Research Article

# The Predictive Value of Systemic Inflammation Score for Adverse Pathology and Biochemical Recurrence in Prostate Cancer Patients Following Radical Prostatectomy

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**Abstract**

**Objective:** To investigate the predictive value of the systemic inflammation score (SIS) for adverse pathology (AP) and biochemical recurrence (BCR) in prostate cancer (PCa) patients undergoing radical prostatectomy (RP), and further develop and validate predictive nomograms based on SIS.

**Background:** The SIS based on serum albumin (ALB) level and lymphocyte to monocyte ratio (LMR), has been verified as a potential biomarker in several types of cancers. However, its impact on the AP and prognosis of PCa remains unclear.

**Methods:** A retrospective analysis was conducted on 516 PCa patients who underwent RP in our institution from 2010 to 2020. The enrolled patients were randomly divided into a training cohort (n=361) and a validation cohort (n=155) in a 7:3 ratio. The nomograms based on SIS were established according to independent predictors identified by multivariate Cox and logistic regression analyses.

**Results:** In the training cohort, the multivariate Cox regression analysis demonstrated that SIS, platelet-lymphocyte ratio (PLR), percentage of positive biopsy cores (PPC) and postoperative prostate-specific antigen (PSA) nadir were independent predictors for BCRFS. The multivariate logistic regression analysis demonstrated that SIS, ALB, PSA and PPC were independent predictors for high-grade (HG), while SIS, PSA density (PSAD) and PPC were independent predictors for lymph node metastasis (LNM). The C-indexes of the nomograms for predicting BCRFS, HG and LNM were 0.731 (95% CI=0.677-0.785), 0.811 (95% CI=0.766-0.855), 0.817 (95%CI=0.764-0.870) in the training cohort and 0.732 (95% CI=0.634-0.830), 0.845 (95% CI=0.785-0.905) and 0.867 (95%CI=0.808-0.926) in the validation cohort. The calibration curves and decision curve analysis further confirmed the reliability and clinical applicability of the nomograms in both training and validation cohorts.

**Conclusion:** The SIS is significantly associated with BCRFS, HG and LNM in PCa patients treated with RP, which could serve as a promising and powerful biomarker.

**Keywords:** *Prostate cancer, radical prostatectomy, systemic inflammation score, adverse pathology, biochemical recurrence*

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## 1. Introduction

Prostate cancer (PCa) is the most common malignant tumor in the male urogenital system and the second leading cause of cancer-related deaths among men worldwide [1]. In the United States alone, it is estimated that there will be around 299,010 new cases of PCa and 35,250 PCa-related deaths in 2024 [2]. Radical prostatectomy (RP) is regarded as the standard treatment for eligible PCa patients with localized

disease [3]. While the majority of RP patients experience favorable rates of biochemical recurrence-free survival (BCRFS), ranging from 73% to 88% over 10 years [4, 5], some individuals will eventually experience relapse. Patients with BCR exhibit significantly worse prognosis due to the increased risk of progression to distant metastases and cancer-specific mortality [6].

Therefore, it is crucial to identify reliable prognostic factors for BCR after RP to guide clinical decision-making and patient counseling. Currently, several traditional clinicopathological factors have been identified as prognostic factors for BCR after RP, such as preoperative prostate-specific antigen (PSA) levels, Gleason score (GS), tumor stage, positive surgical margin, extracapsular extension (ECE) and seminal vesicle invasion (SVI) [7-10]. However, these factors have limitations and irreversible nature, making them unsatisfactory for predicting BCRFS after RP. Consequently, there is an urgent need for a more reliable and reversible prognostic factor to better predict oncological outcomes. In addition, given the significant effect of adverse pathology (AP) on BCR, exploring the potential risk factors of these adverse pathological features and accurately predicting them, which can provide guidance for the preoperative treatment options and postoperative effective management of RP as well.

Cancer-related inflammation is currently recognized as an important hallmark of cancer, characterized by the presence of inflamed tissue, including inflammatory cell infiltration and an activated stroma [11]. Apart from local inflammatory symptoms, many cancer patients, especially those in advanced stages, also experience a systemic inflammatory response. This response is marked by changes in peripheral hematological indicators and levels of inflammation-linked proteins, which play a vital role in the development and progression of cancer [12]. Thus, a range of inflammatory biomarkers based on circulating blood cells and serum proteins have been developed to predict the progression and prognosis of various tumors, such as neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR), C-reactive proteins (CRP)-to-albumin ratio (CAR) and modified Glasgow prognostic score (mGPS) [13-16]. These biomarkers are easily accessible in routine clinical practice at a low healthcare cost, which can provide readily available and objective information to help oncologists evaluate patient outcomes.

However, there is currently no widely accepted inflammatory scoring system for predicting the outcomes of cancer. The systemic inflammation score (SIS), which combines serum albumin (ALB) level and the LMR, was first created by Chang *et al.* [17] as a novel marker for assessing the inflammatory and nutritional status of patients. Previous studies have proven that SIS is a powerful prognostic marker for various types of cancers, including clear-cell renal cell carcinoma (ccRCC), colorectal cancer, and gastric cancer [17-19]. As for PCa, Xie J *et al.* [20] conducted the only study confirming that a higher SIS is associated with unfavorable overall survival (OS) and progression-free survival (PFS) in patients with PCa, but its relationship with BCR remains unclear. In addition, no studies have investigated the predictive role of SIS in adverse pathology of PCa patients. Therefore, to fill the gaps in related fields, this study was conducted to explore the predictive value of SIS for BCR and adverse pathology in PCa patients following RP, and further develop relevant nomograms based on SIS for risk assessment and management strategy guidance in PCa patients.

## 2. Methods

### 2.1. Study Population

We retrospectively assessed 895 PCa patients who underwent RP between January 2010 and December 2020 in the Department of Urology at Peking University Third Hospital (PUTH). Comprehensive clinicopathologic data for each patient were reviewed and collected carefully. Patients who met the following criteria were excluded: i) Patients with pathological types other than adenocarcinoma. ii) Patients who had received neoadjuvant therapy. iii) Patients with incomplete clinicopathologic information or follow-up information. Consequently, a total of 516 PCa patients were deemed eligible for

further analysis. To ensure the reliability and generalizability of our findings, the eligible patients were randomly divided into a training cohort (n=361) and a validation cohort (n=155) in a 7:3 ratio. The flow chart of this study is presented in (Figure 1). This study was conducted in compliance with the Declaration of Helsinki and approved by the Medical Science Research Ethics Committee of PUTH (No. S2020380).

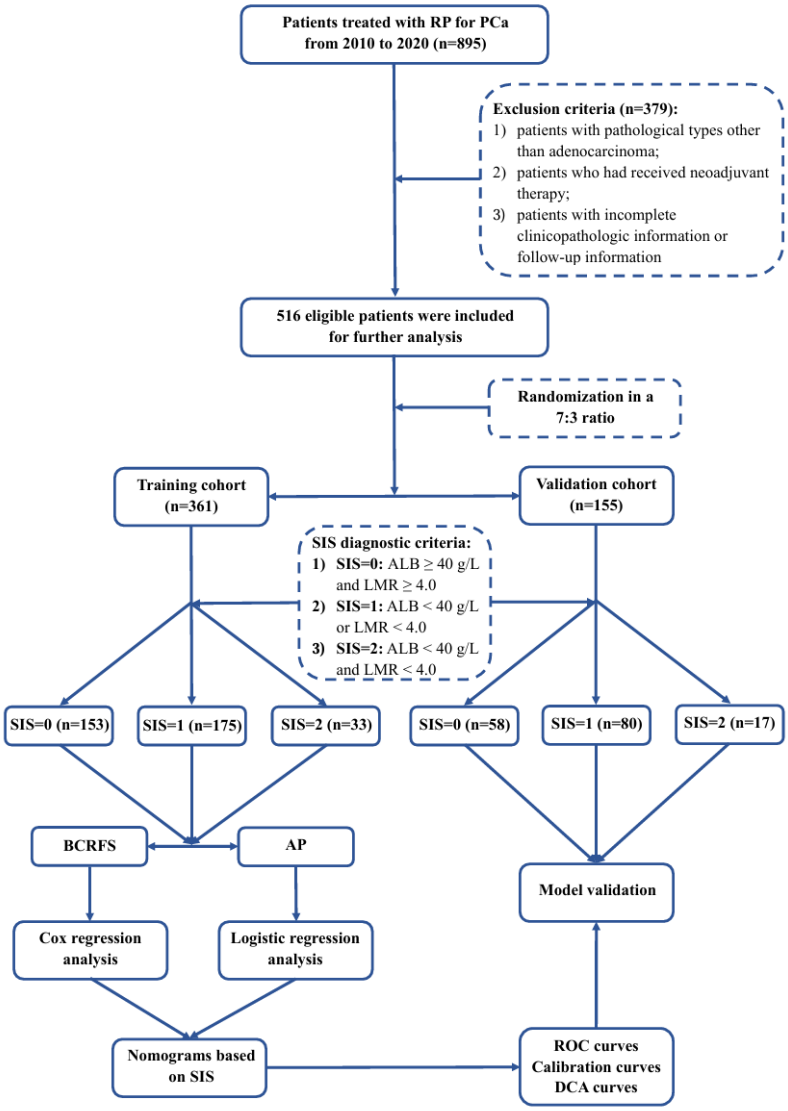



**FIGURE 1.** The flow chart of this study.

ALB: Albumin; AP: Adverse Pathology; BCR: Biochemical Recurrence; BCRFS: BCR-Free Survival; DCA: Decision Curve Analysis; LMR: Lymphocyte-Monocyte Ratio; PCa: Prostate Cancer; ROC: Receiver Operating Characteristic; RP: Radical Prostatectomy; SIS: Systemic Inflammation Score.

### 2.2. Data Extraction and Variable Definition

The clinical and pathological information of the enrolled patients was comprehensively collected, including age, body mass index (BMI), serum ALB level, LMR, NLR, PLR, SIS, percentage of positive biopsy cores (PPC), preoperative PSA level, PSA density (PSAD), postoperative PSA nadir, pathologic T stage, lymph node status, pathologic GS, surgical margin status, ECE and SVI. All study patients underwent blood routine and biochemical tests within 3 days before surgery, during which relevant

information on albumin and inflammatory biomarkers was collected for further analysis. The LMR, NLR and PLR were calculated using the following formula: LMR as the lymphocyte count ($10^9$/L) divided by the monocyte count ($10^9$/L); NLR as the neutrophil count ($10^9$/L) divided by the lymphocyte count ($10^9$/L); and PLR as the platelet count divided by the lymphocyte count ($10^9$/L).

The SIS was established by integrating the serum ALB level and LMR. We adopt the median of LMR (4.0) in this study as a reference value for restricted cubic spline (RCS) analysis and found that LMR=4.0 has excellent discrimination in both BCRFS and various types of adverse pathology (Supplementary Figure 1). Therefore, we used 4.0 as the cut-off value for LMR and combined with the lower limit of the normal range of ALB (40 g/L) to define the SIS: A score of 0 was assigned as ALB ≥40 g/L and LMR ≥4.0; a score of 1 was assigned as either ALB <40 g/L or LMR <4.0; and a score of 2 was assigned as ALB <40 g/L and LMR <4.0 [17]. PPC was calculated by dividing the total number of positive biopsy cores by the total number of biopsy cores obtained. PSAD was calculated by dividing the total PSA (tPSA) by prostate volume (PV). PV was determined using transrectal ultrasonography (TURS) or mp-MRI, and was calculated using the formula: (anteroposterior diameter) × (left and right diameter) × (upper and lower diameter) × 0.52. PSA nadir was defined as the lowest serum PSA level recorded in the first two follow-ups after RP without adjuvant therapy. PSA nadir was categorized as either undetectable (<0.01ng/mL) or detectable PSA (≥0.01ng/mL) [8].

All surgical specimens after RP were processed according to standard pathological procedures. Pathologic report was standardized according to the histological/architectural thresholds proposed by the 2016 WHO classification of tumor of the urinary system and male genital organs [21]. Pathologic staging was performed according to the American Joint Committee on Cancer (AJCC) 8th edition TNM staging system [22]. The Gleason grade was adopted according to the International Society of Urological Pathology (ISUP) 2014 consensus conferences [23]. The presence of any of the following pathological features was defined as adverse pathology (AP): non-organ confined disease (NOCD), lymph node metastasis (LNM), high-grade (HG), ECE and SVI. NOCD was defined as pathologic T stage ≥ pT3. HG was defined as pathologic Gleason score ≥ 8 (ISUP ≥ 4). LNM, ECE and SVI were determined based on postoperative pathologic report.

### 2.3. Follow-Up

All patients in our study were monitored through regular serum PSA assessments and clinical visits at specific intervals. During the first 2 years after surgery, assessments were conducted every 3 months. After that, the frequency was reduced to semiannual assessments for the following 2 years, and subsequently, annual follow-ups were conducted. The primary endpoint in our study was early BCR, defined as the presence of two consecutive postoperative PSA levels ≥0.2 ng/ml [24]. The date of recurrence was determined as the day when the PSA level first reached 0.2 ng/mL or higher. BCRFS was calculated from the date of surgery until the date of BCR or the last follow-up for patients without BCR.

### 2.4. Statistical Analysis

According to the distribution of data, all continuous variables in this study did not conform to normal distribution after being evaluated by the Shapiro-Wilk test for the normality tests, and were presented as the median and interquartile range (IQR). Non-normally distributed variables were compared using the Mann-Whitney U test or the Kruskal-Wallis test. Categorical variables were expressed as numbers and frequencies, and were compared using the $\chi 2$ test or Fisher's exact test. Restricted cubic spline (RCS) regression analysis was conducted to examine the association between continuous values of LMR and BCRFS and AP with three knots. The survival curves of BCRFS were estimated using the Kaplan-Meier method with the log-rank test. Univariate and multivariate Cox proportional hazards regression models were performed to evaluate predictors of BCRFS, with results presented as hazard ratio (HR) and 95% confidence interval (95% CI). Univariate and multivariate logistic regression models were

performed to evaluate predictors of AP, with results presented as odds ratio (OR) and 95% CI. The predictive nomograms were established based on the results of the multivariate Cox and logistic regression analysis.

The discrimination ability of the nomograms was estimated using Harrell's concordance index (C-index) and the area under the receiver operating characteristic (ROC) curve. Calibration curves of the nomograms were plotted to evaluate the consistency between the nomograms' predication and actual observation. In addition, we adopted the decision curve analysis (DCA) to determine the net benefit of the prediction models to further assess the clinical applicability of the nomograms. For the validation of the nomograms, internal validation was performed using the bootstrap technique with repeated sampling (1000 bootstrap resamples) [25], while external validation was conducted using data from the validation cohort. In the external validation, each case in the validation cohort was assigned a total point based on the established nomograms. These points were then used as factors in the Cox and logistic regression model to derive the validation C-index, area under curve (AUC) of the ROC curves, calibration curves and DCA curves [26]. All statistical analyses were conducted using R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria). A two-sided P value <0.05 was considered statistically significant.

## 3. Results

### 3.1. Clinicopathologic Characteristics of Patients

A total of 516 patients who underwent RP for PCa were included in the study. The entire cohort was randomly divided into a training cohort (n=361) and a validation cohort (n=155) in a 7:3 ratio. Except for PLR ($P$=0.028) and surgical margin ($P$=0.020), there were no statistically significant differences in baseline characteristics between the two cohorts. The clinicopathologic characteristics of the training cohort and the validation cohort are presented in (Supplementary Table 1).

The patients in the training cohort were categorized into three groups according to their SIS: 153 (42.4%) patients in the SIS=0 group, 175 (48.5%) patients in the SIS=1 group, and 33 (9.1%) patients in the SIS=2 group. A higher SIS was associated with higher levels of NLR ($P$<0.001) and PLR ($P$<0.001), as well as higher risk of BCR ($P$<0.001). As for AP, SIS was only associated with HG ($P$=0.004) and LNM ($P$<0.001). There were no significant differences in age, BMI, PPC, preoperative PSA level, PSAD, postoperative PSA nadir, pathologic T stage, surgical margin, ECE and SVI among the three groups. The clinicopathologic characteristics of patients stratified by SIS in the training cohort are shown in (Table 1).

**TABLE 1.** Clinicopathologic characteristics of patients stratified by SIS in the training cohort.

| Characteristics | Training cohort (n=361) | | | |
|---|---|---|---|---|
| | SIS=0 (n=153) | SIS=1 (n=175) | SIS=2 (n=33) | *P* value |
| Age (years), median (IQR) | 68.0 (63.0-74.0) | 70.0 (65.0-76.0) | 71.0 (67.0-75.0) | 0.051 |
| BMI (kg/m$^2$), n (%) | | | | 0.438 |
| <25 | 78 (51.0%) | 100 (57.1%) | 16 (48.5%) | |
| ≥25 | 75 (49.0%) | 75 (42.9%) | 17 (51.5%) | |
| ALB (g/L), median (IQR) | 43.3 (41.7-45.0) | 43.1 (41.0-45.4) | 37.8 (37.2-38.9) | <0.001* |
| NLR, median (IQR) | 1.9 (1.5-2.5) | 2.8 (2.1-3.7) | 2.7 (2.0-4.4) | <0.001* |
| PLR, median (IQR) | 112.3 (91.5-140.4) | 139.8 (104.4-178.9) | 114.8 (100.8-172.2) | <0.001* |
| LMR, median (IQR) | 5.3 (4.5-6.2) | 3.3 (2.7-3.8) | 2.9 (2.3-3.5) | <0.001* |
| PPC (%), median (IQR) | 41.7 (25.0-58.3) | 41.7 (25.0-58.3) | 50.0 (33.3-66.7) | 0.260 |
| Preoperative PSA (ng/mL), n (%) | | | | 0.972 |
| <10 | 63 (41.2%) | 76 (43.4%) | 13 (39.4%) | |

| | | | | |
|---|---|---|---|---|
| 10-20 | 50 (32.7%) | 55 (31.4%) | 10 (30.3%) | |
| >20 | 40 (26.1%) | 44 (25.2%) | 10 (30.3%) | |
| PSAD, n (%) | | | | 0.331 |
| <0.15 | 63 (41.2%) | 68 (38.9%) | 9 (27.3%) | |
| ≥0.15 | 90 (58.8%) | 107 (61.1%) | 24 (72.7%) | |
| Postoperative PSA nadir (ng/ml), n (%) | | | | 0.197 |
| <0.01 | 130 (85.0%) | 135 (77.1%) | 27 (81.8%) | |
| ≥0.01 | 23 (15.0%) | 40 (22.9%) | 6 (18.2%) | |
| Pathologic T stage, n (%) | | | | 0.542 |
| ≤T2 (OCD) | 87 (56.9%) | 103 (58.9%) | 16 (48.5%) | |
| ≥T3 (NOCD) | 66 (43.1%) | 72 (41.1%) | 17 (51.5%) | |
| Lymph node status, n (%) | | | | <0.001* |
| N0/Nx | 148 (96.7%) | 135 (77.1%) | 18 (54.5%) | |
| N+ | 5 (3.3%) | 40 (22.9%) | 15 (45.5%) | |
| Pathologic Gleason score, n (%) | | | | 0.004* |
| <8 (low-grade) | 100 (65.4%) | 86 (49.1%) | 14 (42.4%) | |
| ≥8 (high-grade) | 53 (34.6%) | 89 (50.9%) | 19 (57.6%) | |
| Surgical margin, n (%) | | | | 0.409 |
| Negative | 98 (64.0%) | 120 (68.6%) | 19 (57.6%) | |
| Positive | 55 (36.0%) | 55 (31.4%) | 14 (42.4%) | |
| ECE, n (%) | | | | 0.542 |
| Absent | 87 (56.9%) | 103 (58.9%) | 16 (48.5%) | |
| Present | 66 (43.1%) | 72 (41.1%) | 17 (51.5%) | |
| SVI, n (%) | | | | 0.967 |
| Absent | 128 (83.7%) | 146 (83.4%) | 27 (81.8%) | |
| Present | 25 (16.3%) | 29 (16.6%) | 6 (18.2%) | |
| BCR, n (%) | | | | <0.001* |
| Absent | 123 (80.4%) | 113 (64.6%) | 14 (42.4%) | |
| Present | 30 (19.6%) | 62 (35.4%) | 19 (57.6%) | |

ALB: Albumin; BCR: Biochemical Recurrence; BMI: Body Mass Index; ECE: Extra-Capsular Extension; IQR: Interquartile Range; LMR: Lymphocyte-Monocyte Ratio; NLR: Neutrophil-Lymphocyte ratio; NOCD: Non-Organ Confined Disease; OCD: Organ Confined Disease; PLR: Platelet-Lymphocyte Ratio; PPC: Percentage of Positive Biopsy Cores; PSA: Prostate-Specific Antigen; PSAD: Prostate-Specific Antigen Density; SIS: Systemic Inflammation Score; SVI: Seminal Vesicle Invasion.
*, P<0.05.

### 3.2. Survival Analysis of Patients

In the training cohort, the median follow-up period was 27.6 months (IQR: 18.2-46.5 months). BCR occurred in 30 (19.6%) patients in the SIS=0 group, 62 (35.4%) patients in the SIS=1 group and 19 (57.6%) patients in the SIS=2 group. The Kaplan-Meier analysis demonstrated that ALB<40 ($P$<0.001) and higher SIS ($P$<0.001) were significantly associated with worse BCRFS (Figures 2A and 2E), but there was no significant association between LMR (P=0.068) and BCRFS (Figure 2C).

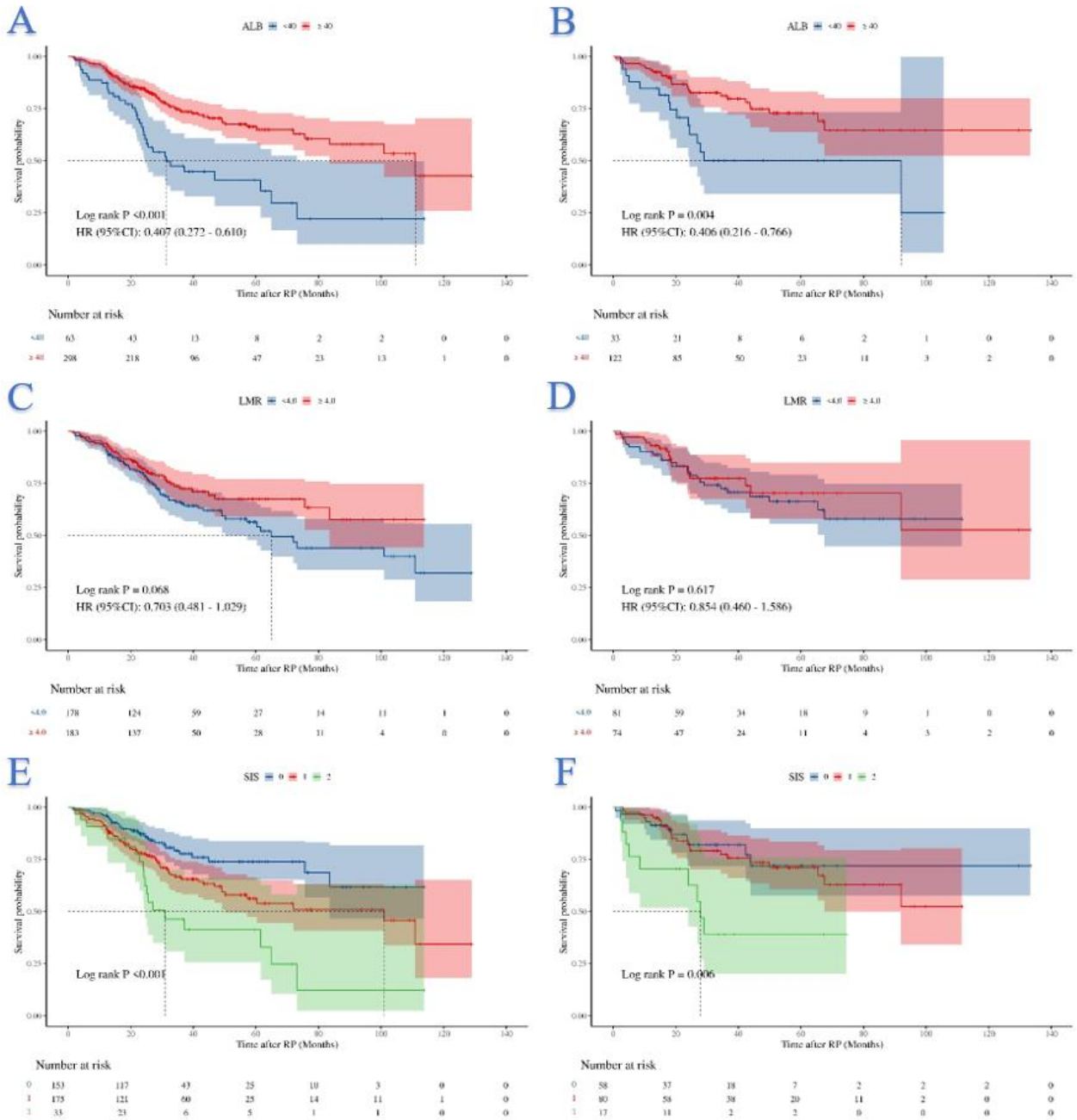



**FIGURE 2.** Kaplan-Meier survival analysis of BCR-free survival stratified by ALB, LMR and SIS in the training cohort and the validation cohort. **A)** ALB in the training cohort; **B)** ALB in the validation cohort; **C)** LMR in the training cohort; **D)** LMR in the validation cohort; **E)** SIS in the training cohort; **F)** SIS in the validation cohort.
ALB: Albumin; BCR: Biochemical Recurrence; CI: Confidence Interval; HR: Hazard Ratio; LMR: Lymphocyte-Monocyte Ratio; RP: Radical Prostatectomy; SIS: Systemic Inflammation Score.

In the validation cohort, the median follow-up period was 32.4 months (IQR: 17.8-52.3 months). BCR occurred in 11 (19.0%) patients in the SIS=0 group, 22 (27.5%) patients in the SIS=1 group and 9 (52.9%) patients in the SIS=2 group. The Kaplan-Meier analysis also revealed that ALB <40 ($P$=0.004) and higher SIS ($P$=0.006) were significantly associated with worse BCRFS (Figures 2B and 2F), but there was no significant association between LMR ($P$=0.617) and BCRFS (Figure 2D).

### 3.3. Independent Predictors for BCRFS, HG and LNM in the Training Cohort

The multivariate Cox regression analysis demonstrated that SIS (SIS=1: HR=1.756, 95% CI=1.107-2.786, *P*=0.017; SIS=2: HR=2.861, 95% CI=1.579-5.184, *P* <0.001), PLR (HR=0.996, 95%CI=0.992-0.999, *P*=0.046), PPC (HR=1.017, 95%CI=1.008-1.026, *P* <0.001), and postoperative PSA nadir (HR=3.656, 95% CI=2.418-5.528, *P* <0.001) were independent predictors for BCRFS (Supplementary Table 2). The multivariate logistic regression analysis demonstrated that SIS (SIS=1: OR=2.252, 95% CI=1.314-3.859, *P*=0.003), ALB (OR=0.840, 95% CI=0.765-0.922, *P* <0.001), PPC (OR=1.030, 95% CI=1.019-1.042, *P* <0.001) and preoperative PSA (PSA >20: OR=6.895, 95% CI=3.523-13.493, *P* <0.001) were independent predictors for HG (Supplementary Table 3). In addition, in the multivariate logistic regression analysis for LNM, SIS (SIS=1: HR=9.598, 95% CI=3.033-30.371, *P* <0.001; SIS=2: HR=25.667, 95% CI=4.804-137.133, *P* <0.001), PSAD (OR=3.057, 95% CI=1.339-6.976, *P*=0.008) and PPC (OR=1.018, 95% CI=1.005-1.031, *P*=0.008) were identified as independent predictors (Supplementary Table 4).

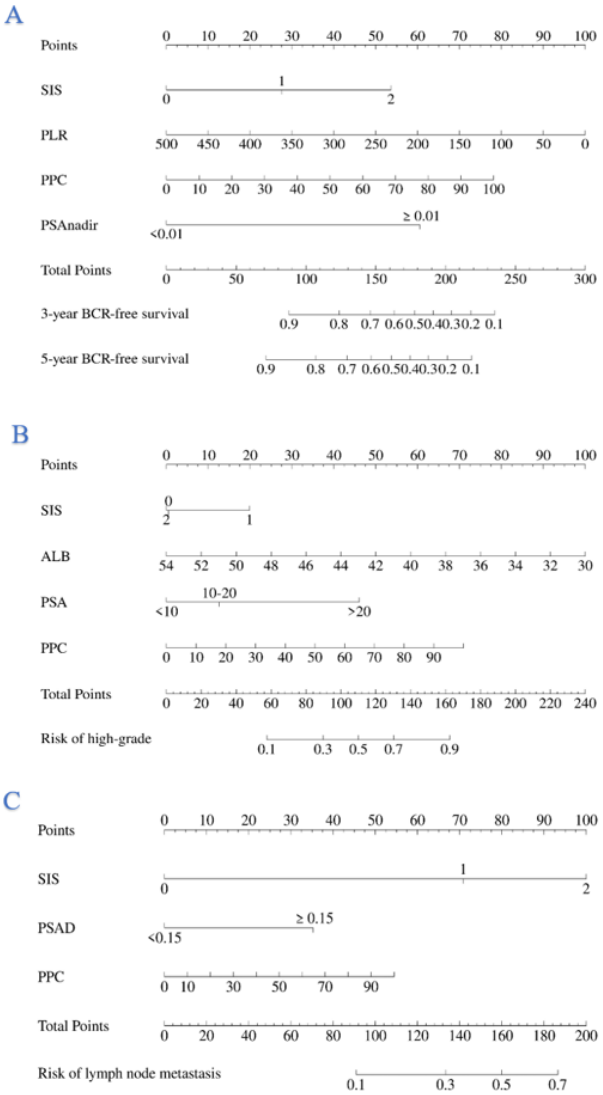



**FIGURE 3. A)** Nomogram for predicting 3-year and 5-year BCRFS in the training cohort; **B)** Nomogram for predicting high-grade in the training cohort; **C)** Nomogram for predicting lymph node metastasis in the training cohort.

ALB: Albumin; BCR: Biochemical Recurrence; BCRFS: BCR-Free Survival; PLR: Platelet-Lymphocyte Ratio; PPC: Percentage of Positive Biopsy Cores; PSA: Prostate-Specific Antigen; PSAD: Prostate-Specific Antigen Density; SIS: Systemic Inflammation Score.

### 3.4. Nomograms for BCRFS, HG and LNM based on SIS in the Training Cohort

The predictive nomograms were established by incorporating all significant independent predictors identified in the training cohort (Figures 3A-3C). The C-index of the nomogram for predicting BCRFS (Figure 3A) was 0.731 (95% CI=0.677-0.785), and the time-dependent ROC curves presented in (Figures 4A & 4B) showed that the AUC of the nomogram for predicting 3-year and 5-year BCRFS were 0.753 (95% CI=0.684-0.823), and 0.799 (95% CI=0.731-0.868), respectively. The C-indexes of the nomograms for predicting HG (Figure 3B) and LNM (Figure 3C) were 0.811 (95% CI=0.766-0.855) and 0.817 (95%CI=0.764-0.870), respectively. The corresponding AUC of the ROC curves, as shown in (Figures 4C & 4D), further supported the predictive performance of the nomograms. In addition, the calibration curves for the three nomograms also exhibited excellent agreement between the predictions made by the nomogram and the actual observation in the training cohort (Figures 5A, 5C, 5E & 5G).

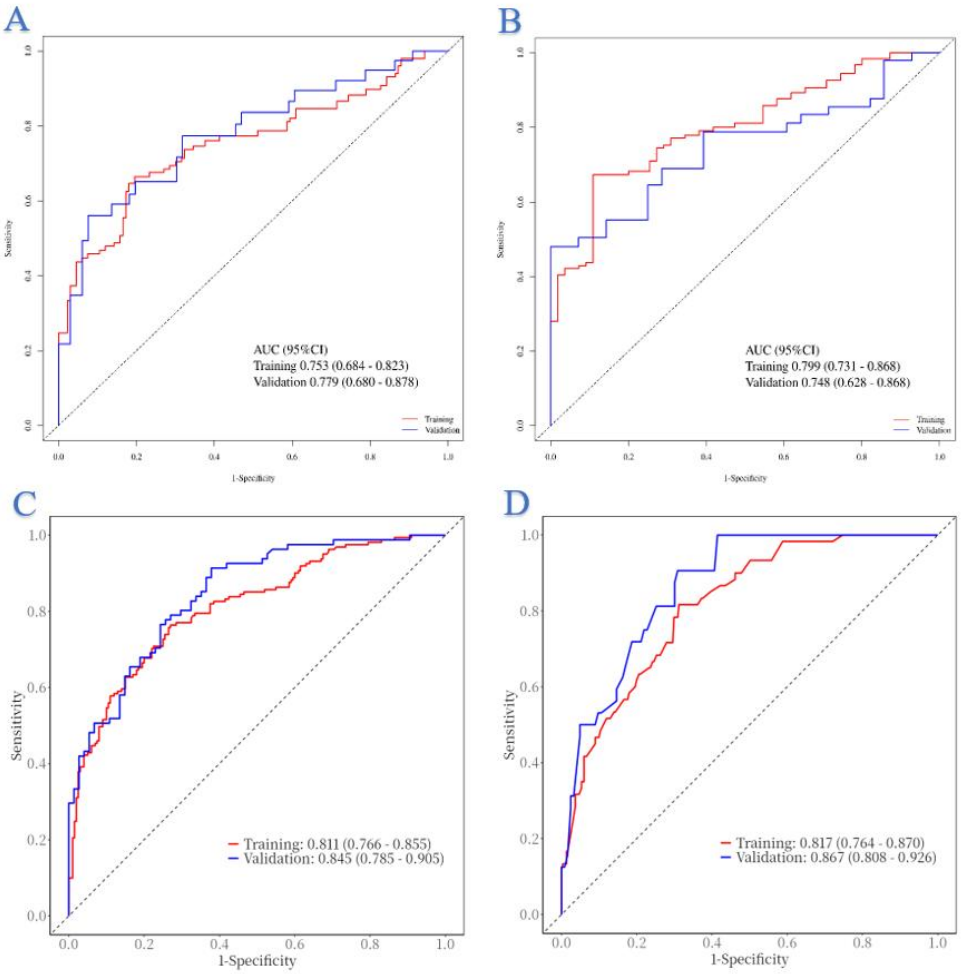



**FIGURE 4. A)** ROC curves of nomogram for predicting 3-year BCRFS; **B)** ROC curves of nomogram for predicting 5-year BCRFS. **C)** ROC curves of nomogram for predicting HG; **D)** ROC curves of nomogram for predicting LNM. AUC: Area Under Curve; BCR: Biochemical Recurrence; BCRFS: BCR-Free Survival; CI: Confidence Interval; HG: High-Grade; LNM: Lymph Node Metastasis; ROC: Receiver Operating Characteristic.

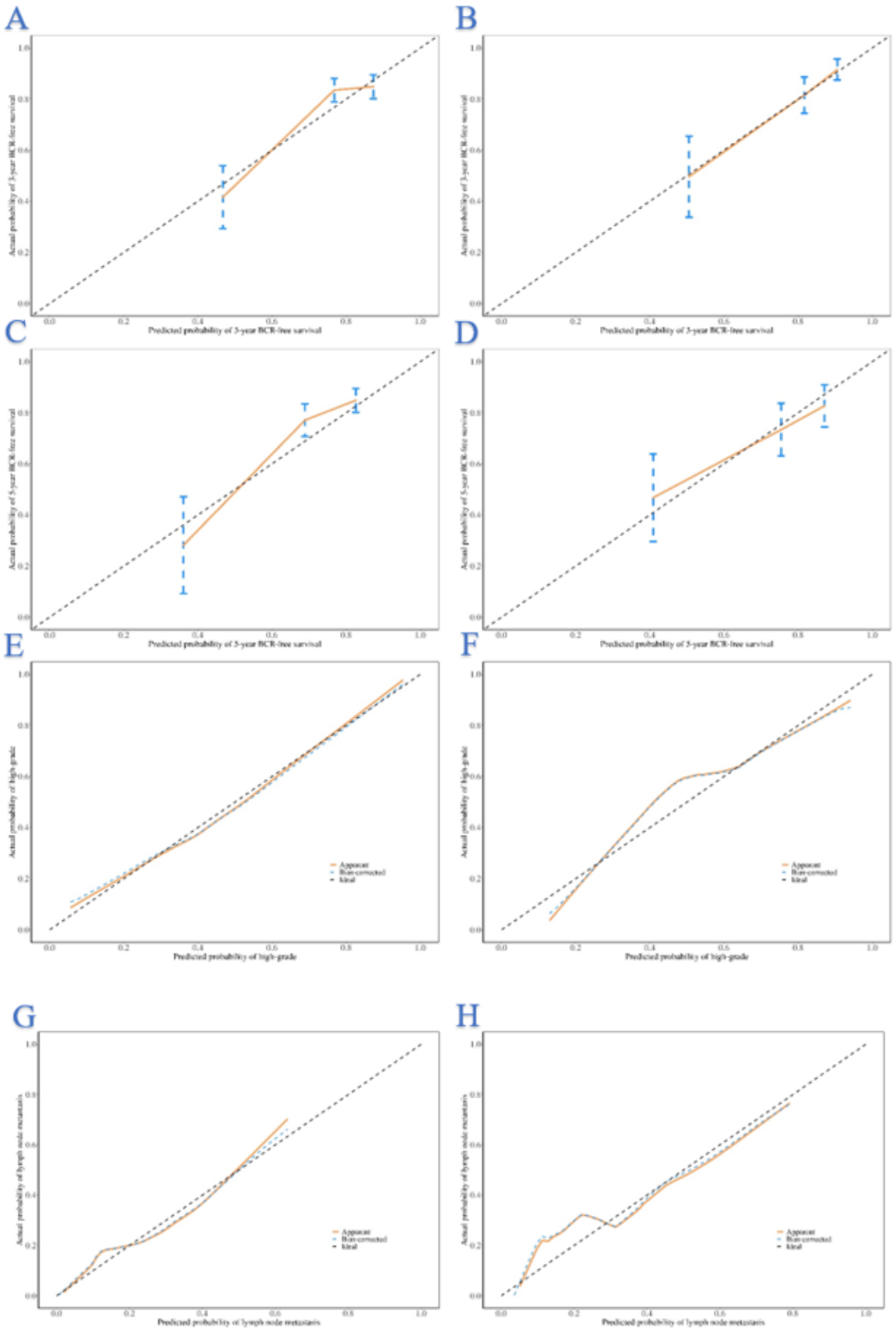
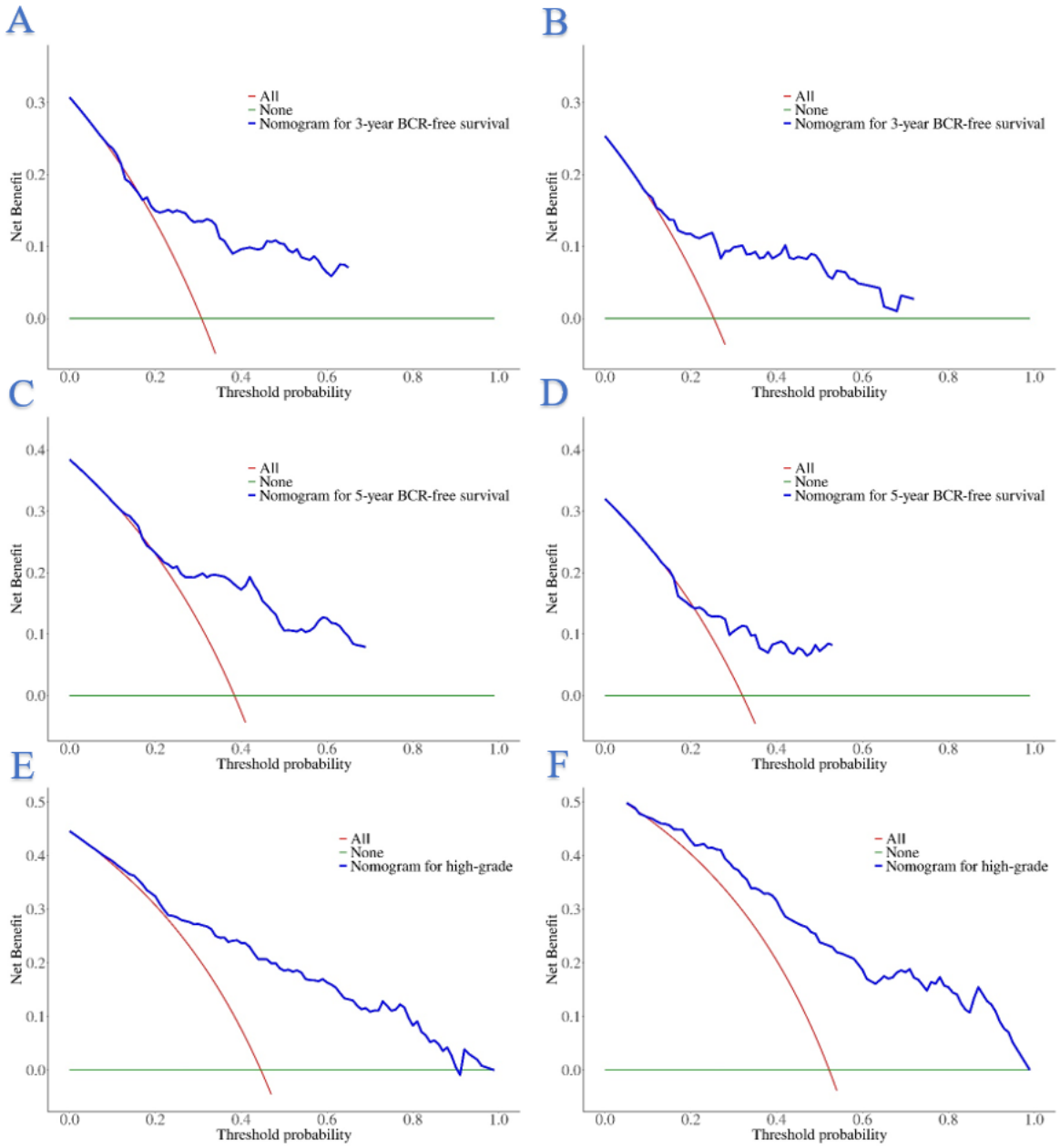



**FIGURE 5. A)** Calibration curves of nomogram for predicting 3-year BCRFS in the training cohort; B) Calibration curves of nomogram for predicting 3-year BCRFS in the validation cohort; **C)** Calibration curves of nomogram for predicting 5-year BCRFS in the training cohort; **D)** Calibration curves of nomogram for predicting 5-year BCRFS in the validation cohort; **E)** Calibration curves of nomogram for predicting HG in the training cohort; **F)** Calibration curves of nomogram for predicting HG in the validation cohort; **G)** Calibration curves of nomogram for predicting LNM in the training cohort; **H)** Calibration curves of nomogram for predicting LNM in the validation cohort.
BCR: Biochemical Recurrence; BCRFS: BCR-Free Survival; HG: High-Grade; LNM: Lymph Node Metastasis.

### 3.5. External Validation of Nomograms

We further conducted external validation on the nomograms through a separate validation cohort. The C-index of the nomogram for predicting BCRFS in the validation cohort was 0.732 (95% CI=0.634-0.830), and the time-dependent ROC curves presented in (Figures 4A & 4B) showed that the AUC of the nomogram for predicting 3-year and 5-year BCRFS were 0.779 (95% CI=0.680-0.878), and 0.748 (95% CI=0.628-0.868), respectively. The C-indexes of the nomograms for predicting HG and LNM in the validation cohort were 0.845 (95% CI=0.785-0.905) and 0.867 (95%CI=0.808-0.926), respectively. The corresponding AUC of the ROC curves, as shown in (Figure 4C & 4D), further supported the predictive performance of the nomograms. Furthermore, the calibration curves for the three nomograms also displayed great agreement between the predicted probabilities and the actual probabilities in the validation cohort (Figures 5B, 5D, 5F and 5H).



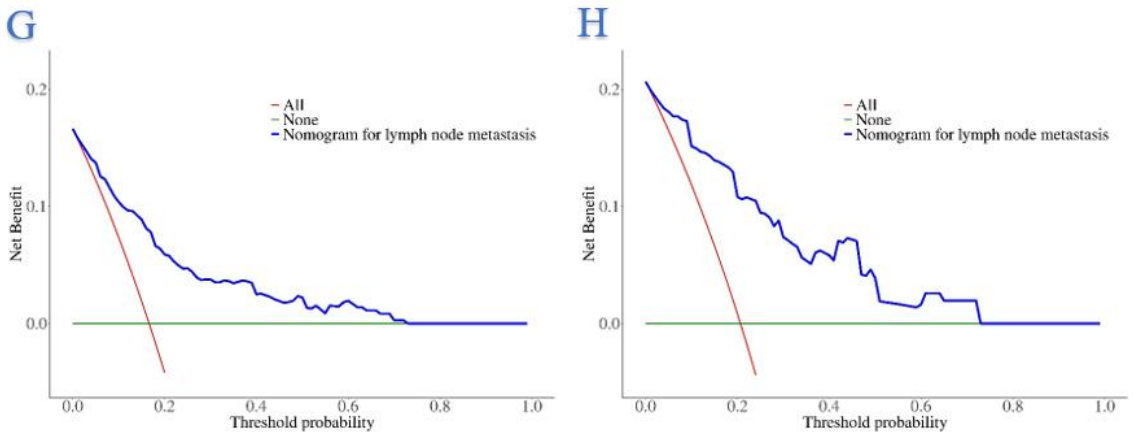



**FIGURE 6. A)** DCA of nomogram for predicting 3-year BCRFS in the training cohort; **B)** DCA of nomogram for predicting 3-year BCRFS in the validation cohort; **C)** DCA of nomogram for predicting 5-year BCRFS in the training cohort; **D)** DCA of nomogram for predicting 5-year BCRFS in the validation cohort; **E)** DCA of nomogram for predicting HG in the training cohort; **F)** DCA of nomogram for predicting HG in the validation cohort; **G)** DCA of nomogram for predicting LNM in the training cohort; **H)** DCA of nomogram for predicting LNM in the validation cohort.

BCR: Biochemical Recurrence; BCRFS: BCR-Free Survival; DCA: Decision Curve Analysis; HG: High-Grade; LNM: Lymph Node Metastasis.

### 3.6. DCA of Nomograms

In addition, decision curve analysis (DCA) was applied to present the clinical applicability of nomograms. As shown in the (Figures 6A-6H), the nomograms for predicting 3-year, 5-year BCRFS, HG and LNM all demonstrated higher net benefits across a wide range of threshold probability both in the training cohort and the validation cohort.

## 4. Discussion

In the current study, we described the distribution of SIS in PCa patients treated with RP and investigated the potential impact of SIS on BCR and AP. Our findings revealed that a higher SIS was independently and significantly associated with worse BCRFS and high risk of HG and LNM in RP patients. Furthermore, we developed three nomograms that incorporated SIS and other significant clinical variables, which illustrated favorable prediction performance and clinical applicability both in the training cohort and the validation cohort. To the best of our knowledge, this is the first study to explore the predictive value of SIS for BCR and AP in PCa patients who underwent RP, which might provide preliminary evidence and direction for future research in related fields.

Regarding BCR, the identified independent predictors of SIS and PLR were in line with previous studies that have emphasized the role of inflammation and tumor burden in PCa recurrence [27-29]. As a comprehensive indicator based on serum ALB and LMR, the prognostic value of SIS might be explained by the biological function of ALB, lymphocytes and monocytes. Serum ALB is a negative acute phase protein synthesized by the liver and is routinely employed to reflect patients' nutritional status. Since nutrition is an important determinant of the immune response, decreased serum albumin not only indicates a malnutrition status but also suggests a persistent systemic inflammatory response [30]. Therefore, ALB provides important prognostic information for various types of cancer, regardless of whether it is included in prognostic systems or not [31, 32].

On the other hand, lymphocytes are an essential component of the immune system. They can assist to enhance cancer immune-surveillance by secreting cytokines that participate in cellular immunity, and inhibiting tumor cell proliferation, invasion and

metastasis [33]. The presence of tumor-infiltrating lymphocytes is associated with improved outcomes in different type of cancers, possibly due to their antitumor activity and inhibition of angiogenesis [34]. A decrease in lymphocytes can weaken the immune response to cancer, and is linked to poor outcomes in cancer patients [35]. Monocytes can be recruited to carcinoma tissues and further differentiate into tumor associated macrophages (TAMs), which play key roles in stimulating angiogenesis, enhancing tumor cell proliferation and invasion, and inhibiting anti-tumor immunity [36, 37]. Thus, an elevated circulating monocyte level may reflect an increased production of TAMs, which is a surrogate marker for high tumor burden. Consequently, a significant decline in LMR, which conveys both monocytosis and lymphocytopenia, plays a strong predictive role for adverse survival outcomes [14, 15].

At present, a number of predictive models have been developed for BCR in PCa [10, 38]. Instead of using the commonly cited clinicopathological variables, we developed our predictive nomogram based on the independent factors identified in our multivariate analysis: PPC and postoperative PSA nadir. A series of studies can provide evidence to support our results. A retrospective study reported that the probability of BCRFS at 5 years decreased from 92.4% to 56.8% in patients with a PSA nadir ≥0.01 ng/mL compared to patients with a PSA nadir <0.01 ng/mL after RP [39]. Similarly, Xia HZ *et al.* [8] discovered the independent predictive role of PSA nadir (≥0.01 ng/mL), and developed a nomogram incorporating maximum tumor diameter and PSA nadir to predict BCRFS, which showed better predictive performance compared to the CAPRA-S score. Therefore, an undetectable level of PSA after RP (less than 0.01 ng/mL) may play an important role in determining whether patients will experience BCR. On the other hand, although PPC is more common used in predicting adverse pathological features of PCa [40, 41], there is still considerable research supporting its significant impact on BCR. Liang Z *et al.* [42] found that a percentage of positive biopsy cores > 50% was an independent factor suggesting worse biochemical relapse-free survival. Similar results can be observed in other retrospective studies [7, 43]. However, there is currently no research considering both PSA nadir and PPC for predicting BCR simultaneously. Therefore, our results provided new insights for establishing future PCa prediction models and contributed to improving the accuracy of postoperative BCR prediction for PCa.

In terms of adverse pathology, the association of SIS with high-grade disease and lymph node metastasis further support its significance in PCa prognosis. A higher SIS was associated with a greater risk of HG and LNM, suggesting that the systemic inflammatory and nutritional imbalance represented by SIS may be involved in the biological processes leading to more aggressive tumor phenotypes. The potential mechanisms could involve the modulation of tumor cell epithelial-mesenchymal transition, angiogenesis, and immune evasion, which are usually associated with advanced PCa features [44, 45]. On the other hand, apart from SIS, our study also identified the independent predictive role of PPC both in HG and LNM, which was consistent with previous findings. A prospective multi-center study by Tosco L *et al.* [40] identified PPC as an independent predictor of high-grade locally advanced disease in patients undergoing robot-assisted laparoscopic prostatectomy.

Sabbagh A *et al.* [46] constructed a machine learning model based on PPC and other common clinical variables to predict the risk of lymph node involvement in PCa, whose predictive performance was significantly better than that of Memorial Sloan Kettering Cancer Center (MSKCC) calculator and Briganti 2012 nomogram. A retrospective analysis of 308 patients with PCa who underwent multi-parameter magnetic resonance imaging (mpMRI) and RP with pelvic lymph node dissection (PLND) also reported that PPC was independently associated with pelvic lymph node metastasis [47]. These abundant research evidence once again confirms the significant role of PPC in the accurate prediction of AP in PCa. In addition, our study also found a significant association between PSAD and LNM for the first time, suggesting that higher PSA levels and smaller prostate volume may be more prone to LNM than high PSA levels alone, which provide new insights and directions for future studies on the prediction of LNM in PCa.

Our findings have several significant clinical implications. Our data highlighted the significant value of SIS in predicting clinical outcomes in RP patients. Incorporating SIS into traditional assessment models was conducive to better distinguishing high risk of BCR and AP patients. Furthermore, our nomograms based on SIS and other independent predictors developed for predicting BCRFS, HG and LNM showed great discrimination and calibration in both the training and validation cohorts. The calibration curves demonstrated that the predicted probabilities closely matched the actual observed outcomes, and the DCA confirmed the clinical applicability of the nomograms. This implies that these nomograms could be valuable tools in clinical practice for individualized risk stratification and treatment decision-making. Additionally, our findings provide new insights into treatment strategies for PCa patients, suggesting that targeting inflammation with drugs may be a promising therapeutic approach. On the other hand, intensive symptomatic treatment and nutritional support for patients with higher preoperative SIS can enhance the surgical tolerability and minimize adverse survival outcomes. Early enteral alimentation has been reported to increase ALB levels and lymphocyte counts, which may improve the clinical prognosis of patients with poor immune-nutritional reserves [48].

We also need to acknowledge that there are several limitations in this study. First of all, this is a single-center retrospective study, with both the training and validation cohorts drawn from the same center, which might lead to inevitable selection bias. Secondly, although we have performed validation using a split-sample approach, the study lacks external validation in a other separate patient cohort, which limited the generalizability of our study findings. It is necessary to further validate our study results in a large sample, multi-center, prospective setting. Thirdly, it is important to consider that various special circumstances, such as infection or inflammation in other tissues, can affect the levels of neutrophil, lymphocyte and monocyte. This can potentially interfere with the measurement of inflammatory markers and ultimately affect the reliability of the results.

Finally, the cut-off value of LMR for SIS in our study was based on the median LMR of our dataset, focusing on patients with prostate adenocarcinoma who underwent RP. Its applicability to different PCa populations, such as those treated with radiotherapy or androgen deprivation therapy (ADT), as well as to different pathological types, such as prostate squamous cell carcinoma and prostate neuroendocrine tumors, remains unclear. Therefore, it is necessary to further optimize the cut-off value of LMR in different PCa populations and tumor pathological subtypes in future studies.

## 5. Conclusion

In conclusion, our study has provided evidence of significant associations between the SIS and BCRFS, HG and LNM in patients with PCa who underwent RP. These findings suggest that the SIS has the potential to serve as a promising and powerful biomarker for this particular group of patients. Moreover, the development of nomograms based on the SIS could offer valuable risk stratification tools for improving the management and prognosis of RP patients.

## Author Contributions

Jian Lu (Corresponding author): Conceptualization, funding acquisition, project administration, supervision. Zenan Liu (First Author): Conceptualization, formal analysis, methodology, writing – original draft. Bin Yang (Co-first Author): Validation, writing – review & editing. Jide He: Investigation, visualization. Ziang Li: Data curation, investigation. Jialong Wu: Investigation. Lei Qiu: Investigation. Zhenkun Zhao: Investigation.

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Not applicable.

## Conflicts of Interest

None.

## Data Availability Statement

The raw data that support the findings of this study are available from the corresponding author upon reasonable request.

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