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A simple prognostic model involving prostate-specific antigen, alkaline phosphatase and albumin for predicting the time required to progress to castration-resistant prostate cancer in patients who received androgen deprivation therapy

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Abstract
Purpose To distinguish potential biomarkers and build a useful model to predict the time required to progress to castration-resistant prostate cancer (CRPC) in patients with prostate cancer who have been treated with androgen deprivation therapy (ADT).
Methods We considered 168 patients who received ADT as the initial therapy. Complete clinical data including age, tumor stage, Gleason score, prostate-specific antigen (PSA), complete blood count and liver function tests were analyzed. Cox proportional hazards regression models were used to estimate their effects on the time required to progress to CRPC, and a simple risk stratification model to predict the time required to progress to CRPC was established.
Results One hundred and sixty-eight patients were evaluated. The median age was 72 years, and the mean time required to progress to CRPC was 15 months. Multivariable analysis indicated that PSA, alkaline phosphatase and albumin were independent predictors of ADT failure. A predictor model using these factors indicated significant differences in the time required to progress to CRPC between the three subgroups: low (score: 0), intermediate (score: 1–2) and high (score: 3–4).
Conclusion The predictor model included PSA, alkaline phosphatase and albumin as independent prognostic factors of the time required to progress to CRPC in patients who had received ADT.

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Keywords Castration-resistant prostate cancer · Androgen deprivation therapy · Prostate-specific antigen · Alkaline phosphatase · Albumin

Abbreviations

ALP	Alkaline phosphatase
CI	Confidence interval
CRPC	Castration-resistant prostate cancer
EAU	European Association of Urology
HR	Hazard ratio
IQR	Interquartile range
LMR	Lymphocyte-to-monocyte ratio
NLR	Neutrophil-to-lymphocyte ratio
PLR	Platelet-to-lymphocyte ratio
PSA	Prostate-specific antigen
ROC	Receiver operating characteristic

Introduction

Androgen deprivation therapy is an initial therapy for locally advanced and metastatic prostate cancer and patients with early-stage disease who are ineligible for local regional treatments. This therapy has better efficiency during the first 12–24 months; however, most patients ultimately progress to castration-resistant prostate cancer [1–4], which means a more aggressive, evasive and deadly stage [1, 5]. However, to date, there have been no reliable clinical models that could provide information for predicting the time required to progress to castration-resistant prostate cancer (CRPC) and guiding therapeutic decision making [6].

Prostate-specific antigen (PSA) has been widely accepted as the reflective for the burden of the disease in men with prostate cancer [7], and prognostic models that

include the serum PSA level as an independent risk factor for mortality have been proposed [8, 9]. There is increasing evidence surrounding alkaline phosphatase (ALP) [10, 11], which has been reported associated with bone metastasis, and its high level expression is associated with poor clinical outcomes. Thus, the role of ALP in the prediction of the time required to progress to CRPC deserved to be defined. Several blood counts, such as hemoglobin, albumin and some inflammatory cytokines, are correlated with prognosis in patients with prostate cancer [12–14]. However, results are inconclusive in predicting time required to progress to CRPC.

Thus, the aims of this study were to investigate potential biomarkers that act as the predictors of the time required to progress to CRPC and to build a simple but reliable model to predict the time required to progress to CRPC in patients who have received ADT.

Methods

Patients

Approval was obtained from the Ethics Committee at the First Affiliated Hospital of Medical College of Xi'an Jiaotong University. Because this was a retrospective study, informed consents were obtained via the telephone. One hundred and sixty-eight patients with prostate cancer who had received ADT as the initial and only therapy prior to progression at the First Affiliated Hospital of Medical College of Xi'an Jiaotong University from January 2009 to July 2014 were retrospectively reviewed. Patients with coagulation-related diseases, cardiovascular diseases, inflammatory diseases, autoimmune diseases, hematological, or liver diseases, or other types of cancer and patients lost to follow-up were excluded.

Clinical and pathological evaluations

Medical data regarding clinical characteristics, including age, serum PSA level, blood cell counts, liver function test, clinical tumor stage and Gleason biopsy score, were collected prior to treatment. For the clinical tumor stage, the patients underwent pelvic computed tomography (CT) or magnetic resonance imaging (MRI). Radionuclide bone imaging was performed to determine the presence of bone metastasis. The European Association of Urology (EAU) guidelines were applied to stratify the patients into low, intermediate and high groups.

ADT was applied according to the EAU guidelines [15], including castration or antiandrogen therapy. Castration includes surgical or medical castration via a luteinizing hormone releasing hormone agonist. Antiandrogen therapy mainly includes bicalutamide.

Follow-up

The patients were followed up regularly every 3 months from the initiation of treatment until the development of CRPC or death. Physical examinations, laboratory tests and radiologic examinations were performed at every visit; CRPC was defined according to the EAU as a castrate serum testosterone level <50 ng/ml or 1.7 nmol/l plus either of the followings: (1) biochemical progression defined as three consecutive rises of PSA, 1 week apart, resulting in two 50% increases over the nadir, with PSA >2 ng/ml, or (2) radiologic progression defined as the appearance of two or more bone lesions on bone scans or enlargement of a soft tissue lesion based on the Response Evaluation Criteria in Solid Tumors (RECIST) [16, 17].

Statistical analysis

Continuous variables are reported as the means and standard deviations (SDs) for parametric distributions or the medians and interquartile ranges (IQRs) for nonparametric distributions. The Chi-square or Fisher's exact tests were used to analyze the categorical variables. Kaplan–Meier survival curves were applied for the progression analyses, and different groups were compared with the log-rank test. Univariate and multivariate analyses were performed using a backward stepwise method. A Cox proportional hazards model was implemented to identify associations between the outcomes and potential prognostic factors. Hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) were estimated from the Cox analyses. Following the multivariable analysis, independent risk factors and their β coefficients were used to create a simple prognostic model. The cutoff values of the biomarkers were selected using receiver operating characteristic (ROC) curve analysis. All statistical analyses were performed using the Statistical Package for the Social Sciences, version 16.0 (SPSS, Chicago, IL, USA), with two-sided p values <0.05 considered statistically significant.

Results

Patient characteristics

One hundred and sixty-eight patients with locally advanced or metastatic prostate cancer who had received ADT as the initial therapy were included in this study. As detailed in Table 1, the median age at diagnosis was 72 (IQR 67–78),

Table 1 Clinicopathological characteristics of patients treated with androgen deprivation therapy

Variables	No. of patients (%)
Age (median, interquartile range), years	72 (67–78)
PSA (median, interquartile range), μg/l	141.7 (41–459.8)
Gleason score	
<7	22 (13.58)
=7	87 (52.73)
>7	56 (33.93)
pT stage	
pT1–pT2	67 (40.61)
pT3–pT4	100 (60.60)
pN stage	
pN0	70 (41.90)
pN1	97 (58.10)
Metastasis	
No	43 (25.70)
Yes	124 (74.30)
Risk stratification	
Low	1 (0.60)
Intermediate	9 (5.40)
High	158 (94.00)
Albumin (median, interquartile range), 10^9 l	39.5 (36.5–41.7)
Hemoglobin (median, interquartile range), 10^9 l	131 (116–141)
Alkaline phosphatase (median, interquartile range)	96.5 (72.8–181.4)
Progressed to CRPC	110 (65.5)
Follow-up time (months)	22 (10–31)

PSA prostate-specific antigen, *CRPC* castration-resistant prostate cancer

and the mean follow-up time was 22 months. At the time of the last follow-up, 110 patients had progressed to CRPC, and 2 patients had died.

Predictive significance of the variables and cutoff value determination

To identify the associations between the biomarkers and the time required to progress to CRPC in the study population, Cox proportional hazard models were used. As illustrated in Table 2, PSA ($p < 0.001$), albumin ($p < 0.001$) and ALP ($p < 0.001$) were statistically significant predictors of the time required to progress to CRPC, as were age at diagnosis ($p = 0.03$), Gleason score ($p = 0.043$), TNM stage (all $p < 0.001$) and hemoglobin ($p < 0.001$). The neutrophil-to-lymphocyte ratio (NLR) or platelet-to-lymphocyte ratio (PLR) was not predictive ($p > 0.05$ for all).

Multivariate Cox proportional hazard analysis was used to assess the independent predictors of ADT failure. As illustrated in Table 2, PSA, ALP and albumin were independent predictors of ADT failure (HR 2.009, 95% CI 1.320–3.057, $p < 0.001$; HR 1.748, 95% CI 1.159–2.635, $p = 0.008$; and HR 0.574, 95% CI 0.371–0.888, $p = 0.013$, respectively).

According to the ROC curves, the best cutoff values (as defined by the maximum joint sensitivity and specificity) for PSA, ALP and albumin were 200.9 μg/l, 114 U/l and 39.65 g/l, respectively (Fig. 1).

Analysis of time required to progress to CRPC with patients stratified according to the cutoff values

The patients were divided into high or low PSA, ALP and albumin groups based on the cutoff values from the ROC curves. The Kaplan–Meier survival curves demonstrated that increased PSA and ALP and decreased serum albumin were associated with shorter times required to progress to CRPC ($p < 0.001$ for all, Fig. 2). Of the high- and low-PSA patients, 85.5 and 37.2%, respectively, progressed to CRPC within 24 months. The corresponding values for the high- and low-ALP groups were 79.6 and 46.5%, respectively. The patients in the low-albumin group progressed to CRPC more rapidly with 72.3% progressing within 24 months compared with 45.8% in the high-albumin group ($p < 0.001$ for all).

Combining PSA, ALP and albumin to provide a simple model

The three statistically significant variables of PSA, ALP, albumin, and their hazard ratios from the multivariate analyses were used to develop a risk stratification model to predict the time required to progress to CRPC in patients with prostate cancer who had received ADT as the initial therapy. One point each was assigned to an ALP level ≥114 and an albumin level ≤39.65, and two points were assigned to a PSA level ≥200.9. All patients were stratified into the following three risk groups: low (score = 0), intermediate (score = 1–2) and high (score = 3–4) (Fig. 3); the 24-month progression to CRPC rates in these groups were 26.4, 51.8 and 89.9%, respectively ($p < 0.001$ for all). The concordance index was 0.72 for this model, and the 95% CI was 0.77–0.67.

Correlations between PSA, ALP, albumin, the prognostic model and other clinical parameters

The clinicopathological characteristics were compared between patients grouped by risk stratification combined with PSA, ALP and albumin as illustrated in Table 3. The high-risk group (score = 3–4) had the most advanced TNM stages and the highest Gleason score ($p = 0.014$, $p = 0.011$, $p < 0.001$ and $p = 0.027$).

Table 2 Univariate and multivariate analysis of parameters in prostate cancer patients treated with androgen deprivation therapy

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age at diagnosis				
≤72	1		1	
>72	0.659 (0.453–0.96)	0.030	0.818 (0.549–1.219)	0.342
Gleason score				
≤7	1		1	
>7	1.906 (1.020–3.559)	0.043	1.110 (0.588–2.209)	0.766
pT stage				
pT1–pT2	1		1	
pT3–pT4	1.976 (1.320–2.958)	<0.001	1400 (0.908–2.160)	0.128
pN stage				
pN0	1		1	
pN1	2.067 (1.393–3.067)	<0.001	1.505 (0.987–2.293)	0.057
Metastasis				
No	1		1	
Yes	3.041 (1.788–5.173)	<0.001	1.535 (0.869–2.713)	0.14
PSA				
<200.9	1		1	
>200.9	3.250 (2.210–4.780)	<0.001	2.009 (1.320–3.057)	<0.001
Albumin				
<39.6	1		1	
>39.6	0.485 (0.332–0.711)	<0.001	0.574 (0.371–0.888)	0.013
Alkaline phosphatase				
<114.56	1		1	
>114.56	2.508 (1.727–3.642)	<0.001	1.748 (1.159–2.635)	0.008
Hemoglobin				
<126.5	2.024 (1.395–2.937)	<0.001	1.193 (0.968–1.471)	0.098
>126.5	1			
PLR				
<149	1			
≥149	1.01 (0.997–1.002)	0.814		
NLR				
<3.3	1			
≥3.3	0.942 (0.644–1.378)	0.760		

PSA prostate-specific antigen, *PLR* platelet-to-lymphocyte ratio, *NLR* neutrophil-to-lymphocyte ratio

Discussion

The clinicopathological characteristics and the time required to progress to CRPC in 168 prostate cancer patients who had received ADT as the initial therapy were retrospectively investigated in this study. Multivariate analysis indicated that the preoperative PSA, ALP and albumin levels were statistically significant predictors of the time required to progress to CRPC. Based on these factors, we developed a simple risk stratification model with three levels: low risk (score = 0), intermediate risk (score = 1–2) and high risk (score = 3–4). Kaplan–Meier curves demonstrated that the high-risk group was associated with the most advanced TNM stage and the highest Gleason scores. The concordance index was 0.72 for this model, which verified that it is a reliable model.

PSA is widely recognized as a diagnostic and prognostic biomarker in patients with prostate cancer. Additionally, the PSA doubling time (PSA DT) and velocity are also prognostic factors for overall survival (OS) in CRPC [6]. Previous study revealed that pretreatment PSA level and nadir have clinical significances as prognostic factors to predict CRPC [18, 19]. However, the role of PSA in predicting time required to progress to CRPC is still unclear. Moreover, this parameter

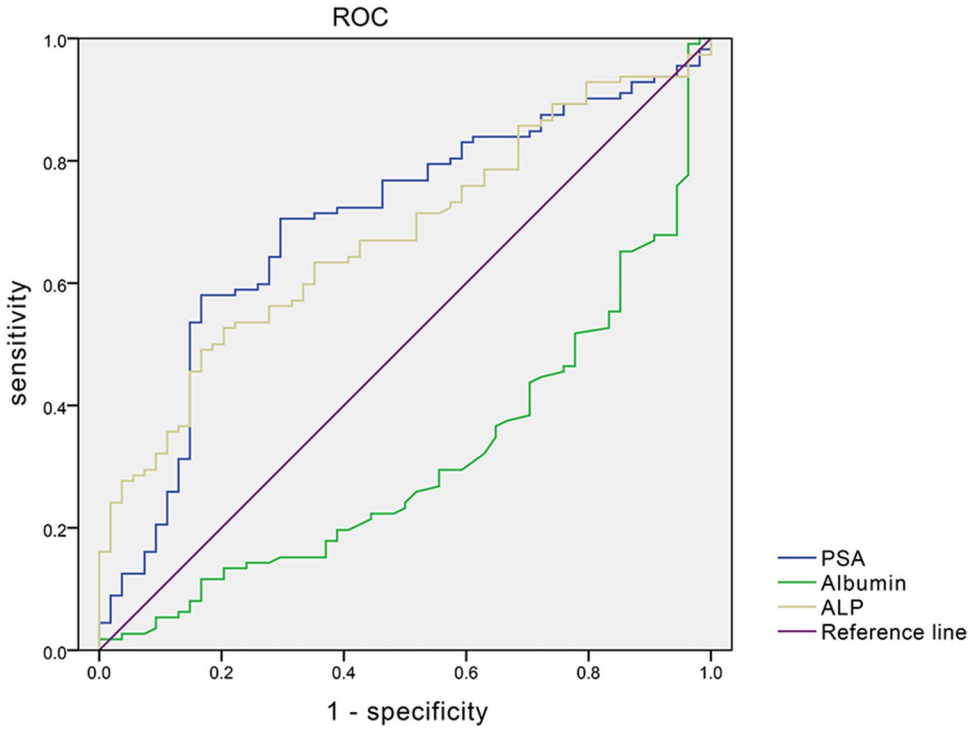

Fig. 1 ROC curves were applied to determine the best cutoff values for PSA, ALP and albumin

has the characteristics of being variable and fluctuating at diagnosis. Thus, the predictive value of PSA for ADT failure deserves to be defined. According to our results, PSA is associated with clinical benefits and it is an independent predictor of the time required to progress to CRPC. According to the hazard ratios in the multivariate analyses, PSA has the strongest correlation with ADT failure. PSA plays the most important role in the prediction of ADT failure among three predictors; thus, two points were assigned to PSA, compared with one point assigned to ALP and albumin. ALP has been demonstrated to be prognostic in patients with prostate cancer who are treated with chemotherapy and radiotherapy [20–23]; thus, the pretreatment ALP level may provide prognostic information regarding the time required to progress to CRPC. To our knowledge, the use of ALP in the prediction of the time required to progress to CRPC has not been previously reported. The multivariate analysis distinguished ALP as one of the biomarkers associated with the time required to progress to CRPC, and it was included in our model.

Several blood count parameters and inflammatory biomarkers, such as albumin, hemoglobin, the NLR and the PLR, have been widely used to evaluate patients and provide prognostic information [10, 13, 14, 24–26]. However, previous studies have seldom identified the prognostic values of these parameters specifically in prostate cancer patients who have received ADT. Using univariate and multivariate analyses, we

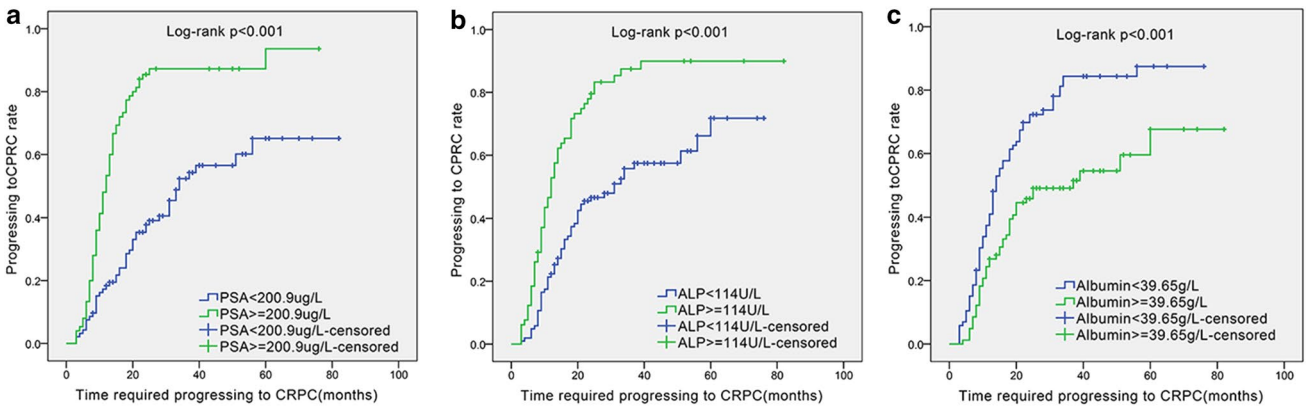

Fig. 2 Kaplan–Meier curves for time required to progress to CRPC according to PSA and ALP and albumin, respectively

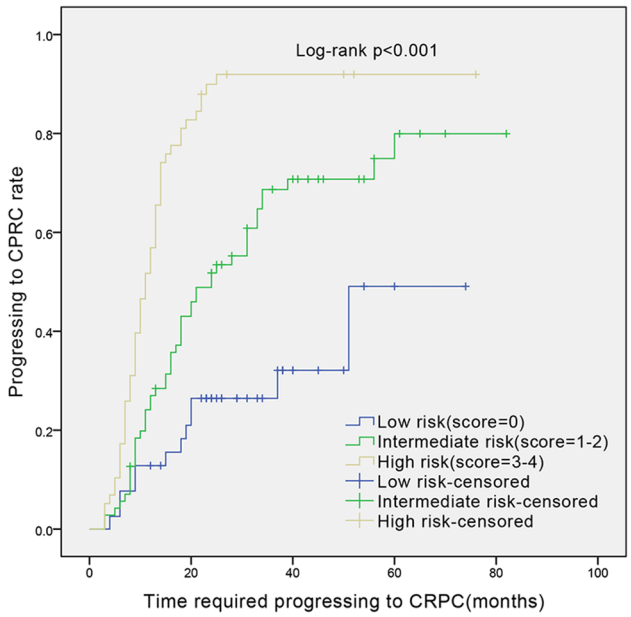

Fig. 3 Kaplan–Meier curves for the time required to progress to CRPC according to risk stratification

demonstrated that albumin comprised an independent predictor in the prediction of the time required to progress to CRPC, whereas hemoglobin, PLR and NLR were not predictors. Synthesized predominantly in the liver [27], albumin is a safe and protective protein. Decreased albumin at diagnosis may indicate an undernourished status in addition to a suppressed immune system [28]. Consistent with previous studied, patients in the lower-albumin group were with a shorter progression time to CRPC. To our knowledge, several inflammatory biomarkers, such as the lymphocyte-to-monocyte ratio (LMR), have also been reported to have prognostic value in cancer [23, 29], but the majority of patients in our study had no monocytes at the diagnosis of prostate cancer. Thus, we exclude LMR for its limited reach. Lactic dehydrogenase and cholesterol [30, 31] were excluded from our study because few patients received these tests for economic reasons.

Univariate and multivariate analyses indicated that the prognostic model, which consisted of a combination of PSA, ALP and albumin, was associated with the time required to progress to CRPC, and these findings remained significant after adjusting for clinicopathological features. These findings indicate that the model served as an independent prognostic factor and may aid in patients assessment and treatment management.

Limitations

This is a retrospective study with relatively small sample size. The assessment of the clinical implications of this model requires further prospective investigations in clinical settings, as well as external validation. Moreover, because the patients chose different therapies after CRPC, we were unable to distinguish the prognostic value of the model in terms of the overall survival (OS).

Conclusion

Our study provides a useful model that includes PSA, ALP, albumin and can be used as a preoperative indicator of the time required to progress to CRPC. This is the first report of prognostic model that includes preoperative PSA, ALP and albumin in patients with prostate cancer who have been treated with ADT as the initial therapy. For it is a pilot study, following prospective studies were required to validate the conclusion.

Table 3 Clinicopathological characteristics of patients according to the risk stratification

Variables	Low risk (score = 0)	Intermediate risk (score = 1–2)	High risk (score = 3–4)	*p* value
	N = 39	*N* = 71	*N* = 58	
Age (years)	74 ± 2.24	71.73 ± 167	70.83 ± 2.17	0.121
pT stage				0.014
pT1–pT2	23	26	18	
pT3–pT4	15	45	39	
pN stage				0.011
pN0	21	33	15	
pN1	17	38	42	
Metastasis				<0.001
No	19	20	4	
Yes	19	51	53	
Gleason				0.027
≤7	7	13	2	
>7	32	58	56	

Compliance with ethical standards

Conflict of interest None.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the First Affiliated Hospital of Xi'an Jiaotong University and the 1964 Declaration of Helsinki, as well as with its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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