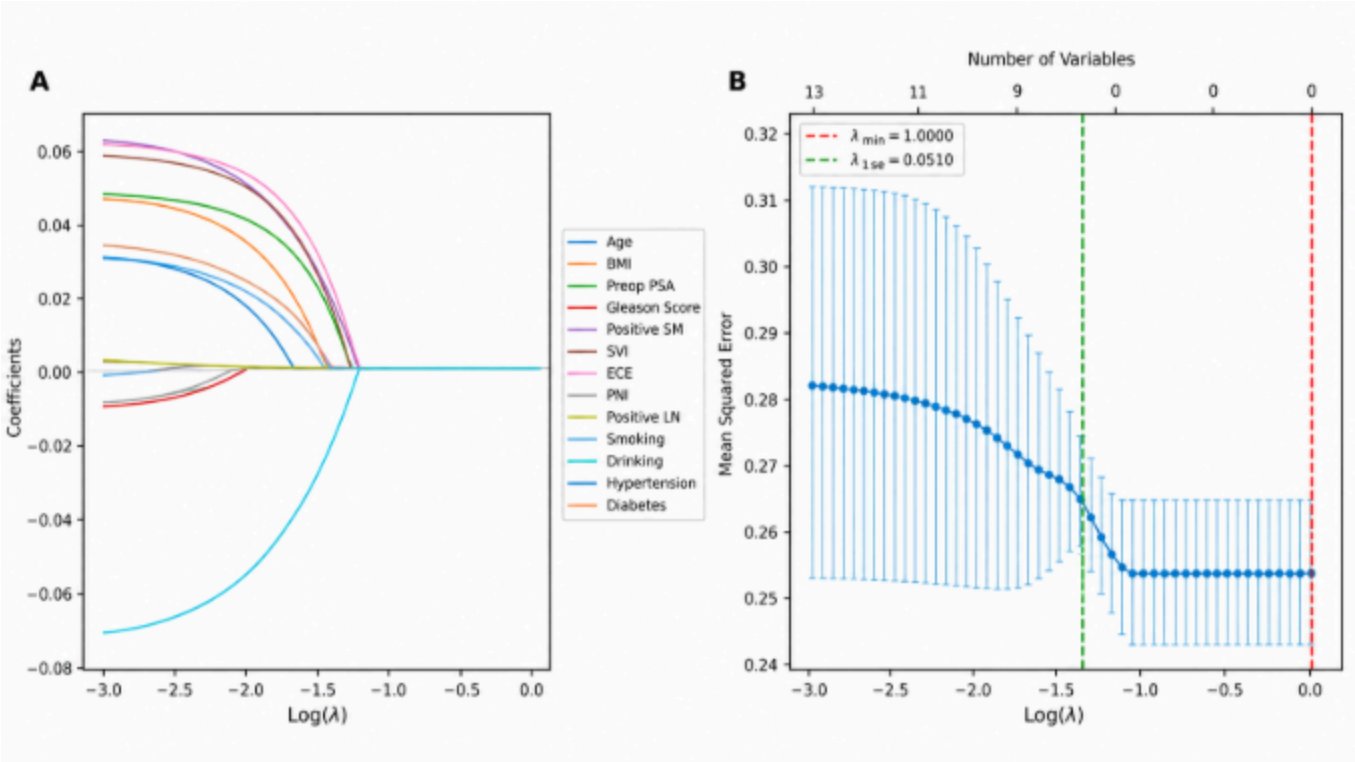


Figure 1

LASSO regression analysis for variable selection. (A) LASSO coefficient profiles of the 13 candidate variables. (B) Ten-fold cross-validation for tuning-parameter selection; vertical dashed lines indicate lambda-min and lambda-1se.

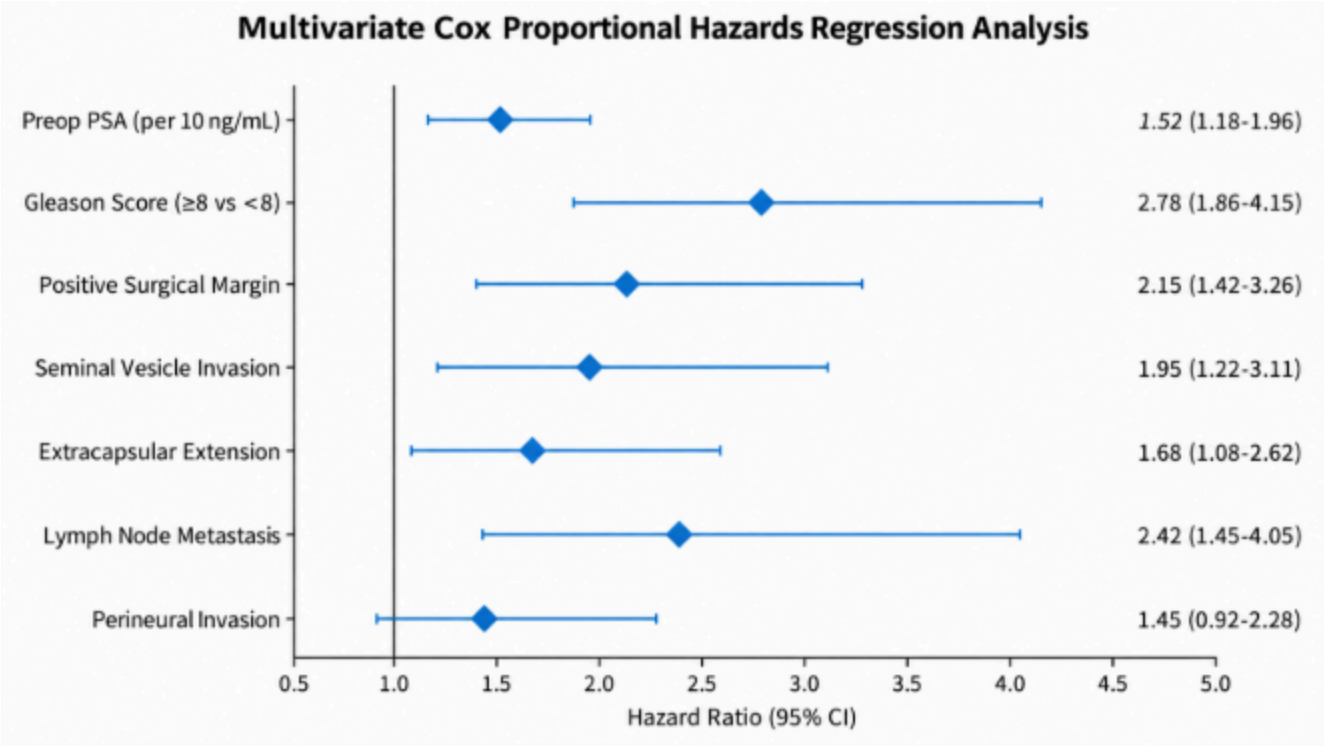


Figure 2

Forest plot of multivariable Cox proportional hazards regression analysis. Diamonds represent hazard ratios and horizontal lines represent 95% confidence intervals; the vertical dashed line at HR = 1 indicates no effect.

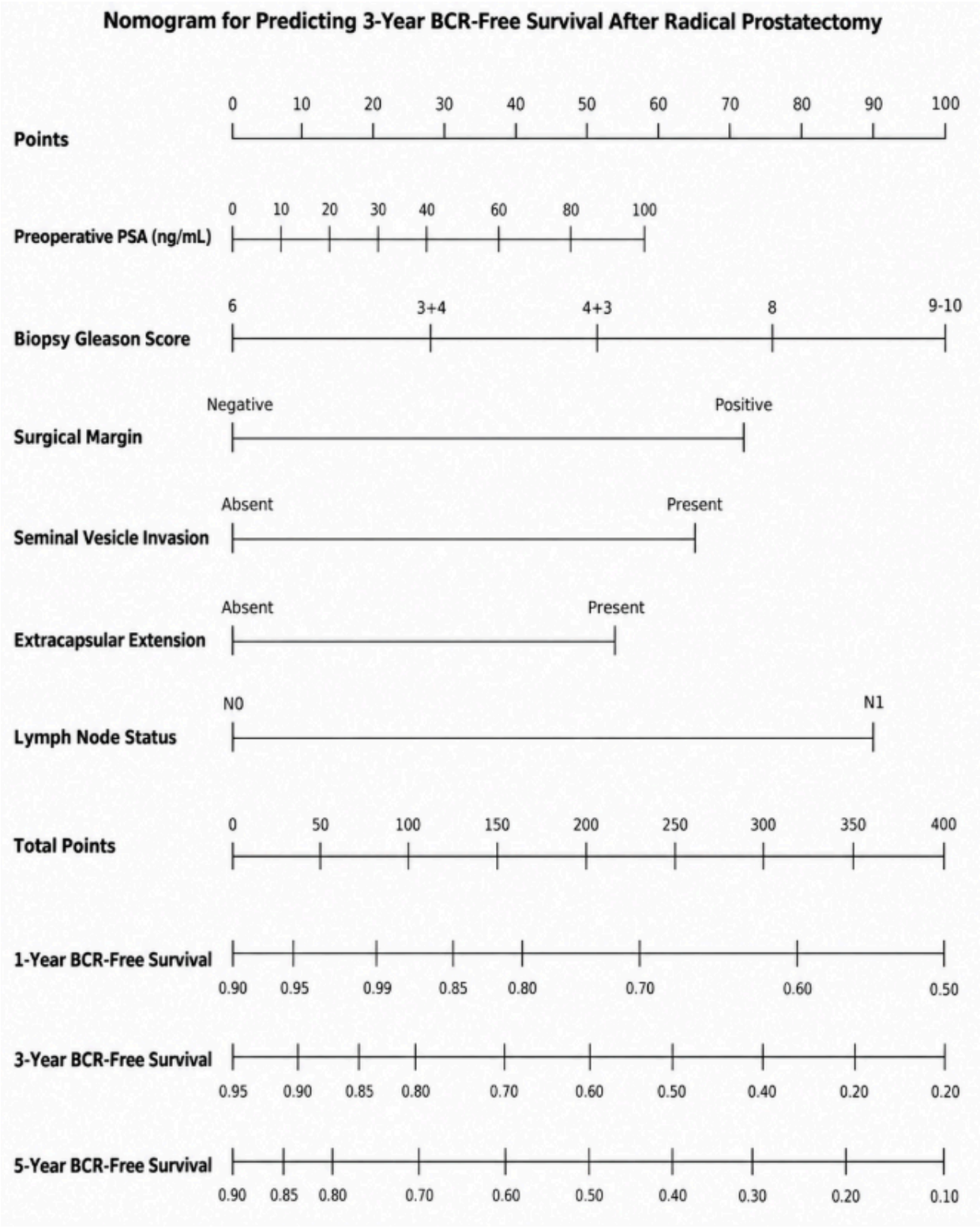


Figure 3

Nomogram for predicting 1-, 3-, and 5-year biochemical recurrence-free survival after radical prostatectomy. Each variable corresponds to a point value; the sum of points is projected to the predicted survival probability. The 5-year estimate should be interpreted as exploratory because of limited long-term follow-up.

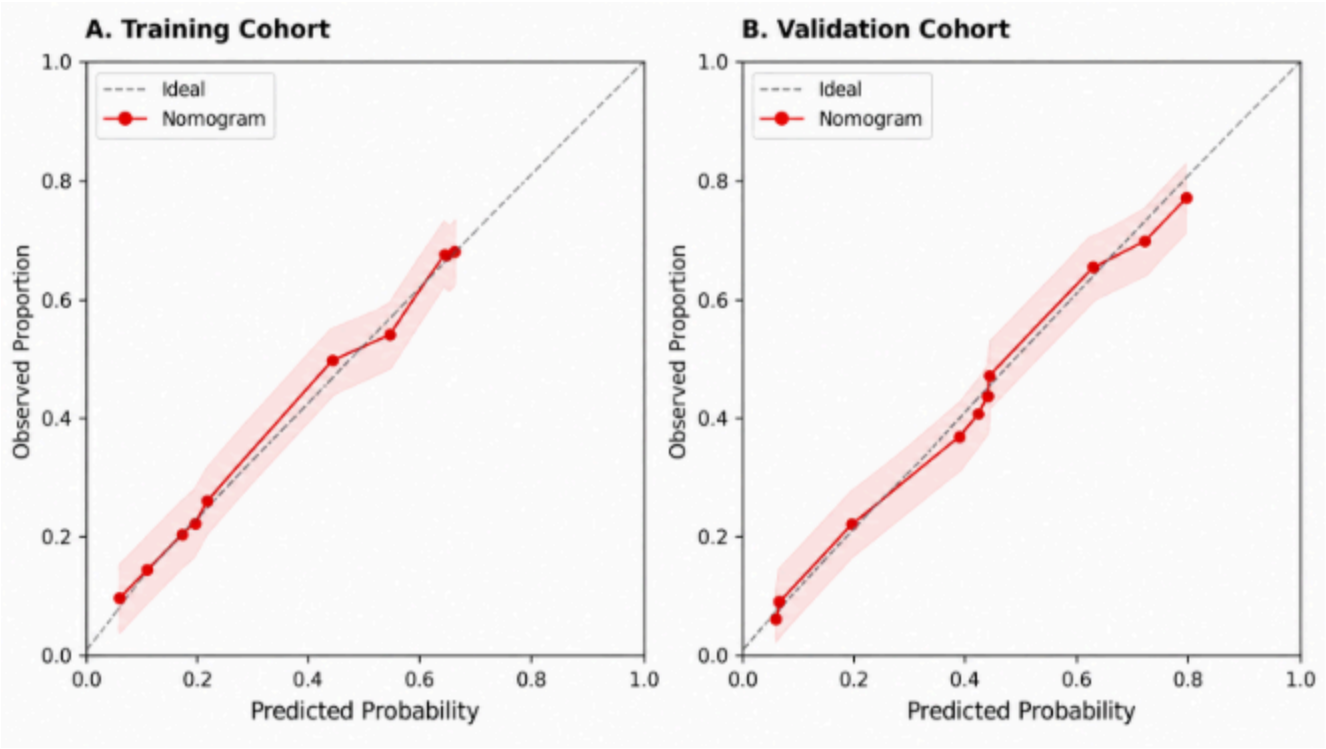


Figure 4

Calibration curves for 3-year biochemical recurrence-free survival in the training cohort (A) and validation cohort (B). The diagonal line represents ideal calibration.

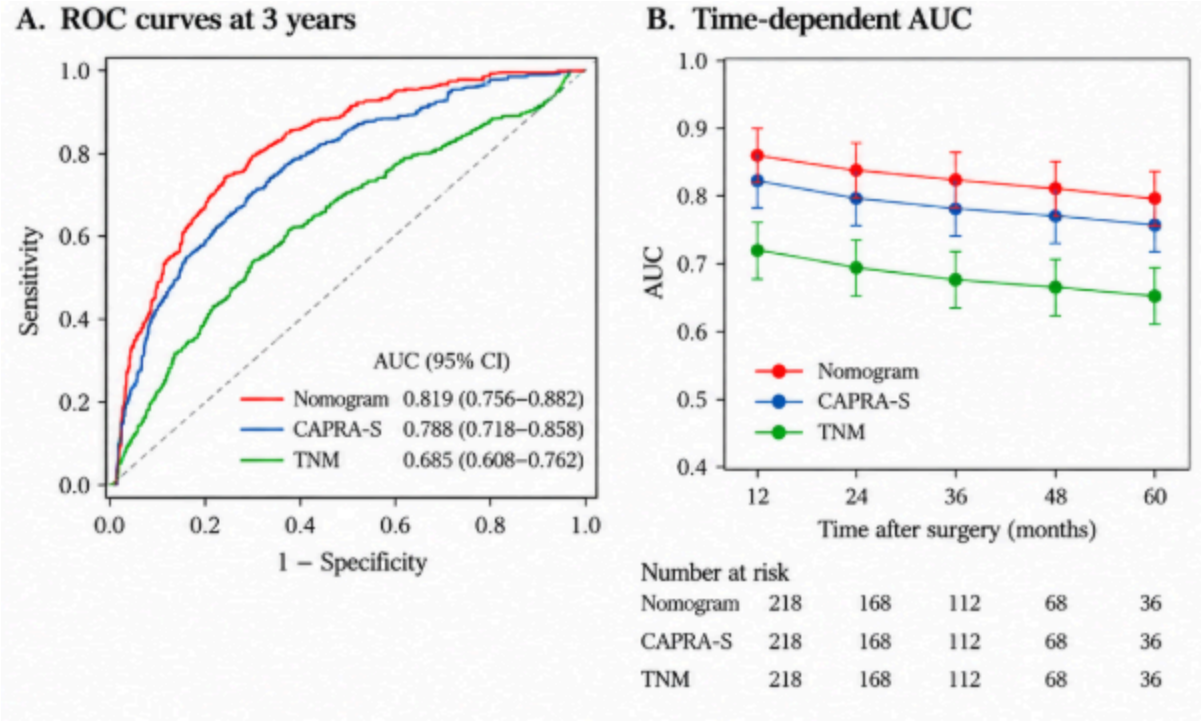


Figure 5

Discrimination of the proposed nomogram compared with CAPRA-S and TNM staging. (A) Time-dependent receiver operating characteristic curves at 3 years, with area under the curve (AUC) and 95% confidence intervals. (B) Time-dependent AUCs from 12 to 60 months with 95% confidence intervals and numbers at risk. Estimates at 60 months should be interpreted cautiously because fewer patients remained under observation.

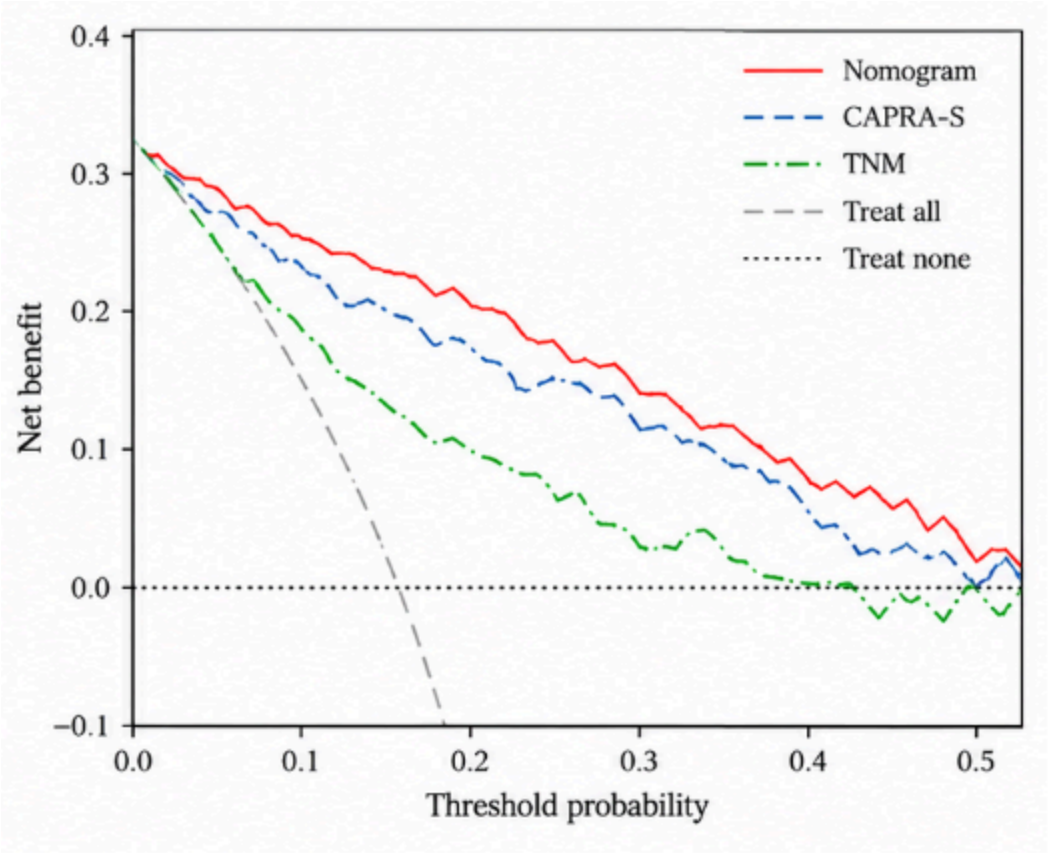


Figure 6

Decision curve analysis at the 3-year horizon comparing the proposed nomogram, CAPRA-S, TNM staging, and the default treat-all and treat-none strategies. Net benefit was estimated using a survival-outcome approach accounting for censoring.

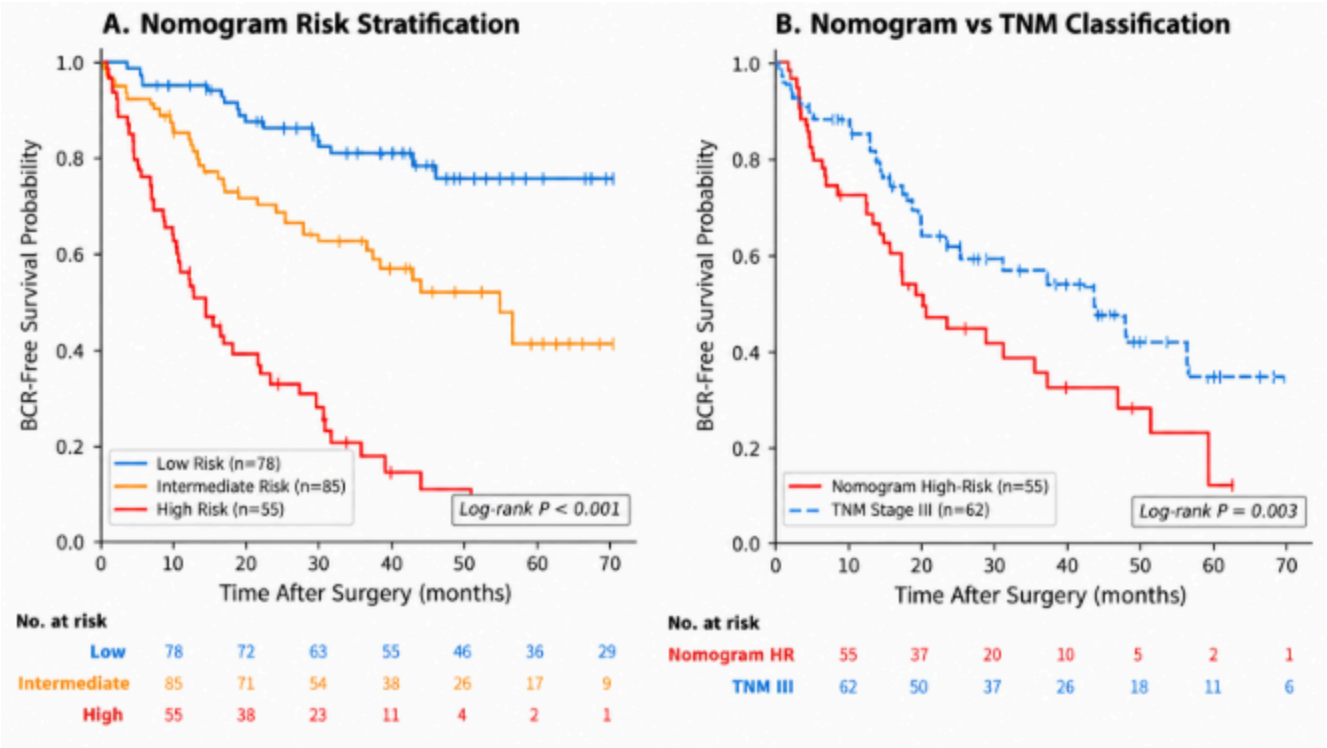


Figure 7

Kaplan-Meier biochemical recurrence-free survival curves. (A) Nomogram-based low-, intermediate-, and high-risk groups using training-derived score cutoffs of 98 and 168. (B) Descriptive comparison of the nomogram high-risk group and TNM stage III classification.