



# A Novel Nomogram for Identifying the Patients at Risk for Rapid Progression of Advanced Hormone-Sensitive Prostate Cancer

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**Purpose:** The goal of this study was to assess the prognostic impact of the lower urinary tract symptoms (LUTS) in advanced prostate cancer (PCa) patients before progression to castration-resistant prostate cancer (CRPC).

**Methods:** A retrospective analysis of the follow-up data for 152 CRPC patients was performed. Severe LUTS symptom was defined as an International Prostate Symptoms Score (IPSS)  $\geq 20$  at baseline. Cox regression analysis was conducted to assess CRPC prognostic factors. Nomogram model was created and assessed using the concordance index (C-index), calibration curves, receiver operating characteristic (ROC) curves, and decision curve analyses (DCA).

**Results:** The median CRPC free survival of patients with severe LUTS was 20.5 months, significantly longer than that (7.5 months) of less symptomatic patients. Furthermore, severe LUTS, the hemoglobin, albumin, lymphocyte, and platelet (HALP) score, and Gleason sum were determined to be independent prognostic markers and combined to establish a nomogram, which performed well in the customized prediction of CRPC progression at 6th, 12th, 18th and 24th month. The C-index (0.794 and 0.816 for the training and validation cohorts, respectively), calibration curve, and ROC curve all validated the prediction accuracy. DCA curve showed that it could be effective in helping doctors make judgments. The Nomogram-related risk score separated the patients into two groups with notable progression differences.

**Conclusion:** Severe LUTS was significantly associated with decreased risk for rapid progression to CRPC. The developed nomogram could help identify patients who are at a high risk of rapid CRPC progression and provide tailored follow-up and therapeutic advice.

**Keywords:** LUTS, HALP, castration-resistant prostate cancer, nomogram

## Introduction

Prostate cancer (PCa) is currently one of the leading causes of cancer-specific death in males, accounting for approximately 350,000 fatalities globally each year.<sup>1</sup> Androgen deprivation therapy (ADT), the cornerstone of care for people with locally or metastatic hormone-sensitive prostate cancer (HSPC), slows the growth of PCa by lowering the level of circulating testosterone. But most patients who received ADT eventually developed to castration-resistant prostate cancer (CRPC), which has a median survival period of just 14 months.<sup>2,3</sup> Hussain et al's theory states that if the CRPC stage appeared within the first seven months of ADT, the risk of death would increase four times.<sup>4</sup> In order to execute an early follow-up plan to rapidly detect progression and optimize treatment regimens, such as chemotherapy, immunotherapy and so on, it is vital to clarify the signs that potentially predict progression to CRPC in patients with locally advanced PCa and metastatic PCa.<sup>5-10</sup>

Lower urinary tract symptoms (LUTS), which include issues with urine storage and voiding, are quite prevalent in men and are thought to affect 80% of men over the age of 60.<sup>11</sup> One of the most frequent reasons for patient visits to urologists is LUTS, which are always considered to be a possible symptom of PCa. Thus, a link between LUTS and PCa is almost inevitable given the high prevalence of LUTS in elderly men. In our clinical setting, we discovered that patients

with advanced PCa who originally sought care for LUTS symptoms had a better prognosis than those who sought care for other conditions including elevated PSA, bone pain, etc. Although several studies about LUTS and PCa have been published, they mainly focused on effect of LUTS on PCa screening,<sup>12</sup> describing the LUTS-related quality of life in patients with PCa.<sup>13</sup> Ours is the first study to investigate the effect of LUTS on the progression from HSPC to CRPC for identifying HSPC patients with a rapid progression.

Nomogram use has been compared favorably to the conventional cancer staging systems, and as a result, it has been suggested as a substitute or even as a new benchmark.<sup>14</sup> In order to develop a model for predicting the advancement of CRPC and assisting clinicians in recommending personalized therapeutic guidance, the follow-up information of advanced HSPC was retrospectively analyzed in conjunction with clinico-pathological data.

## Materials and Methods

### Patient Recruitment and Clinico-Pathological Variables Collection

One hundred and fifty-two PCa patients with complete follow-up information were included in this retrospective analysis from November 2016 to November 2022 in the Second Hospital of Dalian Medical University. The protocol was accepted by the ethical committee of the Second Hospital of Dalian Medical University complying with the Declaration of Helsinki (approval number: 2023064), all patients submitted written informed consent prior to the research. The inclusion criteria were as follows: (1) Patients with prostate adenocarcinoma newly confirmed by pathology; (2) patients received LHRH agonists coupled with anti-androgen as initial and only therapy before progression; (3) patients with adequate imaging evidence were diagnosed with locally advanced or metastatic disease; and (4) patients with complete clinico-pathological variables and follow-up data. Exclusion criteria were as follows: (1) PCa patients with other pathological types; (2) patients had received ADT; and (3) patients with other blood systems or solid tumors. Clinico-pathological variables at the time of PCa diagnosis, such as age, PSA levels, clinical TNM stage, Gleason sum and platelet, lymphocyte, haemoglobin, and serum albumin values, were collected and given in Table 1. LUTS symptoms

**Table 1** Clinico-Pathologic Characteristics of Study Participants

Characteristics		Total (n=152)	Severe LUTS	
			Yes (n=80)	No (n=72)
Age	<70	56 (36.84%)	21 (26.25%)	35 (48.61%)
	≥70	96 (63.16%)	59 (73.75%)	37 (51.39%)
Gleason sum	7	28 (18.42%)	15 (18.75%)	13 (18.06%)
	8	58 (38.16%)	34 (42.50%)	24 (33.33%)
	9	54 (35.53%)	25 (31.25%)	29 (40.28%)
	10	12 (7.89%)	6 (7.50%)	6 (8.33%)
T-stage	T4	74 (48.68%)	36 (45.00%)	38 (52.78%)
	T3	57 (37.50%)	31 (38.75%)	26 (36.11%)
	T2	21 (13.82%)	13 (16.25%)	8 (11.11%)
N-stage	N1	101 (66.45%)	44 (55.00%)	57 (79.17%)
	N0	51 (33.55%)	36 (45.00%)	15 (21.43%)
M-stage	M1c	19 (12.50%)	9 (11.25%)	10 (13.89%)
	M1a/b	108 (71.05%)	53 (66.25%)	55 (76.39%)
	M0	25 (16.45%)	18 (22.50%)	7 (9.72%)
t-PSA (ng/dl)	<50	25 (16.45%)	17 (21.25%)	8 (11.11%)
	50–100	34 (22.37%)	19 (23.75%)	15 (20.83%)
	>100	93 (61.18%)	44 (55.00%)	49 (68.06%)
HALP	<25	34 (22.37%)	12 (15.00%)	22 (30.56%)
	25–34	30 (19.74%)	14 (17.50%)	16 (22.22%)
	>34	88 (57.89%)	54 (67.50%)	34 (47.22%)
Time to CRPC (months)	Median [min-max]	12.5 [2.00,65.00]	20.5 [3.00,65.00]	7.5 [2.00,43.00]

**Abbreviations:** CRPC, castration-resistant prostate cancer; LUTS, lower urinary tract symptoms; HALP, hemoglobin, albumin, lymphocyte, and platelet score.

were assessed at baseline using the International Prostate Symptoms Score (IPSS). The seven symptom questions have a severity scale of 0 to 5, and the total IPSS ranges between 0 and 35. Total IPSS values of 20–35 indicate severe urinary symptoms. The hemoglobin, albumin, lymphocyte, and platelet (HALP) score was calculated as hemoglobin (g/L) × albumin (g/L) levels × lymphocyte count (/L)/platelet count (/L). Patients progressed to CRPC met the following criteria: 1) serum testosterone level <50 ng/dl, or 1.7 nmol/L; 2) PSA progression: PSA value >2.0 ng/mL, interval 1 week, three times over the baseline level >50%. All patients were followed up to the advancement of CRPC.

## Establish a Nomogram for Predicting the CRPC Progression

In this study, 152 patients were randomly assigned to training set of 108 samples (~7/10), and internal validation set of 44 samples (~3/10). The R package “survival” was used to integrate data on survival time, survival status, and the clinico-pathological characteristics. The multivariate Cox regression analysis was used to determine the prognostic significance of these characteristics in the training set. On the basis of multivariate Cox proportional hazards analysis, nomogram predicting rates of disease progression at 6, 12, 18, and 24 months were created using the “RMS” software. The nomogram presents graphical data for these factors, and from the points linked with each risk factor, the prognosis risk of an individual patient may be computed. During the validation of the nomogram, the total points of each patient in the validation cohort were calculated according to the established nomogram. The concordance index (C-index) and the receiver operating characteristic (ROC) curve were used to evaluate the discriminating ability of the nomogram. The calibration plots and decision curve analysis (DCA) were used to assess the predictive power and clinical utility of the nomogram.

## Survival Analysis of Patients with High-Risk and Low-Risk Score Based on Nomogram

The best risk score cut-off value was determined for the entire cohort using the R package “maxstat” (Maximally selected rank statistics with multiple p-value approximations, version: 0.7–25). The minimum and maximum numbers of samples in each category were set at more than 25% and less than 75%, respectively. Based on available information, patients were divided into high-risk and low-risk groups. The prognosis difference between the two groups was examined using the Survfit function of the R software package, and the significance of the prognostic difference between the several groups of samples was assessed using the Log rank test.

## Statistical Analysis

The ideal cutoff values for age and HALP score were determined using X-tile software v3.6.1 (Yale University).<sup>15</sup> For continuous variables, the medians and interquartile ranges were evaluated; frequencies and proportions are given for categorical variables. The corresponding hazard ratios (HRs) and 95% confidence intervals (CIs) were determined using multivariate Cox regression analysis of “survival” R package. For DCA, the “ggDCA” R package was utilized. ROC analysis was performed using the R software package pROC to determine the area under the curve (AUC) (version 1.17.0.1). In particular, we gathered the patients’ follow-up duration and risk score and performed ROC analysis using the ROC function of pROC at 6, 12, 18, and 24 months. For all analyses, a P value of <0.05 was considered statistically significant.

## Results

### Clinico-Pathologic Characteristics of Patients

The clinicopathological characteristics of all patients are summarized in Table 1. Based on the results obtained using X-tile software, the following cutoff values were observed: 70 for age and 25–34 for HALP. Among the 152 PCA patients, at the time of diagnosis, 108 (71.05%) and 19 (12.50%) patients were diagnosed as M1a/b and M1c stage. One hundred and one (66.45%) patients had lymph node metastasis. Seventy-four (48.68%), 57 (37.50%) and 21 (13.82%) patients were diagnosed as T4, T3 and T2 stages, respectively. Among the Gleason sum values, 28 (18.42%), 58 (38.16%), 54 (35.53%) and 12 (7.89%) patients had a score of 7, 8, 9 and 10, respectively. The median CRPC-free

survival of entire cohort was 12.5 months (range: 2–65 months). On the other hand, the median CRPC-free survival of patients with severe LUTS was 20.5 months, significantly longer than that (7.5 months) of less symptomatic patients.

## Construction of a Combined Nomogram for Individualized Prediction

The clinico-pathologic factors, including age, PSA levels, clinical TNM stage, Gleason sum, HALP score and severe LUTS were used for multivariate Cox regression analyses (Table 2). The results demonstrated that severe LUTS, HALP and Gleason sum were independent risk factors for CRPC progression.

By the multivariate Cox regression analysis, a nomogram integrated with the severe LUTS, HALP and Gleason sum was established (Figure 1A). The C-index was 0.794 (95% CI, 0.759–0.829), indicating a good consistency. The calibration plots (Figure 1B) showed that the nomogram performed well in the individualized prediction of progression to CRPC. DCA curve revealed that the nomogram provided obvious net benefit at 6, 12, 18 and 24 month to the none or all strategy, which represented patients correctly treated (Figure 2A). As shown in the ROC curve, the 6-month, 12-month, 18-month and 24-month AUC of the nomogram were 0.921 (95% CI, 0.870–0.971), 0.897 (95% CI, 0.833–0.961), 0.897 (95% CI, 0.836–0.957) and 0.857 (95% CI, 0.788–0.926), respectively (Figure 2B).

## Validation of Predictive Accuracy of the Nomogram

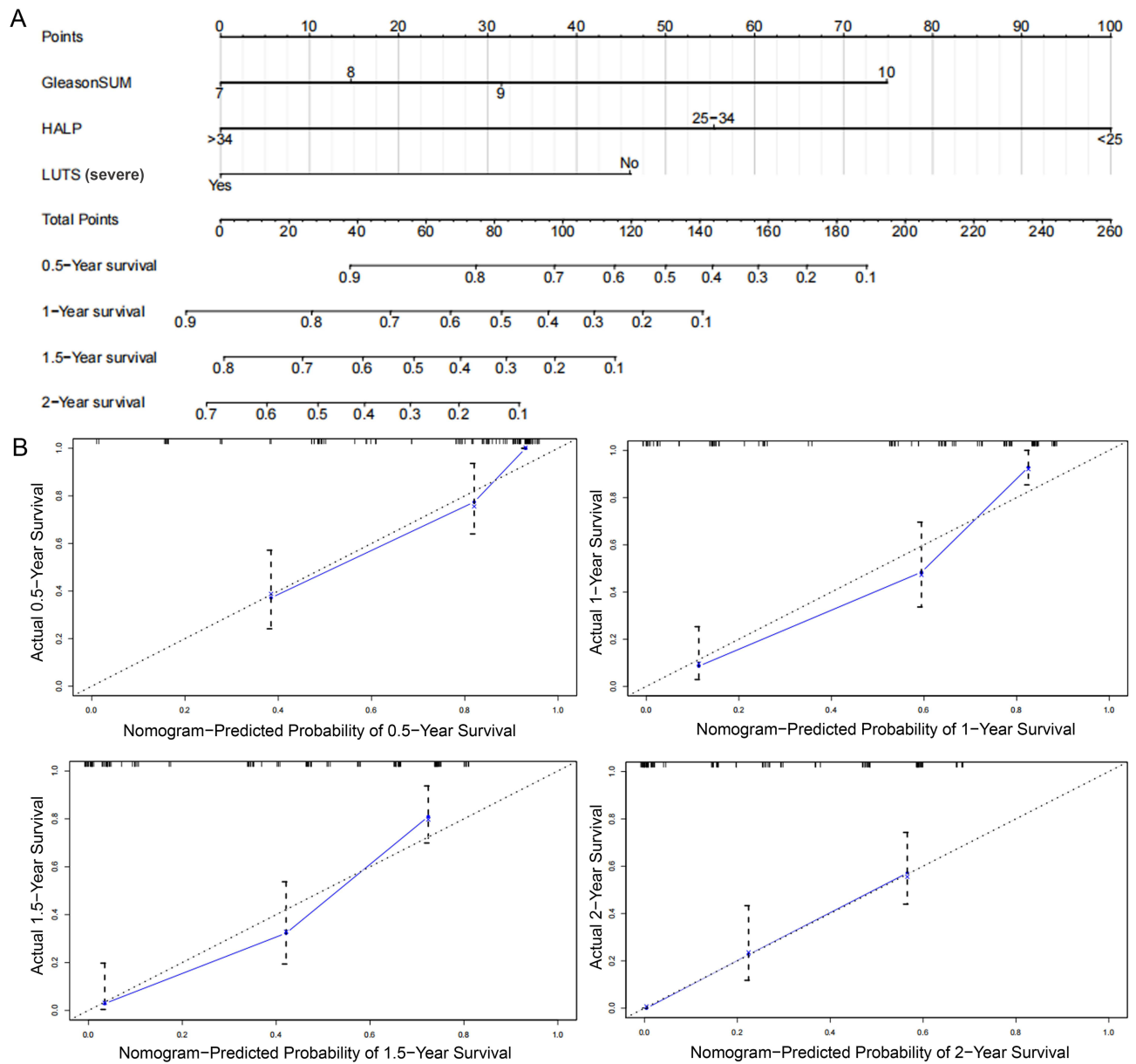
In the validation cohort, the C-index of the nomogram for predicting CRPC progression was 0.816 (95% CI, 0.757–0.875), the calibration curve showed good agreement between prediction and observation in the probability of 6-month, 12-month, 18-month and 24-month survival (Figure 3A). DCA curve also showed favorable net advantages for assisting with clinical judgments (Figure 3B). Anymore, the AUC for predicting 6-month, 12-month, 18-month and 24-month survival were 0.915 (95% CI, 0.829–1.0), 0.909 (95% CI, 0.815–1.0), 0.937 (95% CI, 0.870–1.0) and 0.948 (95% CI, 0.890–1.0), respectively (Figure 4A). Each patient in this investigation was converted into a single risk score using nomogram modeling. The best risk score cutoff value was calculated as 0.33. Based on this information, patients were

**Table 2** Multivariate Analyses of Factors Associated with CRPC Progression

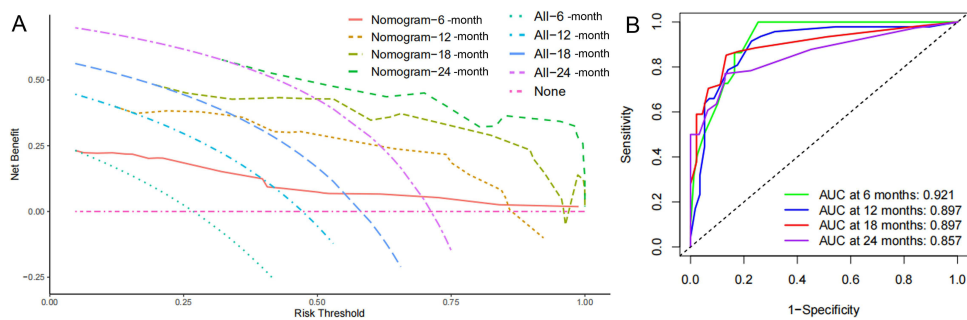
Variable		Multivariate Analysis	
		HR (95% CI)	P value
Age	≥70 vs <70	0.993 (0.614–1.605)	0.979
Gleason sum	7	–	–
	8	1.462 (0.776–2.752)	0.239
	9	1.827 (0.991–3.370)	0.053
	10	4.581 (1.518–13.830)	0.007**
T-stage	T2	–	–
	T3	1.150 (0.590–2.245)	0.681
	T4	1.258 (0.660–2.401)	0.486
N-stage	N0 vs N1	1.159 (0.676–1.987)	0.591
M-stage	M0	–	–
	M1a/b	0.735 (0.382–1.418)	0.359
	M1c	0.832 (0.360–1.927)	0.668
t-PSA (ng/dl)	<50	–	–
	50–100	0.752 (0.363–1.556)	0.442
	>100	1.237 (0.663–2.309)	0.503
Severe LUTS	Yes vs No	0.348 (0.205–0.593)	<0.001***
HALP	<18	–	–
	18–35	0.455 (0.233–0.890)	0.021*
	>35	0.131 (0.069–0.250)	<0.001***

**Notes:** \*P < 0.05, \*\*P < 0.01, \*\*\*P < 0.001.

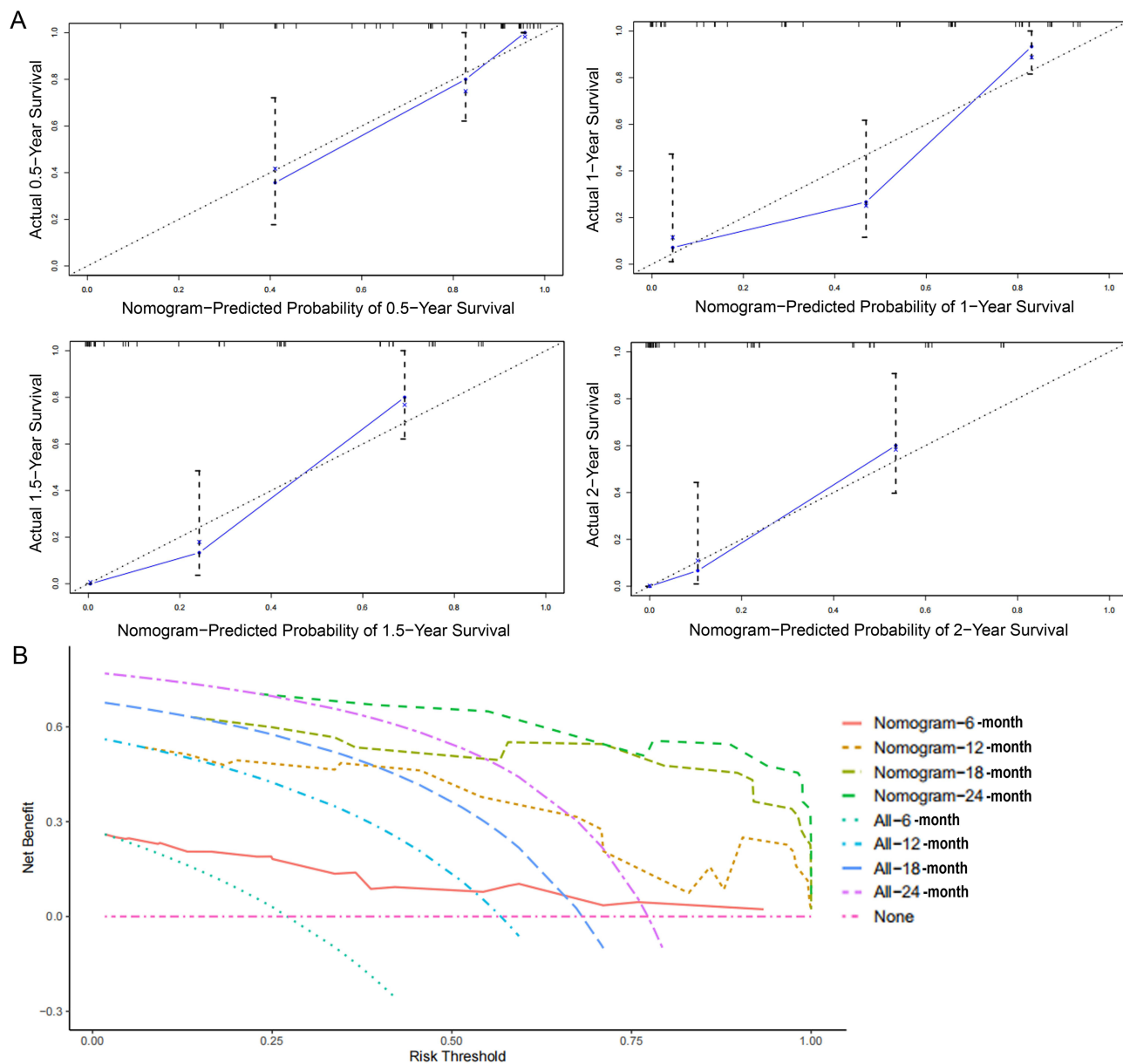
**Abbreviations:** CRPC, castration-resistant prostate cancer; LUTS, lower urinary tract symptoms; HALP, hemoglobin, albumin, lymphocyte, and platelet score.



**Figure 1** Establishment and validation of a combined nomogram in the training cohort. **(A)** Nomogram based on lymphocyte, albumin, HALP score and Gleason sum, was constructed to predict the 0.5-, 1-, 1.5 and 2-year CRPC free survival. **(B)** Predictive accuracy of the nomogram was assessed by the calibration plots.



**Figure 2** Validation of predictive value of the Nomogram in the training cohort. **(A)** The prognostic value of the nomogram was confirmed by the ROC analysis. **(B)** Predictive capacity of the nomogram was assessed by DCA.



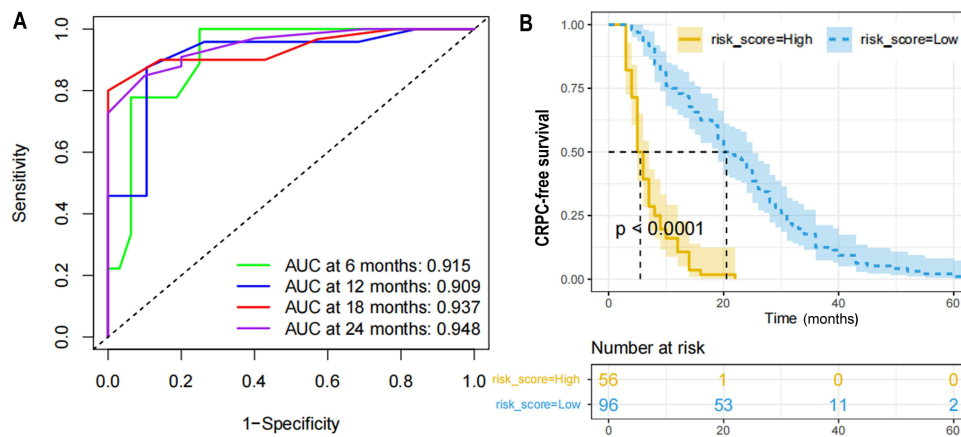
**Figure 3** Validation of predictive capacity of the Nomogram in the validation cohort. **(A)** Predictive accuracy of the nomogram was assessed by the calibration plots. **(B)** Predictive capacity of the nomogram was assessed by DCA.

split into high and low risk groups, with 36.84% ( $n = 45$ ) in the high risk group and 63.16% ( $n = 95$ ) in the low risk group. Between the two groups, there was a statistically significant difference in prognosis (Figure 4B).

## Discussion

In this study, we assessed the prognosis role of severe LUTS (IPSS  $\geq 20$ ) in HSPC patient, who received LHRH agonists coupled with anti-androgen as initial and only therapy before progression. It was observed to be significantly associated with the HSPC prognosis. Furthermore, we established a nomogram model, comprising severe LUTS, HALP score and Gleason sum, hypothesized that its predictive significance could help clinicians to identify high-risk HSPC patients in a timely manner as well as to provide reasonable treatment options.

The clinical staging of newly diagnosed HSPC patients in China differs from western developed countries. A multi-center Chinese study showed that only 1/3 of the newly diagnosed HSPC patients are clinically localized, most patients



**Figure 4** Validation of predictive value of the Nomogram. **(A)** The prognostic value of the nomogram was confirmed by the ROC analysis in the testing cohort. **(B)** The CRPC free survival curves based on nomogram correlated risk score in the whole cohort.

are in the locally advanced or metastatic stage at the diagnosis.<sup>16</sup> Due to its heterogeneity, HSPC has a complex disease spectrum, ranging from clinically indolent subtypes to aggressive ones. The progress span to CRPC varies significantly among patients. Multiple randomized controlled clinical phase-III trials, such as CHAARTED<sup>17</sup> and LATITUDE,<sup>18</sup> reported that ADT plus docetaxel or abiraterone acetate in the early hormone-sensitive phase would result in longer overall survival in patients with high-volume or high-risk HSPC. An early and suitable follow-up and treatment approach can be put in place when HSPC patients are determined to have either a long- or short-term progression to CRPC before initial treatment. Predicting and identifying HSPC patients at risk for quick development to CRPC is therefore crucial.

One of the most frequent reasons for patient visits to urologists is LUTS. The onset of PCa has not traditionally been linked to these symptoms. In our clinical setting, we discovered that patients with advanced PCa who originally sought care for LUTS symptoms had a better prognosis than those who sought care for other conditions including elevated PSA, bone pain, etc. As seemed to be expected, our findings showed that severe LUTS was significantly associated with decreased risk for rapid progression to CRPC. It remains unclear why a severe LUTS is associated with a better prognosis of HSPC. The onset of LUTS in patients with PCa is the parallel increase in prostate volume due to benign prostatic hypertrophy.<sup>19</sup> Interestingly, recent studies showed that men with low testosterone had significantly larger prostate volume than those in the normal testosterone group.<sup>20,21</sup> Several works of literature to assess the relationship between serum testosterone and PCa have been reported, the authors concluded that the relationships among serum testosterone levels, the incidence, aggressiveness, and oncological outcomes showed conflicting results and has been controversial.<sup>22,23</sup> Accordingly, our findings could support the hypothesis that a severe LUTS may represent a relatively low baseline testosterone, which is related to a good prognosis of HSPC.

HALP score has been identified as a significant predictive factor in patients with various malignancies and is thought to be an easily computed index of systemic inflammation and nutritional status.<sup>24,25</sup> In men with PCa and benign prostatic hyperplasia, Kaya et al investigated the diagnostic value of the preoperative HALP score.<sup>26</sup> However, it is unknown whether the HALP score can predict CRPC progression in HSPC patients who receive ADT as their first and only treatment. According to our findings, the prognosis of HSPC was substantially correlated with HALP score. Consistently, Gleason sum and HALP were found to be particular risk factors for progression-free survival in metastatic PCa patients who underwent cytoreductive radical prostatectomy by Guo et al.<sup>27</sup>

The nomogram has been used extensively by oncologists to produce prognostic information for specific patients owing to its intuitive design and statistical probability.<sup>28,29</sup> With the aid of multivariate Cox regression analysis, a unique nomogram was created in this work by combining the severe LUTS, HALP score, and Gleason sum. The combined nomogram worked well as an all-encompassing scoring system for predicting the progression of CRPC, the calibration curve and C-index (0.794, 95% CI: 0.759–0.829 and 0.816, 95% CI: 0.757–0.875 for the training and validation cohorts, respectively) provided support for this prediction. DCA curve also demonstrated positive net benefits

in guiding clinical decisions. The ROC curve revealed that the nomogram in this study demonstrated accurate discrimination in both training and validation cohort, especially for 6-month progression (0.921, 95% CI: 0.870–0.971 and 0.915, 95% CI: 0.829–1.0), when is important for identifying HSPC patients with worse prognosis.<sup>4</sup>

Although more recent techniques such as fluid biopsy and genetic testing appear to improve the precision of PCa prognostic predication, they have limitations such as a high cost and labor-intensive analysis.<sup>30–32</sup> Additionally, the bulk of them are still through clinical trials. In clinical practice, a prostate biopsy can be used to determine the Gleason sum, and laboratory investigations can be used to calculate the HALP when a patient with prostate cancer visits a doctor. The total points of all the variables in the nomogram could therefore aid us in making informed choices regarding adjuvant therapy and follow-up plans because it is a quick, precise, and affordable risk assessment.

After dividing the patients into groups with low- and high-risk score, the group with a high-risk score developed rapidly and had a bad prognosis. For patients with low risk scores, the most common palliative therapy, ADT+bicalutamide/flutamide, is recommended. Current clinical research suggests that patients in the high-risk score category should receive more potent medication, such as ADT coupled with chemotherapy or new endocrine therapy. Large-scale clinical trials are necessary to validate the specific treatment.

This study is limited by a small sample size, which must be increased for future validation. Second, in clinical practice, ADT combination with bicalutamide and flutamide is gradually being replaced by new endocrine medicines. In the future, individuals with several treatment approaches will be able to be enrolled and compared to determine the benefits of various treatment strategies.

In conclusion, our study demonstrated a significant positive association between severe LUTS and CRPC-free survival at 6 months, 12 months, 18 months and 24 months, suggesting that severe LUTS at admission may act as a powerful indicator of better prognosis. Further, a novel combined nomogram was established and validated for individualized risk prediction of HSPC patients. Although the prognostic ability of this nomogram has been preliminarily confirmed, it still needs further demonstration by clinical research, which will be our effort in the future.

## Data Sharing Statement

The data analyzed during the current study are available from the corresponding author on reasonable request.

## Ethics Approval

The protocol was accepted by the ethical committee of the Second Hospital of Dalian Medical University complying with the Declaration of Helsinki (approval number: 2023064), all patients submitted written informed consent prior to analysis.

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## Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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