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Original Article

Development of a predictive model for progression to castration-resistant prostate cancer in patients with high bone tumor burden

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Abstract: Objective: To identify key risk factors and construct a predictive model for the progression of high bone tumor burden prostate cancer (HBTB-PCa) to castration-resistant prostate cancer (CRPC). Methods: This retrospective study included 367 HBTB-PCa patients treated between January 2018 and May 2021, with 286 cases progressed to CRPC (progression group) and 81 cases did not (non-progression group). Patients were randomly divided into training (n=257) and validation (n=110) sets at a 7:3 ratio. Logistic regression was used to identify independent risk factors, and a Nomogram was built to predict progression risk. Model performance was evaluated using receiver operating characteristic (ROC) curves, calibration plots, and decision curve analysis (DCA). Results: Compared with the non-progression group, patients in the progression group had significantly higher rates of perineural invasion (P=0.011), Gleason score ≥8 (P=0.002), and T4 stage (P=0.012). Laboratory markers including ALP (P<0.001) and LDH (P<0.001) were also elevated in the progression group. Multivariate analysis identified perineural invasion (P=0.032), Gleason score (P=0.002), initial PSA (P=0.025), ALP (P=0.011), LDH (P<0.001), and ALB (P=0.019) as independent predictors of progression to CRPC. The Nomogram demonstrated strong discrimination power (AUC=0.845 in the training set; AUC=0.746 in external validation), with LDH being the most influential predictor. DCA indicated a net clinical benefit up to 77.82%. Conclusions: Perineural invasion, Gleason score ≥8, and elevated ALP and LDH are closely associated with progression from HBTB-PCa to CRPC. The constructed Nomogram (internal AUC=0.845; external AUC=0.746) offers a practical tool for individualized risk assessment and guiding treatment planning in clinical settings.

Keywords: High tumor burden, bone metastasis, prostate cancer, castration-resistant prostate cancer, prediction model

Introduction

Prostate cancer (PCa) is one of the most common malignancies of the male genitourinary system [1, 2]. According to GLOBOCAN 2020, Pca ranks second in incidence and fifth in mortality among male cancers worldwide [3]. The incidence and mortality of PCa in China, though lower than the global average, are rising rapidly due to population aging and the increasing use of PSA screening [4]. In 2020, there were approximately 115,000 new PCa cases and 51,000 PCa-related deaths in China, posing a threat to people's health [3].

PCa is often asymptomatic in its early stages, resulting in low rates of early diagnosis, and the lack of widespread screening programs further contributes to a high proportion of patients being diagnosed at intermediate or advanced

stages [5-7]. Many newly diagnosed patients present with metastatic hormone-sensitive PCa, often accompanied by dysuria and skeletal complications, with a five-year survival rate of only 28.2% [8]. In addition, up to 70% of advanced PCa patients develop bone metastases, as the bones microenvironment are conducive for tumor cell proliferation, leading to complications such as bone pain and pathological fractures [9]. High bone tumor burden (HBTB) Pca refers to a clinically severe state characterized by bone metastasis, typically with more than four bone metastatic sites, with at least one lesion outside the axial skeleton (i.e., beyond the spine, pelvis, or ribs), or accompanied by visceral metastasis such as those in lung or liver [10, 11]. These patients experience higher mortality and require more complex treatment strategies.

Androgen deprivation therapy (ADT) remains the cornerstone of treatment for advanced PCa. Although most patients initially respond to ADT, progression to castration-resistant prostate cancer (CRPC) is common, with highly variable time to progression [12]. Research has shown that patients with high tumor burden exhibit more rapid progression to CRPC and shorter overall survival compared to those low tumor-burden [13]. Clinically, bone metastases are typically assessed using whole-body bone scintigraphy via single-photon emission computed tomography (SPECT), with contrast-enhanced MRI employed when needed. While these modalities provide anatomic information, they fail to account for other prognostic variables, such as Gleason score or clinical stage [14]. Therefore, there is still a lack of an accurate predictive tools for determining the timing of progression from HBTB-PCa to CRPC.

Nomograms offer a graphical prediction tool that integrates multiple predictors to estimate the probability of clinical events. It provides an individual risk assessment, turning complex data models into intuitive graphs that are easy for doctors and patients to understand. In this study, we developed a nomogram model based on the risk factors identified through Logistic regression to predict the risk of progression from HBTB-PCa to CRPC, facilitating personalized treatment planning and improving patient outcomes.

Methods and materials

Patient source

This retrospective study included HBTB-PCa patients treated at the Second Affiliated Hospital of Guangzhou Medical University between January 2018 and May 2021. The study was approved by the Medical Ethics Committee of the Second Affiliated Hospital of Guangzhou Medical University). Given the retrospective nature of this study, informed consent was waived by the Ethics Committee.

Eligibility and exclusion criteria

Inclusion criteria: 1) Histologically confirmed diagnosis of PCa via transrectal ultrasound-guided prostate biopsy [6]; 2) Diagnosis of HBTB-PCa based on chest, abdomen, and pelvic CT scanning, SPECT whole body bone imaging, or whole body PET-CT imaging; 3) Availability of complete baseline data and pre-treatment hematological findings.

Exclusion criteria: 1) Patients who were not initially diagnosed or treated with endocrine therapy at our institution; 2) Those had a history of other malignancies; 3) Those had recently received radiotherapy or chemotherapy; 4) Those with no definite diagnosis of HBTB-PCa (**Figure 1**).

Definition of CRPC

According to the *Chinese Guidelines for the Diagnosis and Treatment of Urology and Andrology Diseases (2022 edition)* [15], disease progression in PCa patients receiving androgen deprivation therapy (ADT) is defined as either prostate-specific antigen (PSA) progression or radiographic progression despite achieving castration-level serum testosterone (<1.7 nmol/L or <50 ng/dL).

PSA progression is defined by three consecutive tests (at least 1-week intervals) showing elevated PSA levels, with the last test showing an increase by more than 50% from the baseline value and the final PSA value exceeding 2 ng/mL. This persistent elevation indicates disease activity despite appropriate testosterone suppression.

Radiographic progression is defined by the appearance of new lesions on imaging, includ-

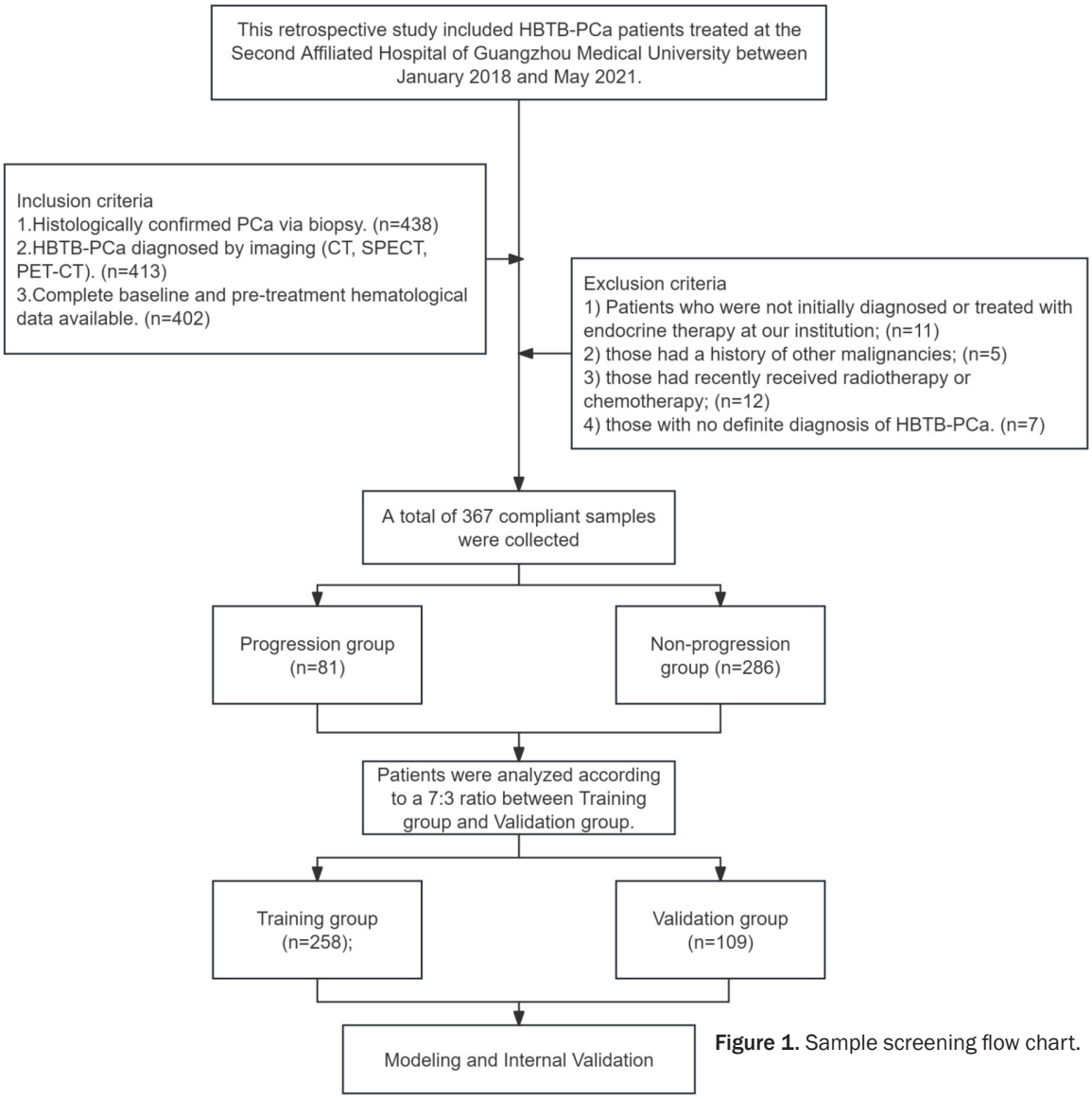

Figure 1. Sample screening flow chart.

ing at least two new bone lesions on bone scintigraphy, or new soft tissue lesions evaluated using RECIST criteria.

Patient grouping

According to the eligibility and exclusion criteria, a total of 367 cases were included, including 286 patients in the progression group and 81 patients in the non-progression group. Then the patients were assigned to a training group (n=257) and a validation group (n=110) at a 7:3 ratio.

Data collection

Patient data were obtained from electronic medical records and follow-up records. Baseline data (recorded at first admission) included age, body mass index (BMI), ethnicity, marital status, education level, family history of cancer, intraductal carcinoma, perineural invasion (PNI), comorbidities (hypertension and diabetes), T stage, N stage, and Gleason score. Laboratory parameters included PSA, serum testosterone, hemoglobin (HGB), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), and albumin (ALB).

Statistical analysis

Data analyses were conducted using SPSS 26.0. The normality of continuous variables were analyzed using the Kolmogorov-Smirnov test. Normally distributed data were expressed

as mean ± standard deviation and compared using independent sample t-tests. Non-normally distributed data were presented as interquartile range (IQR) and analyzed using the Mann-Whitney U test. For the comparison of categorical variables, we used chi-square (χ^2) tests. When the expected frequencies were greater than or equal to 5, the standard chi-square test was applied. For cases where the expected frequencies were less than 5, we used the Yates' continuity correction to ensure the accuracy of the test results. A two-tailed *P*-value <0.05 was considered statistically significant.

Logistic regression was used to identify factors associated with progression from HBTB-Pca to CRPC. The predictive performance of significant factors was evaluated using the receiver operating characteristic (ROC) curves. Model calibration and clinical utility were assessed using calibration curves, the Hosmer-Lemeshow (H-L) goodness-of-fit test, and decision curve analysis (DCA). The Nomogram was developed using the *rms* package in R software.

Results

Comparison of baseline data with laboratory indicators between the two groups

No significant differences were observed in terms of age, BMI, ethnicity, marital status, education level, family history of cancer, intraductal carcinoma, hypertension, diabetes, or N staging between the two groups (P>0.05, **Table 1**). However, the progression group showed higher proportions of PNI (P=0.011), Gleason score ≥8 (P=0.002), and T4 stage (P=0.012) compared to the non-progression group.

Analysis of laboratory indicators showed no significant differences in initial PSA, testosterone, HGB, or ALB between the two groups (P>0.05). In contrast, ALP (P<0.001) and LDH (P<0.001) levels were significantly elevated in the progression group (**Table 2**).

Predictive value of laboratory indicators for progression to CRPC

The predictive value of laboratory indicators was assessed using ROC curves. The results showed that all laboratory indicators demonstrated AUC values greater than 0.5, indicating varying degrees of predictive capability. LDH exhibited the highest predictive performance (AUC=0.721; **Figure 2E**; **Table 3**), followed by ALP (AUC=0.637; **Figure 2D**; **Table 3**). In contrast, initial PSA (AUC=0.563, **Figure 2A**), testosterone (AUC=0.545, **Figure 2B**), HGB (AUC=0.512, **Figure 2C**), and ALB (AUC=0.568, **Figure 2F**) showed limited predictive value (**Table 3**).

Grouping for model development and validation

Patients were randomly assigned to training (n=257) and validation (n=110) cohorts at a 7:3 ratio. No statistically significant differences were found in baseline characteristics or laboratory parameters between the two groups (P>0.05, **Table 4**), confirming the comparability of the two cohorts.

Identification of predictive factors for the progression from HBTB-PCa to CRPC

Logistic regression analysis was performed to identify factors associated with progression from HBTB-PCa to CRPC. Univariate analysis revealed that PNI (P=0.008), T stage (P=0.039), Gleason score (P<0.001), initial PSA (P=0.021), ALP (P<0.001), LDH (P<0.001), and ALB (P<0.001) were significantly associated with disease progression of HBTB-PCa to CRPC (**Table 5**). Multivariate analysis subsequently identified PNI (P=0.032), Gleason score (P=0.002), initial PSA (P=0.025), ALP (P=0.011), LDH (P<0.001), and ALB (P=0.019) as independent risk factors for HBTB-PCa progression to CRPC (**Table 6**).

Nomogram model construction and validation

A nomogram was developed based on the six independent predictors identified: PNI, Gleason score, initial PSA, ALP, LDH, and ALB. LDH demonstrated the most significant effect on the progression risk, followed by the other five variables, each contributing significantly to the model (**Figure 3A**).

ROC curve, calibration curve, and DCA were used to evaluate the discrimination, calibration, and clinical practical value of the model, respectively. In the training set, the DCA curve revealed a high net clinical benefit, with the threshold probability curve (red line) consistently above the "treat-all" and "treat-none" lines, indicating strong clinical utility, with the highest

Table 1. Comparison of baseline data between the two groups

Variables	Progression group (n=81)	Non-progression group (n=286)	χ^2	P
Age (years old)			0.959	0.327
≥65 years old	34	103		
<65	47	183		
BMI			1.903	0.168
≥25 kg/m^2	20	51		
<25 kg/m^2	61	235		
Ethnicity			2.954	0.086
Han	68	214		
Others	13	72		
Marital status			0.363	0.547
Married	75	272		
Divorced	6	14		
Education level			0.396	0.529
≥ High school	47	177		
< High school	34	109		
Family history of cancer			0.165	0.685
With	4	20		
Without	77	266		
Intraductal carcinoma			0.485	0.486
With	6	31		
Without	75	255		
Perineural invasion			6.454	0.011
With	41	189		
Without	40	97		
Hypertension			1.479	0.224
With	36	149		
Without	45	137		
Diabetes			1.322	0.25
With	28	80		
Without	53	206		
T-staging			6.379	0.012
T4	42	192		
<T4	39	94		
N-staging			0.565	0.452
N1	49	186		
N0	32	100		
Gleason score			10.017	0.002
≥8	36	183		
<8	45	103		

Note: BMI: Body Mass Index, PI: Perineural Invasion, PSA: Prostate-Specific Antigen, HGB: Hemoglobin, ALP: Alkaline Phosphatase, LDH: Lactate Dehydrogenase, ALB: Albumin.

yield reaching 77.82% (**Figure 3B**). The calibration curve generated using Bootstrap (iterations =500) showed close alignment between the predicted and observed probabilities in the training set, with the calibration line overlapping the diagonal reference line, indicating good model calibration; the concordance index (C-index) was 0.845 (95% CI: 0.787-0.903), and the goodness-of-fit test yielded a *P*-value of 0.552, indicating adequate model fit (**Figure**

Table 2. Comparison of laboratory parameters between the two groups

Indicators	Progression group (n=81)	Non-progression group (n=286)	T/Z	P
Initial PSA (ng/mL)	167.49±18.28	172.12±24.58	1.855	0.065
Testosterone (nmol/L)	17.03±7.92	18.11±7.50	1.092	0.277
HGB (g/L)	119.79±18.33	120.72±15.61	0.416	0.678
ALP (U/L)	155.37±28.02	142.90±28.72	3.469	<0.001
LDH (U/L)	219.08±26.39	196.86±25.88	6.79	<0.001
ALB (g/L)	38.00 [33.00, 42.00]	40.00 [34.00, 45.00]	1.861	0.063

Note: PSA: Prostate-Specific Antigen, HGB: Hemoglobin, ALP: Alkaline Phosphatase, LDH: Lactate Dehydrogenase, ALB: Albumin.

3C). Furthermore, ROC curve analysis demonstrated strong discriminatory performance, with an AUC of 0.845 for predicting progression from HBTB-PCa to CRPC (**Figure 3D**).

The predictive model was then validated using the validation cohort. The DCA curve also demonstrated a high net benefit in the validation set (**Figure 4A**). Similarly, the calibration curve showed close alignment between the predicted and observed probabilities in the validation set. The C index was 0.746 (95% CI: 0.628-0.865), and the goodness-of-fit test yielded a *P*-value of 0.401, indicating good model fit (**Figure 4B**). Additionally, ROC curve showed an AUC of 0.746 in the validation set, supporting the model's discriminatory ability in predicting the progression of HBTB-PCa to CRPC though it is slightly lower than the AUC obtained in the training set (**Figure 4C**).

Discussion

Prostate cancer (PCa) is one of the most common malignancies among older men, ranking high in both incidence and mortality rates globally [16, 17]. While early-stage or localized PCa can often be effectively controlled with radical surgery or radiotherapy, advanced PCa remains prevalent in China, especially in patients with HBTB. These patients typically experience poor prognosis and significant psychological stress [10]. Given these challenges, identifying reliable predictors for progression to CRPC is critical in guiding timely interventions, optimizing clinical decision-making, and improving patient quality of life.

In this study, Logistic regression analysis identified six key risk factors independent associated with progression from HBTB-PCa to CRPC: PNI, Gleason score, initial PSA, ALP, LDH, and ALB. These variables reflect distinct aspects of tumor biology, disease burden, and systemic response. Among them, PNI is particularly noteworthy, as it illustrates how tumor cells can utilize nerve sheaths to invade surrounding tissues. This phenomenon is closely related to alterations in tumor microenvironment and neurotrophic signaling pathways that facilitate cancer cell migration [18, 19]. Van et al. [20] reported that PNI significantly increases the risk of aggressive disease and is associated with higher chances of positive surgical margins, influencing postoperative outcomes. A comprehensive review by Niu et al. [21] similarly highlighted that PNI is frequently observed in multiple malignancies, including PCa, and correlates with adverse clinicopathological parameters. Further, Reeves et al. [22] identified PNI as an independent predictor for biochemical recurrence in patients undergoing radical prostatectomy.

Another essential predictor is the Gleason score, which reflects the level of histological differentiation and aggressiveness of PCa. A high Gleason score (≥8) signifies a more heterogeneous and poorly differentiated tumor population, which is often associated with reduced sensitivity to conventional therapies and an increased risk of progression to CRPC [23, 24]. Notably, PCa with a Gleason score of 9-10 has been associated with significantly worse outcomes under androgen deprivation therapy compared to those with a Gleason score below 8 [25, 26]. In line with this, Ham et al. [27] highlighted that a Gleason score of 9-10 was associated with higher all-cause and PCa-specific mortality than a Gleason score of 8, reinforcing the importance of thorough risk stratification in clinical management.

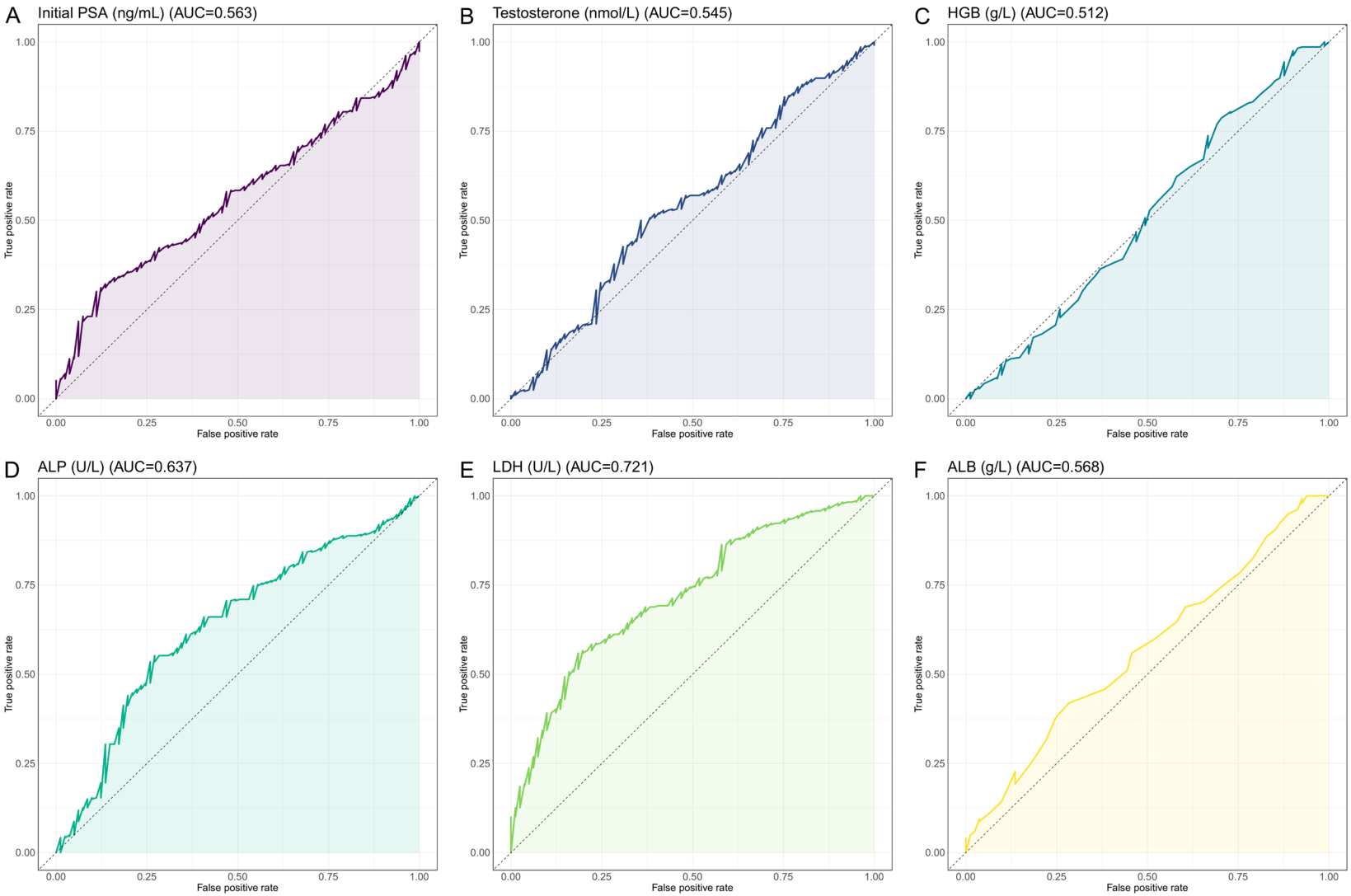

Figure 2. ROC curves for predicting patient progression using laboratory indicators. A. ROC curve of initial PSA for predicting patient progression. B. ROC curve of testosterone for predicting patients' progression. C. ROC curve of HGB for predicting patient progression. D. ROC curve of ALP for predicting patient progression. E. ROC curve of LDH for predicting patients' progression. F. ROC curve of ALB for predicting patients' progression. Note: Receiver Operating Characteristic (ROC), Prostate-Specific Antigen (PSA), Hemoglobin (HGB), Alkaline Phosphatase (ALP), Lactate Dehydrogenase (LDH), Albumin (ALB).

Table 3. ROC curve parameters for laboratory parameters in predicting disease progression

Marker	AUC	95% CI	Specificity	Sensitivity	Youden index	Cutoff
Initial PSA	0.563	0.498-0.563	88.89%	30.07%	18.96%	186.980
Testosterone	0.545	0.473-0.545	64.20%	50.00%	14.20%	18.835
HGB (g/L)	0.512	0.436-0.512	29.63%	78.67%	8.30%	108.500
ALP (U/L)	0.637	0.569-0.637	72.84%	55.24%	28.08%	153.650
LDH (U/L)	0.721	0.661-0.721	81.48%	55.94%	37.43%	215.435
ALB (g/L)	0.568	0.498-0.568	71.60%	41.96%	13.56%	41.500

Note: AUC: Area Under the Curve, PSA: Prostate-Specific Antigen, HGB: Hemoglobin, ALP: Alkaline Phosphatase, LDH: Lactate Dehydrogenase, ALB: Albumin.

Table 4. Comparison of baseline data between validation and training groups

Variables	Training group (n=257)	Validation group (n=110)	χ^2	P
Age (years old)			0.063	0.802
≥65 years old	97	40		
<65	160	70		
BMI			0.615	0.433
≥25 kg/m^2	47	24		
<25 kg/m^2	210	86		
Ethnicity			0.159	0.690
Han	196	86		
Others	61	24		
Marital status			0.000	0.998
Married	243	104		
Divorced	14	6		
Education level			0.189	0.664
≥High school	155	69		
<High school	102	41		
Family history of cancer			1.022	0.312
With	19	5		
Without	238	105		
Intraductal carcinoma			1.213	0.271
With	23	14		
Without	234	96		
Perineural invasion			0.000	0.988
With	161	69		
Without	96	41		
Hypertension			0.312	0.577
With	132	53		
Without	125	57		
Diabetes			1.194	0.275
With	80	28		
Without	177	82		
T-staging			0.461	0.497
T4	161	73		
<T4	96	37		
N-staging			0.138	0.710
N1	163	72		
N0	94	38		

Gleason score			0.715	0.398
≥8	157	62		
<8	100	48		
Initial PSA			1.386	0.239
≥186.980	195	77		
<186.980	62	33		
Testosterone			0.109	0.741
≥18.835	138	57		
<18.835	119	53		
HGB (g/L)			0.169	0.681
≥108.500	58	27		
<108.500	199	83		
ALP (U/L)			0.483	0.487
≥153.650	134	53		
<153.650	123	57		
LDH (U/L)			0.016	0.901
≥215.435	135	57		
<215.435	122	53		
ALB (g/L)			0.063	0.802
≥41.500	160	64		
<41.500	97	46		

Note: BMI: Body Mass Index, PI: Perineural Invasion, PSA: Prostate-Specific Antigen, HGB: Hemoglobin (HGB), ALP: Alkaline Phosphatase, LDH: Lactate Dehydrogenase, ALB: Albumin.

Table 5. Univariate analysis of risk factors for the progression of high bone tumor burden prostate cancer to castration-resistant prostate cancer

Variable	β	SE	P	OR	95% CI	
					Lower	Upper
Age (years old)	-0.235	0.306	0.442	0.790	0.435	1.449
BMI	-0.366	0.368	0.319	0.693	0.343	1.464
Ethnicity	-0.792	0.414	0.055	0.453	0.188	0.972
Marital status	0.360	0.612	0.556	1.434	0.381	4.478
Education level	0.222	0.304	0.466	1.248	0.684	2.261
Family history of cancer	0.448	0.648	0.489	1.565	0.498	6.907
Intraductal carcinoma	0.330	0.572	0.564	1.391	0.497	4.953
Perineural invasion	0.814	0.305	0.008	2.256	1.242	4.122
Hypertension	0.387	0.302	0.200	1.473	0.816	2.681
Diabetes	-0.529	0.312	0.090	0.589	0.321	1.094
T-staging	0.628	0.304	0.039	1.874	1.031	3.410
N-staging	0.015	0.311	0.962	1.015	0.545	1.856
Gleason score	1.293	0.314	0.000	3.643	1.987	6.827
Initial PSA	-0.997	0.434	0.021	0.369	0.146	0.816
Testosterone	-0.404	0.307	0.187	0.667	0.362	1.210
HGB	-0.265	0.347	0.444	0.767	0.394	1.547
ALP	-1.303	0.339	0.000	0.272	0.136	0.517
LDH	-1.935	0.390	0.000	0.144	0.063	0.297
ALB	-0.666	0.333	0.046	0.514	0.261	0.970

Note: BMI: Body Mass Index, PI: Perineural Invasion, PSA: Prostate-Specific Antigen, HGB: Hemoglobin, ALP: Alkaline Phosphatase, LDH: Lactate Dehydrogenase, ALB: Albumin.

Table 6. Multivariate analysis identifying independent risk factors for the progression of high bone tumor burden prostate cancer to castration-resistant prostate cancer

Variable	β	SE	P	OR	95% CI	
					Lower	Upper
Perineural invasion	0.767	0.358	0.032	2.154	1.071	4.394
T-staging	0.561	0.363	0.122	1.753	0.861	3.592
Gleason score	1.133	0.357	0.002	3.105	1.556	6.351
Initial PSA	-1.092	0.487	0.025	0.336	0.120	0.830
ALP	-0.977	0.383	0.011	0.376	0.173	0.785
LDH	-1.911	0.430	0.000	0.148	0.060	0.329
ALB	-0.930	0.397	0.019	0.395	0.176	0.841

Note: BMI: Body Mass Index, PI: Perineural Invasion, PSA: Prostate-Specific Antigen, HGB: Hemoglobin, ALP: Alkaline Phosphatase, LDH: Lactate Dehydrogenase, ALB: Albumin.

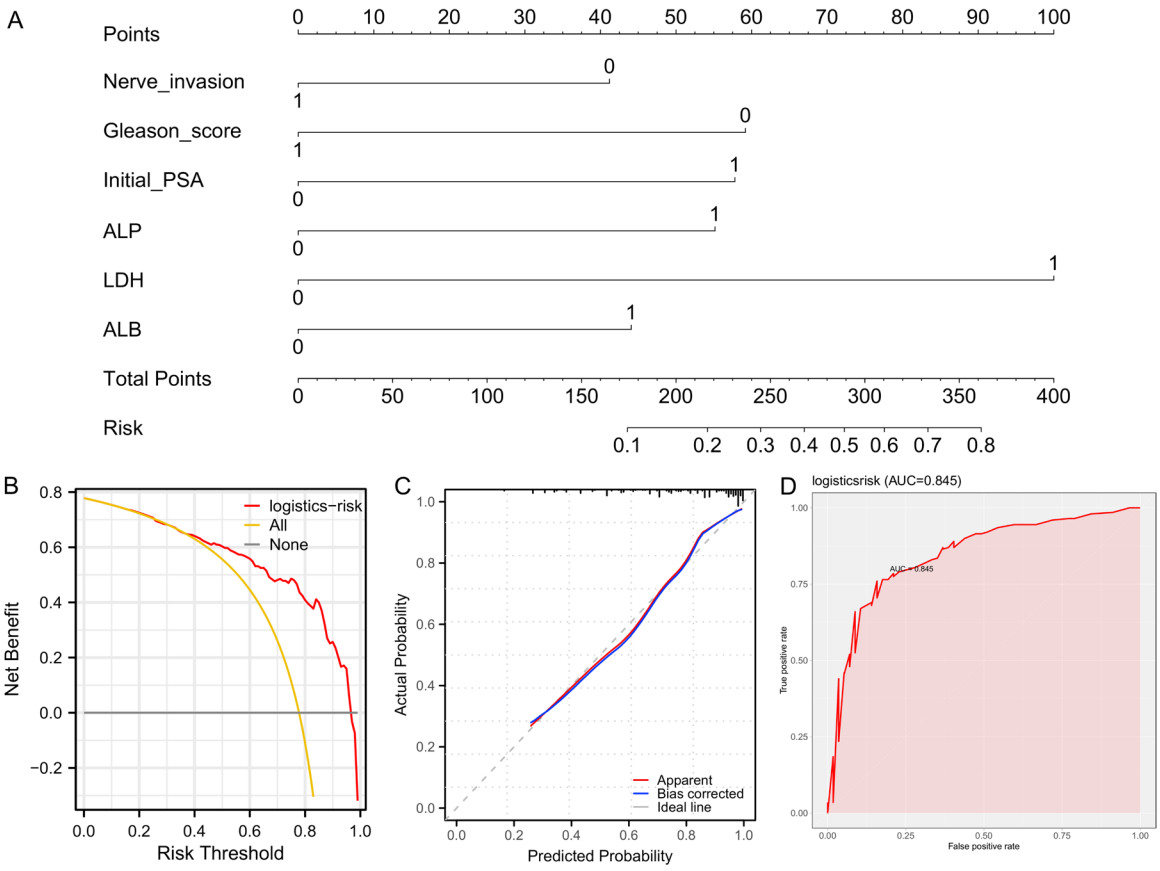

Figure 3. Construction of a Nomogram model for the prediction of progression from HBTB-PCa to CRPC and its internal validation. A. Construction of the Nomogram model. B. Clinical benefit of the Nomogram model in predicting the progression of HBTB-PCa to CRPC. C. Consistency between the predicted probability and the observed probability. D. ROC curve for analyzing the discrimination ability of the Nomogram. Note: Castration-Resistant Prostate Cancer (CRPC), High Bone Tumor Burden (HBTB), Prostate Cancer (PCa), Receiver Operating Characteristic (ROC), Alkaline Phosphatase (ALP), Lactate Dehydrogenase (LDH), Albumin (ALB).

In terms of laboratory indicators, initial PSA, ALP, LDH, and ALB were identified as significant predictors of progression in HBTB-PCa patients. Elevated PSA generally suggests an increased tumor burden and more aggressive disease behavior [28]. Increased ALP and LDH levels are commonly associated with active bone involvement and enhanced tumor metabolic acti-

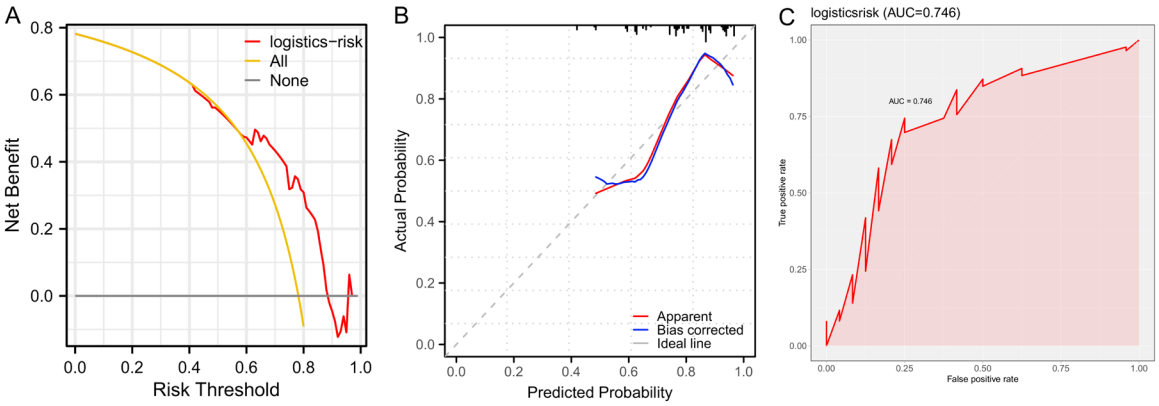

Figure 4. External validation of the Nomogram model. A. Clinical benefit of the Nomogram model in predicting the progression of HBTB-PCa to CRPC in validation cohort. B. Consistency between the predicted probability and the observed probability in validation cohort. C. ROC curve for analyzing the discrimination ability of the Nomogram in validation cohort. Note: Castration-Resistant Prostate Cancer (CRPC), High Bone Tumor Burden (HBTB), Prostate Cancer (PCa), Receiver Operating Characteristic (ROC).

vity, suggesting both skeletal metastases and systemic disease progression [29, 30]. Schlack et al. [29] noted that elevated ALP levels during enzalutamide therapy were associated with worse prognosis in osseous metastatic CRPC patients, while Poteska et al. [30] observed that dynamic changes in ALP and LDH levels may correlate with clinical benefit, disease-free survival, and overall survival, even in the absence of a PSA response. Additionally, hypoalbuminemia may reflect poor nutritional status and a systemic pro-inflammatory state, both of which are correlated with more advanced disease states and worse outcomes.

Building on these observations, we integrated the six independent risk factors (PNI, Gleason score, initial PSA, ALP, LDH, and ALB) to construct a Nomogram model for predicting HBTB-PCa progression to CRPC. The model demonstrated strong predictive performance, with an AUC of 0.845 in the training set and an AUC of 0.746 in the validation, underscoring its discrimination and robustness. Among the predictors, LDH contributed the most to the model, potentially reflecting an association with hypoxic tumor microenvironments and heightened metabolic activity. Moreover, the Nomogram incorporated other biological and clinical factors into an individualized risk profile, which may facilitate in making more personalized treatment strategies, such as early intensification of ADT, prompt initiation of radiotherapy, or the incorporation of novel hormonal agents.

While the Nomogram demonstrated favorable discrimination and clinical utility, slight deviations at higher probability thresholds were observed in the calibration analysis. These discrepancies could stem from a relatively modest sample size during external validation or the heterogeneity of patient characteristics. To improve generalizability, further validation in larger, multicenter cohorts with broader demographic and clinical diversity is warranted. Moreover, future studies may consider incorporating emerging biomarkers-such as genomic alterations, molecular imaging parameters-to further enhance the model's predictive accuracy. Incorporating such advanced diagnostic tools could also contribute to a deeper understanding of the mechanisms underlying disease progression.

Limitations

Despite providing important insights, this study has several limitations. First, its retrospective, single-center design may introduce selection and information biases, thereby limiting causal inferences and generalizability. Second, the relatively short follow-up period for some patients restricted the evaluation of long-term outcomes and survivorship trends. Third, although internal and external validations were performed, the overall sample size remains modest for constructing a comprehensive prediction tool; larger cohorts are needed to improve the model's reliability and refine cut-off points. Fourth, certain potentially relevant variables-such as

genetic alterations (e.g., BRCA mutations) and advanced imaging findings-were not included in the analysis but may have enriched our understanding of disease progression.

Future directions

To address these concerns, future studies should adopt prospective, multicenter designs with standardized protocols. Increasing the sample size and diversity of patient populations will improve the robustness and external validity of the nomogram. Furthermore, incorporating novel biomarkers and leveraging next-generation sequencing data may provide deeper insights into the molecular pathways driving CRPC progression. Incorporating these factors with traditional clinical and laboratory variables could yield an even more powerful, personalized tool. Meanwhile, extended follow-up periods would shed light on the Nomogram's utility for long-term prognostic assessments and support more dynamic decision-making regarding therapeutic escalation or de-escalation.

Conclusion

In summary, this study highlights several key risk factors-PNI, Gleason score ≥8, initial PSA, elevated ALP and LDH, and decreased ALB-that are independently associated with HBTB-PCa progression to CRPC. By integrating these variables into a Nomogram (internal AUC=0.845; external AUC=0.746), we offer a practical and user-friendly clinical tool for individualized risk assessment and treatment planning. This model has the potential to facilitate early identification of high-risk patients and guide personalized therapeutic strategies, ultimately improving clinical outcomes in HBTB-PCa patients.

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Disclosure of conflict of interest

None.

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