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ORIGINAL RESEARCH

Development and Validation of a Clinic Machine Learning Classifier for the Prediction of Risk Stratifications of Prostate Cancer Bone Metastasis Progression to Castration Resistance

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Objective: To explore the predictive factors and predictive model construction for the progression of prostate cancer bone metastasis to castration resistance.

Methods: Clinical data of 286 patients diagnosed with prostate cancer with bone metastasis, initially treated with endocrine therapy, and progressing to metastatic castration resistant prostate cancer (mCRPC) were collected. By comparing the differences in various factors between different groups with fast and slow occurrence of castration-resistant prostate cancer (CRPC). Kaplan-Meier survival analysis and COX multivariate risk proportional regression model were used to compare the differences in the time to progression to CRPC in different groups. The COX multivariate risk proportional regression model was used to evaluate the impact of candidate factors on the time to progression to CRPC and establish a predictive model. The accuracy of the model was then tested using receiver operating characteristic (ROC) curves and decision curve analysis (DCA).

Results: The median time for 286 mCRPC patients to progress to CRPC was 17 (9.5–28.0) months. Multivariate analysis showed that the lowest value of PSA (PSA nadir), the time when PSA dropped to its lowest value (timePSA), and the number of BM, and LDH were independent risk factors for rapid progression to CRPC. Based on the four independent risk factors mentioned above, a prediction model was established, with the optimal prediction model being a random forest with area under curve (AUC) of 0.946[95% CI: 0.901–0.991] and 0.927[95% CI: 0.864–0.990] in the training and validation cohort, respectively.

Conclusion: After endocrine therapy, the PSA nadir, timePSA, the number of BM, and LDH are the main risk factors for rapid progression to mCRPC in patients with prostate cancer bone metastases. Establishing a CRPC prediction model is helpful for early clinical intervention decision-making.

Keywords: metastatic prostate cancer, resistance to castration, PSA minimum value, lactate dehydrogenase, prediction model

Introduction

Prostate cancer is the most common malignant tumor in elderly men and the second leading cause of cancer death in men worldwide, second only to lung cancer.[1,2] According to the global cancer statistics in 2022, the incidence of prostate cancer in the world in recent years has continued to grow, and has become an important disease burden for all countries in the world.[3] Localized prostate cancer often has a better prognosis after radical treatment, but epidemiological data shows that the vast majority of patients are already in the advanced stage of the disease at the time of treatment, experiencing bone metastasis and losing the opportunity for radical treatment.[4] Prostate cancer bone metastasis not only causes bone related symptoms such as bone pain, limited mobility, and increased risk of fractures but also leads to patients losing the opportunity for curative surgery.[5]

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Androgen deprivation therapy (ADT) is the gold standard for treating prostate cancer patients with bone metastases.[6] Although this endocrine therapy has a significant initial therapeutic effect on these patients, most patients inevitably progress to castration resistant prostate cancer (CRPC) after 1 to 2 years of treatment.[6,7] The survival time of patients who progress to CRPC is significantly shortened, and currently the treatment options for CRPC are limited. The effective time window for second-generation androgen drugs such as abiraterone and enzalutamide is only about 7 months.[8] Nowadays, the occurrence of CRPC is a challenging issue in the clinical diagnosis, treatment, and basic treatment of prostate cancer. There is a significant difference in the time it takes for different patients to develop CRPC after receiving ADT treatment in clinical practice, especially for prostate cancer patients who have significant individual differences. Therefore, exploring the speed at which prostate cancer patients with bone metastasis progress to CRPC can better indicate which patients will benefit from ADT treatment, while other patients may benefit more from chemotherapy, which has certain guiding significance for the clinical diagnosis and treatment of prostate cancer patients.

Up to now, there is a lack of accurate and ideal risk prediction models for the occurrence of CRPC.[9,10] Previous studies have found that factors such as age, prostate specific antigen at diagnosis, the lowest value and time of PSA descent, Gleason score, number of bone metastases, alkaline phosphatase, etc. may be closely related to the time of progression to CRPC.[11–13] Fortunately, with the rapid development of artificial intelligence and the increasing scale and complexity of biological data, the use of artificial intelligence represented by machine learning in biology has become increasingly frequent. Currently, it has been widely applied in the processing of big data information and numerous heterogeneous data in medical research.[14] Currently, there are many studies on predictive models for prostate cancer bone metastasis both domestically and internationally.[15–17] However, due to limitations in sample size and research methods, there are significant differences and limitations between different studies. In the process of model building, logistic regression analysis has been used to screen predictive factors in small sample data, and then directly train and model in the overall sample, however, this may lead to overfitting problems in the model, where the model exhibits superior performance in the training samples but performs poorly in the validation and test sets, resulting in a large generalization error and an increasingly prominent overfitting problem.[18,19] In addition, molecular indicators have gradually been used for disease diagnosis and treatment prediction in recent years, especially as non-invasive diagnosis and prognosis evaluation. Molecular indicators have demonstrated their unique advantages.[20,21] In view of this, the aim of this study is to use molecular indicators combined with clinical features to construct a predictive model for the progression of metastatic prostate cancer to metastatic castration resistant prostate cancer (mCRPC), which can guide the clinical diagnosis and treatment of prostate cancer patients with bone metastasis to a certain extent.

Materials and Methods

Crowd Queue

We retrospectively analyzed prostate cancer patients diagnosed with bone metastasis in the urology department of our hospital from January 2016 to December 2022. All patients underwent liver and kidney function, PSA, testosterone, blood routine, and bone scan examinations at the time of diagnosis. Regular re-examination of liver and kidney function and blood routine should be conducted in the first 3 months after the patient receives treatment, and then every 3 to 6 months thereafter; PSA and testosterone should be rechecked once a month after the start of treatment. If the patient's condition is stable, they should be rechecked every 2 to 3 months after 1 year. After endocrine therapy, if the patient progresses to CRPC, the time of receiving endocrine therapy, the time when PSA and testosterone decrease to their lowest values should be recorded in a timely manner.

The endpoint event of this study was CRPC, which is defined as the duration from the patient receiving ADT to the diagnosis of CRPC. According to the guidelines of the European Association of Urology (EAU), the diagnostic criteria for CRPC are defined as follows: 1. Patients with serum testosterone <50ng/dL or 1.7 nmol/L; 2. Patients with continuous increase in PSA (ie, PSA is elevated three times in a week, and the increase is greater than 50% compared to the lowest value); 3. Patients with PSA >2ng/mL or imaging progression.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: 1. Patients diagnosed with prostate cancer with bone metastasis through imaging and pathological biopsy; 2. Patients who receive standardized ADT treatment and progress to CRPC; 3. Patients who have complete clinical data and voluntarily participate in this study have signed an informed consent form. Exclusion criteria: 1. Patients with other malignant tumors; 2. Patients with prostate cancer accompanied by visceral metastasis; 3. Patients with incomplete follow-up or incomplete data. In addition, the diagnostic criteria for bone metastasis in prostate cancer are initially screened using bone scans to identify the presence of bone metastases (ie, increased or decreased uptake of local lesions). For suspicious lesions that cannot be diagnosed clearly, imaging examinations (such as CT or MRI) are performed on the patient, and imaging experts are invited for consultation if necessary. This retrospective study has been approved by the Ethics Committee of Baotou Cancer Hospital for unified implementation (No. 20220120). The study complies with the Helsinki Declaration, and all patients are aware of and have signed informed consent forms for this study. The patient inclusion and prediction model construction process for this study is shown in Figure 1.

Prediction Model Construction and Evaluation Criteria

This study used the strategies of logistic regression and Least absolute shrinkage and selection operator (LASSO) regression in machine learning algorithms to screen predictive variables and select candidate variables by taking the intersection. As previously reported in literature, in LASSO regression analysis, parameters are optimal values determined through cross-validation methods.[22,23] These changes will gradually compress most of the feature variables to zero, and then adjust the corresponding minimum mean square error λ accordingly, thus considering it as the optimal subset of variables.

In addition, the population queue included in this study will be randomly divided into a 7–3 training set and an internal testing set using a random number method for the construction and internal testing of the prediction model. In the process of establishing and validating the prediction model, we will select sixteen candidate prediction variables and incorporate them into four machine learning prediction model algorithms, namely: generalized linear regression mode (GLRM), random forest model (RFM), decision tree model (DTM), and neural network model (NNM). Based on the training set data, this study used ten-fold cross validation to train and internally validate the model. Finally, the predictive classification performance of each machine learning prediction model was comprehensively evaluated by calculating the area under the curve (AUC) and decision curve analysis (DCA) based on the receiver operating characteristic (ROC) curve.

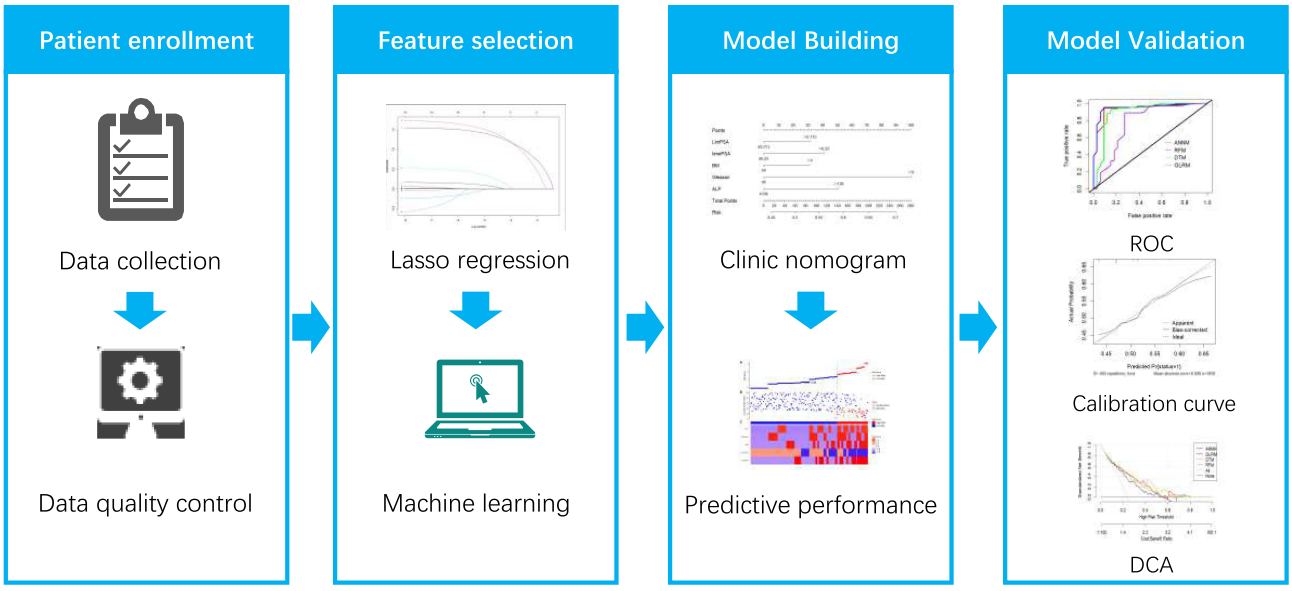

Figure 1 The flowchart of patient enrollment and data preprocessing.

Statistical Analysis

The statistical analysis software involved in this study includes R software (version 4.3.2, download address: https://www.r-project.org/). Among them, econometric data that conform to normal distribution are presented using mean ± standard deviation, and intergroup comparisons are conducted using *t*-test; Measurement data that do not conform to a normal distribution are represented by median and interquartile intervals, and intergroup comparisons are conducted using Mann Whitney rank sum tests. Classification data is represented by frequency, and inter-group comparisons are conducted using chi square test. $P < 0.05$ is considered to have significant statistical significance for the difference.

Results

Basic Characteristics of Prostate Cancer Patients

The median time for patients to progress to CRPC was 17 (9.5–28.0) months. Among them, there were 112 cases (39.16%) and 174 cases (60.84%) in the rapid progression group and slow progression group, respectively. Among them, the lowest PSA value (PSA nadir), time to reach the lowest value of PSA (timePSA), number of bone metastases (BM), Gleason score and alkaline phosphatase (ALP) between the rapid progression group and the slow progression group were statistically significant ($P < 0.05$). A comparison of the basic characteristics of clinical information of all patients was shown in Table 1 and Supplementary Table 1.

Table 1 Clinical Characteristics of Patients with Metastatic Prostate Cancer

Variables	Overall(N=286)	RPG(N=112)	SPG(N=174)	P-value
Age (%), year				
≤72	141 (49.3)	56 (50.0)	85 (48.9)	0.945
>72	145 (50.7)	56 (50.0)	89 (51.1)	
PSA (%), ng/mL				
≤149.45	141 (49.3)	49 (43.8)	92 (52.9)	0.166
>149.45	145 (50.7)	63 (56.2)	82 (47.1)	
LimPSA (%), ng/mL				
≤0.715	165 (57.7)	33 (29.5)	132 (75.9)	<0.001
>0.715	121 (42.3)	79 (70.5)	42 (24.1)	
timePSA (%), d				
≤6.25	136 (47.6)	87 (77.7)	49 (28.2)	<0.001
>6.25	150 (52.4)	25 (22.3)	125 (71.8)	
BM (%)				
≤4	157 (54.9)	28 (25.0)	129 (74.1)	<0.001
>4	129 (45.1)	84 (75.0)	45 (25.9)	
Gleason (%), score				
≤9	161 (56.3)	39 (34.8)	122 (70.1)	<0.001
>9	125 (43.7)	73 (65.2)	52 (29.9)	
Hb (%), g/L				
≤128	145 (50.7)	54 (48.2)	91 (52.3)	0.58
>128	141 (49.3)	58 (51.8)	83 (47.7)	
Alb (%), g/L				
≤39.4	117 (40.9)	48 (42.9)	69 (39.7)	0.679
>39.4	169 (59.1)	64 (57.1)	105 (60.3)	
ALP (%), U/L				
≤136	159 (55.6)	36 (32.1)	123 (70.7)	<0.001
>136	127 (44.4)	76 (67.9)	51 (29.3)	
LDH (%), U/L				
≤199.6	145 (50.7)	52 (46.4)	93 (53.4)	0.299
>199.6	141 (49.3)	60 (53.6)	81 (46.6)	

(*Continued*)

Table 1 (Continued).

Variables	Overall(N=286)	RPG(N=112)	SPG(N=174)	P-value
UA (%), μmol/L				
≤338.6	137 (47.9)	57 (50.9)	80 (46.0)	0.49
>338.6	149 (52.1)	55 (49.1)	94 (54.0)	
CysC (%), mg/L				
≤1.02	145 (50.7)	58 (51.8)	87 (50.0)	0.862
>1.02	141 (49.3)	54 (48.2)	87 (50.0)	
LimTESTO (%), nmol/L				
≤0.1	141 (49.3)	53 (47.3)	88 (50.6)	0.677
>0.1	145 (50.7)	59 (52.7)	86 (49.4)	
timeTESTO (%), d				
≤11	141 (49.3)	51 (45.5)	90 (51.7)	0.368
>11	145 (50.7)	61 (54.5)	84 (48.3)	
Diabetes (%)				
Yes	143 (50.0)	53 (47.3)	90 (51.7)	0.545
No	143 (50.0)	59 (52.7)	84 (48.3)	
Metformin (%)				
Yes	141 (49.3)	49 (43.8)	92 (52.9)	0.166
No	145 (50.7)	63 (56.2)	82 (47.1)	

Abbreviations: RPG, rapid progress group; SPG, slow progress group; PSA, prostate specific antigen; LimPSA, the lowest value of PSA; timePSA, the time when PSA dropped to its lowest value; BM, bone metastases; Hb, hemoglobin; Alb, albumin; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; UA, uric acid; CysC, Cystatin C; LimTESTO, the lowest value of testosterone; timeTESTO, the time when testosterone dropped to its lowest value.

Risk Factors for Metastatic Prostate Cancer

The Results of univariate analysis showed that the lowest value of PSA, the time when PSA dropped to the lowest value, EOD, alkaline phosphatase and LDH were significantly related to the time of CRPC occurrence ($P < 0.05$). Then, we used whether the patient developed CRPC within 2 years as the dependent variable, and included variables with statistical significance in single-factor analysis into multivariate Cox regression. The results showed that the PSA nadir, the time PSA, the number of bone metastases (BM), and LDH were independent prognostic factors for time to CRPC development (Table 2). In addition, we conducted a survival analysis on the occurrence of CRPC in patients with different clinical factors.

Establishment and Verification of mCRPC Risk Prediction Model

We constructed a prediction model for the risk of mCRPC based on the above candidate variables. The ROC curve analysis results showed that the AUC of the RFM, ANNM and DTM in the training set were 0.946 (95% CI: 0.901~0.991), 0.824 (95% CI:0.671~0.977), 0.793 (95% CI:0.640~0.946). In addition, the above three prediction models were included in the validation set for testing (Table 3, Figure 2 and Supplementary Figure 1). The results showed that the areas under the curve of the random forest model, neural network model and decision tree model in the testing set were 0.927 (95% CI: 0.864–0.990), 0.819 (95% CI: 0.666–0.972), 0.803 (95% CI: 0.650–0.956). At the same time, we also fit the risk prediction model of mCRPC based on Cox risk regression and included statistically significant candidate predictor variables into the prediction model.The results suggest that the areas under the curve of nomogram in the training set and validation set are 0.767 (95% CI: 0.579–0.955) and 0.779 (95% CI: 0.610–0.948), respectively (Figure 3).

Validation of mCRPC Prediction Model Performance

We included the mCRPC prediction models constructed based on different machine learning algorithms into DCA curve analysis. The results showed that the prediction performance of RFM showed the optimal prediction performance in both the training set and the validation set (Figure 4). At the same time, the visual mCRPC patient risk stratification analysis

Table 2 Univariate and Multivariate COX Risk Regression Analysis of Progression to CRPC in Patients with Bone Metastatic Prostate Cancer

Variables	Univariate			Multivariate		
	HR	95% CI	P-value	HR	95% CI	P-value
Age	0.652	0.441–1.007	0.061			
PSA	1.118	0.731–1.867	0.572			
LimPSA	3.071	1.362–4.910	<0.001	2.566	1.452–3.993	<0.001
timePSA	0.382	0.251–0.592	<0.001	0.417	0.217–0.791	<0.001
BM	1.889	1.021–3.557	0.018	2.278	1.223–4.281	0.004
Gleason	1.692	1.017–2.745	0.082			
Hb	0.842	0.553–1.307	0.417			
Alb	1.112	0.724–1.768	0.479			
ALP	2.006	1.223–3.257	0.002	1.261	0.781–2.072	0.126
LDH	1.646	1.032–2.559	0.017	1.667	1.034–2.717	0.022
UA	1.041	0.610–1.754	0.671			
CysC	0.976	0.607–1.553	0.829			
LimTESTO	0.776	0.425–1.091	0.663			
timeTESTO	1.113	0.558–1.827	0.371			
Diabetes	0.829	0.353–1.822	0.562			
Metformin	1.426	0.661–3.017	0.181			

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval; PSA, prostate specific antigen; LimPSA, the lowest value of PSA; timePSA, the time when PSA dropped to its lowest value; BM, bone metastases; Hb, hemoglobin; Alb, albumin; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; UA, uric acid; CysC, Cystatin C; LimTESTO, the lowest value of testosterone; timeTESTO, the time when testosterone dropped to its lowest value.

Table 3 Comparison of Predictive Efficacy of Progression to CRPC Prediction Models via ROC Curves

Model	Training Set			Internal Validation set		
	AUC Mean	AUC 95% CI	Variables[&]	AUC Mean	AUC 95% CI	Variables[&]
GLRM	0.767	0.579–0.955	5	0.779	0.610–0.948	5
RFM	0.946	0.901–0.991	5	0.927	0.864–0.990	5
ANNM	0.824	0.671–0.977	7	0.819	0.666–0.972	7
DTM	0.793	0.640–0.946	5	0.803	0.650–0.956	5

Note: [&]Variables included in the model.

shows that RFM can accurately separate the possibility of patients developing mCRPC (Figure 5), which has extremely forward-looking guiding significance for clinical diagnosis and treatment.

Discussion

The proportion of early-stage prostate cancer patients has shown a significant increasing trend worldwide. Due to the widespread popularity of PSA screening, the diagnosis rate of prostate cancer has been significantly improved, and the diagnosis time for suspected prostate cancer patients has also been advanced.[24] However, there are still some patients who have already experienced bone metastasis at the initial diagnosis, and previous studies have reported an incidence of prostate cancer bone metastasis of approximately 2.8% to 27.5%.[25–27] Therefore, identifying the risk factors for mCRPC and early assessing the time when patients benefit from ADT treatment is of great clinical significance for guiding individualized treatment and improving patient prognosis.

This study is the first to construct a machine learning prediction model that can be applied to clinical time based on clinical parameters of prostate cancer patients. It can provide a basis for predicting the early occurrence of CRPC in prostate cancer patients with bone metastases, and thus determine the benefit time of patients from receiving ADT

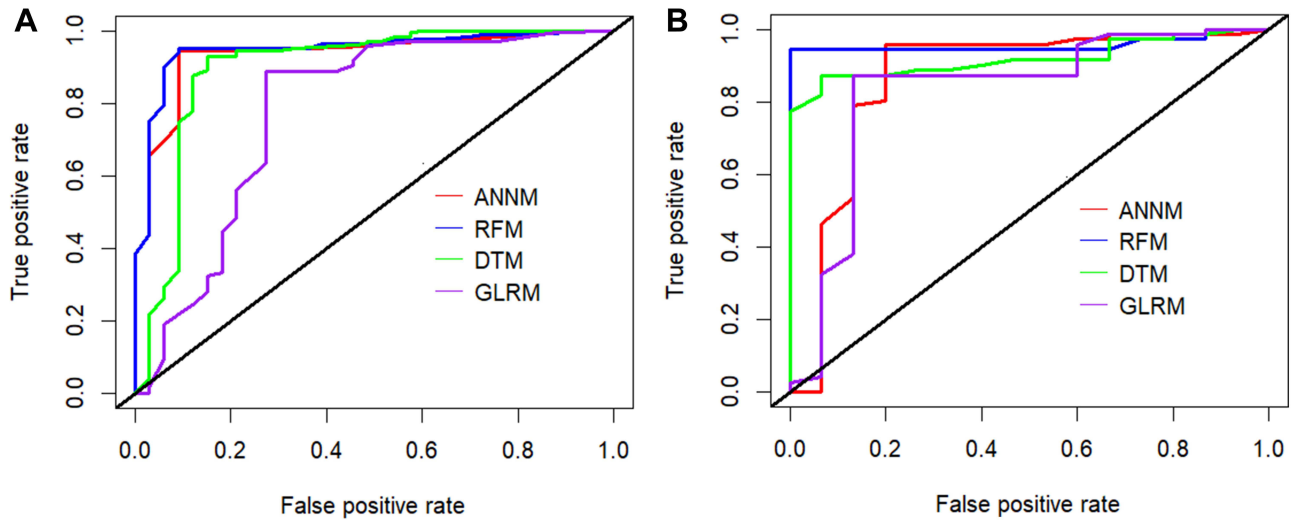

Figure 2 ROC of four machine learning algorithm. (**A**) Training set; (**B**) Validation set.

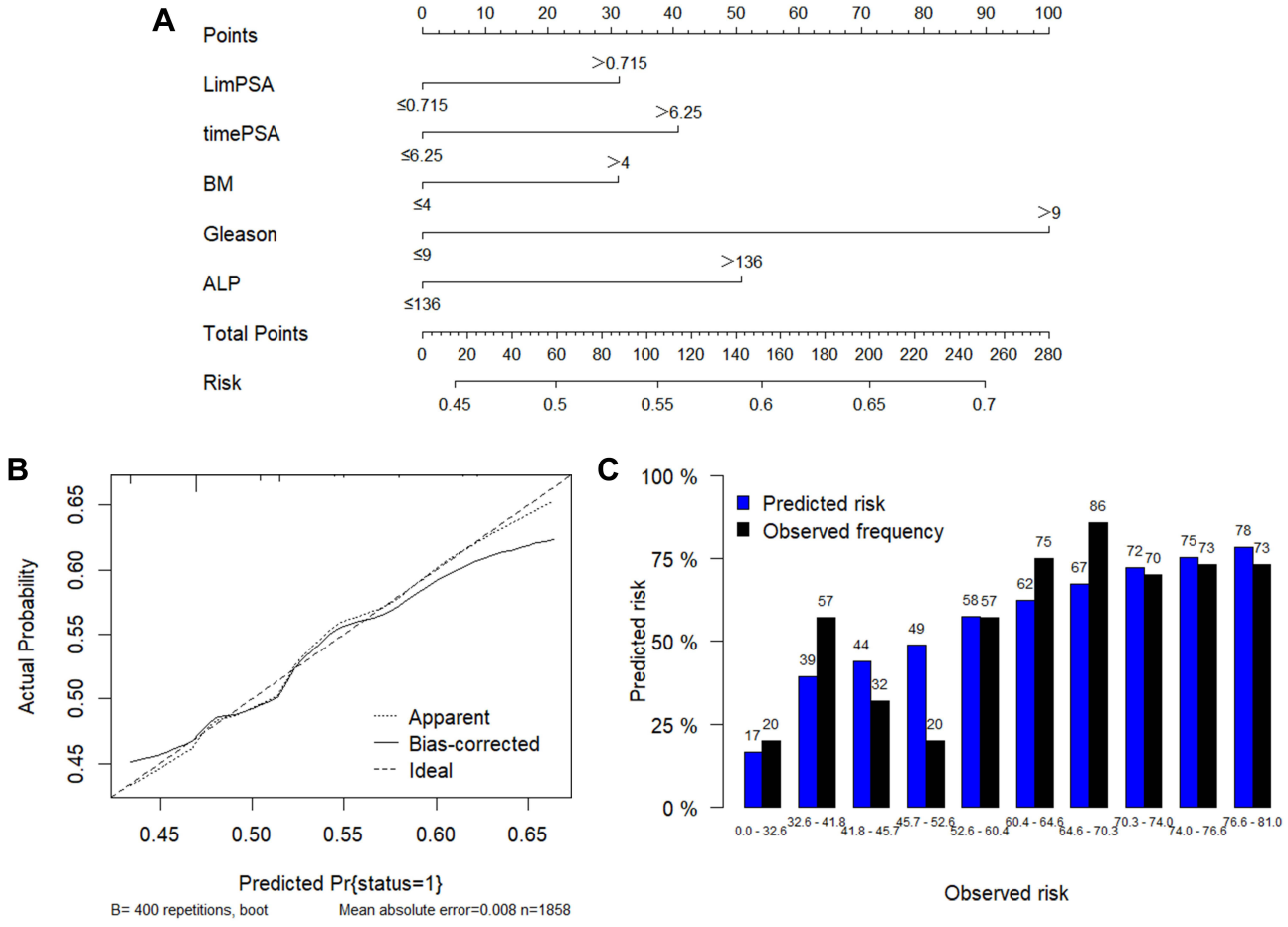

Figure 3 A clinic nomogram based on machine learning algorithms. (**A**) Nomogram; (**B**) Calibration curve; (**C**) Predicted frequency histogram.

treatment, so that clinical physicians can better formulate clinical diagnosis and treatment plans for patients. Although previous studies have explored predictive factors for the occurrence time of CRPC, a unified predictive factor has not yet been established.[28–30] For example, for patients receiving intermittent endocrine therapy, due to PSA fluctuations,

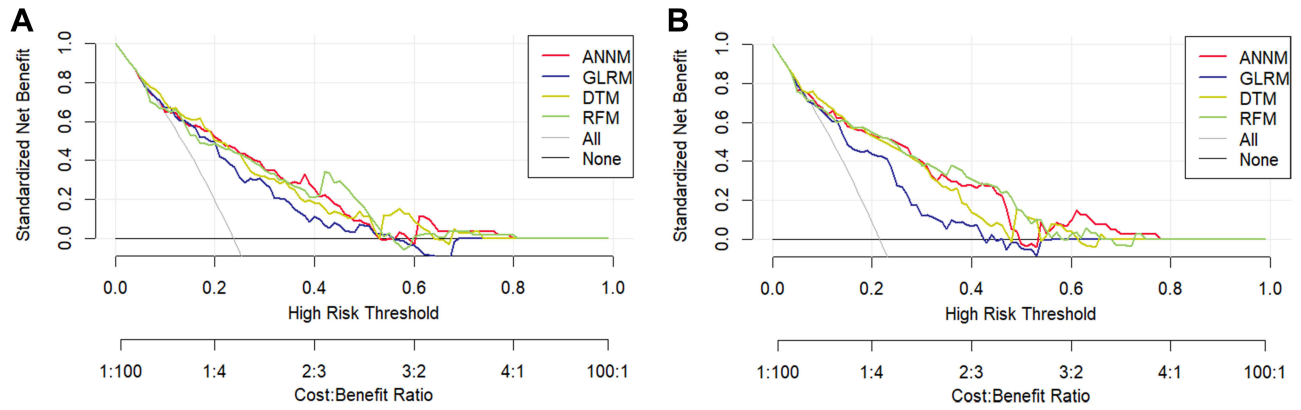

Figure 4 DCA of four machine learning algorithm. (**A**) Training set; (**B**) Validation set.

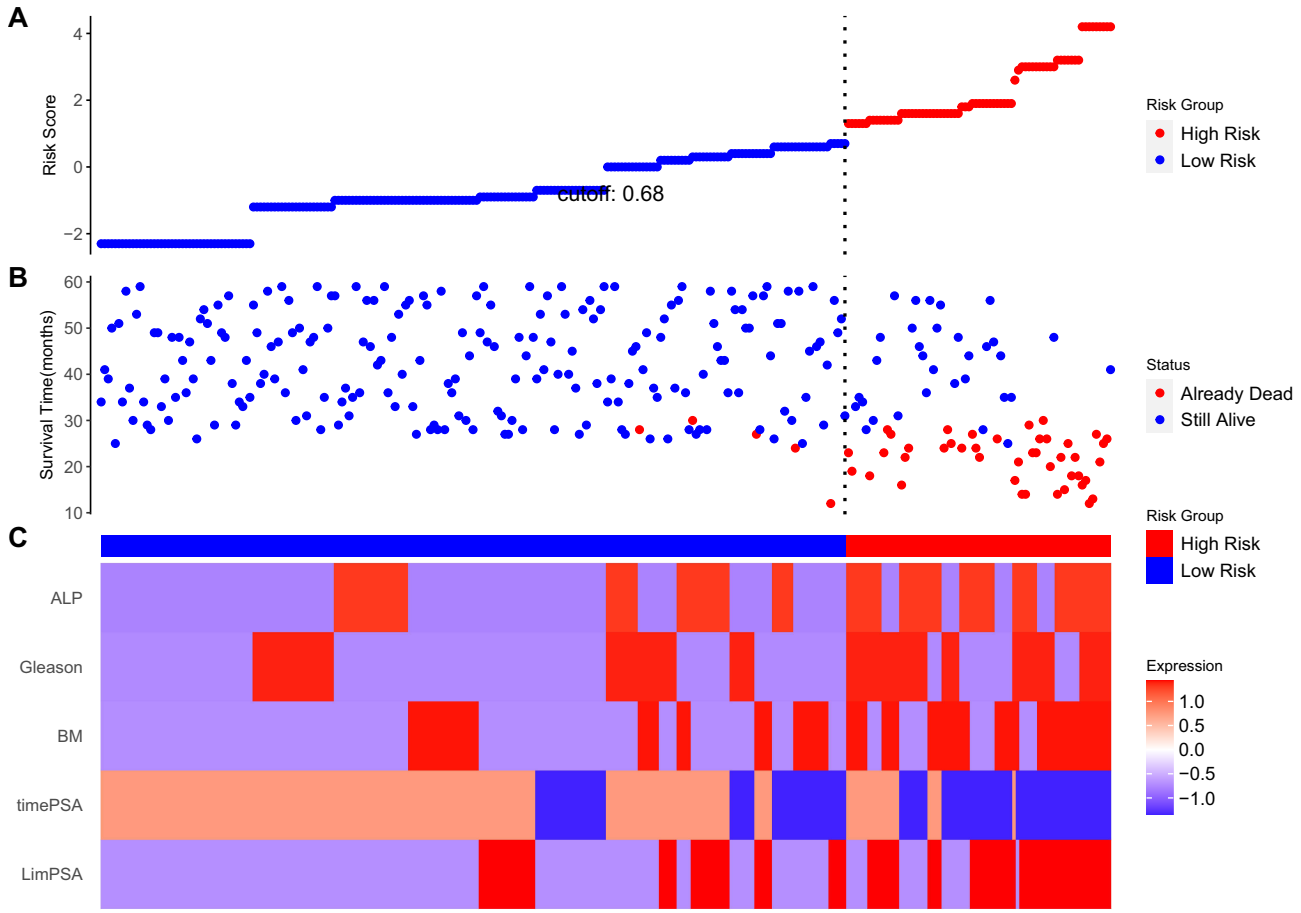

Figure 5 Number of prostate cancer patients in low-, and high-risk groups according to the clinic-ML nomogram predictive scores. (**A**) Risk score; (**B**) Survival time; (**C**) Prediction parameters.

especially for prostate cancer patients undergoing radical surgery or radiation therapy, the longer the interval between PSA rises, the longer it will take for the patient to develop CRPC.

In addition, studies have shown that prostate cancer patients who undergo radical prostatectomy or radiation therapy have a faster rate of decrease in PSA after intermittent ADT treatment, and their time to develop CRPC is also longer.[31,32] However, studies have also shown that prostate cancer patients who receive ADT have faster PSA declines and shorter progression-free survival and overall survival, which is consistent with the conclusions drawn in this

study.[33,34] We speculate that the larger the minimum PSA value, the shorter the time it takes to reach the minimum value, and the more likely patients are to develop CRPC in the early stages. This may be due to the fact that the lowest PSA level and the time it takes to reach the lowest PSA reflect the "adaptation window period" of androgen independent (or trend resistant) prostate cancer.[35] Coincidentally, previous studies have found that the number of bone metastases is an important predictor of rapid progression to CRPC in patients with metastatic prostate cancer, which is consistent with the conclusions of this study. However, this study found no significant correlation between Gleason score and the occurrence time of CRPC, suggesting a potential correlation with a small sample size.[36,37] In fact, patients with higher Gleason scores also have an increased risk of developing CRPC, which still needs to be further validated by expanding the population cohort.

Previous studies have shown that elevated lactate dehydrogenase (LDH) may be closely related to the overall survival of mCRPC patients.[38] As a key enzyme in the glycolysis process, LDH is mainly involved in the conversion of pyruvate to lactate under hypoxic conditions. LDH may be regulated by the HIFα signaling pathway, ensuring high levels of α in serum LDH and HIF1 in the body. Besides, the degree of activation of the VEGF angiogenesis signaling pathway is consistent, therefore we speculate that serum LDH levels may have important application significance in predicting CRP.[39,40] This study suggests that incorporating LDH into risk prediction models significantly improves the sensitivity and specificity of various prediction models, which is consistent with previous research results. In addition, previous studies have shown that LDH has relatively ideal predictive performance in various other malignant tumor prediction models, and LDH in circulating blood is easily obtainable in clinical practice, which also means that LDH has the potential to become a candidate biomarker for predicting prostate cancer bone metastasis. In summary, this study integrates potential candidate predictive parameters such as the lowest PSA value, time for PSA to decrease to the lowest value, number of bone metastases, LDH, etc. in prostate cancer patients with bone metastases who receive ADT treatment. It provides an exponential equation model for whether metastatic prostate cancer progresses to mCRPC in the early stage, which has convincing guiding significance for clinical treatment.

In this study, we found that machine learning algorithm prediction models can discover and identify different patterns and nonlinear relationships between multidimensional factors, thereby making accurate predictions for risk stratification. Among them, the prediction model constructed based on the random forest algorithm shows the optimal discrimination, especially when the same candidate variables are included as prediction parameters. The random forest algorithm can improve the prediction performance to 0.899, indicating that in clinical decision-making, candidate parameters may not be the only factor determining prediction performance, and the correction and testing of the prediction model algorithm should also be fully considered. Consistent with the training set, we further validated the predictive performance of the random forest prediction model in the internal test set. Compared to neural networks and support vector machines, the random forest algorithm exhibits more robust predictive performance, which is incomparable to the generalized linear regression prediction model. In future research, we will continue to expand the external test set to fully evaluate the generalizability of the random forest prediction model.

Our study inevitably has the following limitations. Firstly, this study belongs to a retrospective cohort study, therefore, the patients included in this study are affected by selection bias, and future prospective studies are still needed for verification; Secondly, the data included in this study is from a single center source, so the research results still need to be validated by multiple centers and a large sample to ensure the robustness and generalizability of the model; Thirdly, although the machine learning prediction established in this study has convincing predictive performance, it still cannot reflect the clinical operability of the prediction model's decision-making. Therefore, in the future, it is still necessary to choose a prediction model with better interpretability to achieve clinical decision-making.

Conclusion

In summary, this study established a predictive model for early warning and stratification of CRPC bone metastases based on machine learning algorithms. In addition, the selected candidate variables include the PSA nadir, the timePSA, the number of BM, and LDH, which can jointly evaluate the potential risk of rapid progression to mCRPC in prostate cancer patients, thereby saving medical expenses for patients. Encouragingly, using the random forest algorithm as the optimal prediction model can help clinicians evaluate the risk of prostate cancer bone metastasis and make personalized diagnosis and treatment recommendations to improve patient prognosis.

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Disclosure

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