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Risk factor analysis and nomogram construction in patients with distant metastatic prostate cancer at different PSA levels: a study based on the SEER database

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Abstract. – OBJECTIVE: Prostate cancer (PCa) is the most common malignant tumor in the male genitourinary system. Once PCa has metastasized, it is very difficult to cure. The purpose of this study was to investigate the prognostic risk factor analysis of patients with different prostate-specific antigen (PSA) levels in distant metastatic PCa. At the same time, we construct effective models for predicting the survival rate of prostate cancer patients.

PATIENTS AND METHODS: Data on prostate cancer patients with the presence of distant metastases were obtained from the Surveillance, Epidemiology, and End Results (SEER) database. PCa patients with distant metastases were categorized into two groups based on PSA levels, one with PSA <20 ng/mL and the other with PSA ≥20 ng/mL. Univariate and multivariate COX regression analyses were used to identify independent factors affecting the prognosis of the patients. A nomogram was constructed using the independent prognostic factors, and the results were evaluated using calibration curves, timeROC curves, and Kaplan-Meier curves.

RESULTS: In the PSA <20 ng/mL group, there were a total of 1,832 patients. COX regression analysis showed that age, marital status, N stage, grade, Gleason score, and medical household income inflation were independent prognostic factors for overall survival (OS) in patients. In addition, we found that age, marital status, N stage, bone metastasis, grade, and Gleason score were independent prognostic factors for cancer-specific survival (CSS) in patients. In the PSA ≥20 ng/mL group, there were a total of 5,314 patients. It was found that age, ethnicity, marital status, bone metastasis, first malignant primary indicator, grade, Gleason score, and medical household income inflation were patients' independent prognostic factors for OS. For CSS, we found that age, ethnicity, marital status, T stage, radiotherapy, bone metastasis, Gleason score, and Median household income inflation were independent prognostic factors. Constructing a nomogram can accurately predict the prognosis of this group of patients.

CONCLUSIONS: We found different independent prognostic factors for different PSA levels in patients with distant metastatic PCa. A new nomogram was constructed to predict OS and CSS in patients, which helps in clinical-assisted decision-making.

Key Words:
Prostate cancer, Distant metastasis, Prostate-specific antigen, Risk factors, Prognosis.

Introduction

Prostate cancer (PCa) is the most common malignancy in American men. According to the latest data, in 2022, the number of PCA cases in the United States reached 268,490, including 34,500 deaths[1]. Prostatic intraepithelial neoplasia is the first step in malignant transformation of the prostate, followed by limited prostate cancer, then advanced locally invasive prostate adenocarcinoma, and finally metastatic prostate cancer[2]. Unfortunately, about 10-15% of patients are diagnosed with prostate cancer when metastasis has already occurred[3]. Most of these patients with metastatic prostate cancer develop bone metastases, leading to a poor prognosis for the patient[4]. In addition, recent studies[5] have found that secondary colorectal cancer in prostate cancer patients is an independent risk factor for patient prognosis. Patients who developed secondary cancers had significantly lower survival rates.

PSA is a commonly used screening test for PCa, which was introduced into the clinic in the 1980s and has been effective in increasing the detection rate of PCa[6]. In terms of diagnosis, it is generally accepted that once a patient's prostate-specific

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antigen (PSA) level is >20 ng/mL, they are likely to have PCa[7]. In therapy, studies[8] have found that when PSA >20 ng/mL, the risk of treatment failure exceeds 50%, and the risk of developing metastasis reaches 2.5%. Previous studies[9] have shown that patients with PSA levels of 10 to 20 ng/mL have a higher stage of prostate cancer than those with 3.5 to 10 ng/mL. However, patients with PSA levels <3.5 ng/mL are likely to have a higher stage of prostate cancer than patients with 3.5 to 10 ng/mL. When PSA is >20 ng/mL, patients are likely to have a worse prognosis[10].

The level of PSA is associated with the risk of prostate cancer, pathological grade, and the likelihood of metastasis. However, PSA as a biomarker is deficient. PSA levels do not determine the nature of the disease, especially when PSA levels are below 20 ng/mL[11]. In many PCa patients with distant metastases, there are also more patients with low PSA levels. Thus, PSA cannot accurately determine the prognosis of PCa patients. Worryingly, for reasons that prostate cancer is usually painless, it can lead to higher mortality rates due to delays in treatment[12]. In this study, we collected clinical data from patients with distant metastases of prostate cancer based on the SEER database to determine the differences in independent prognostic factors of patients under different PSA value groupings. Based on these independent prognostic factors, a nomogram was constructed to provide a more personalized and precise prediction of the survival rate of specific PCa patients, which can provide auxiliary decision-making for clinicians and patients.

Patients and Methods

Patient Selection

Clinical data from prostate cancer patients from 2000-2020 were retrieved from the SEER database. Inclusion criteria for this study were (1) pathologic diagnosis of prostate cancer and (2) active follow-up. The exclusion criteria were (1) unknown ethnicity, (2) unknown T-stage, (3) unknown N-stage, (4) patients with no surgical record, (5) unknown bone metastasis, (6) unknown grade, (7) unknown median household income status, (8) unknown marital status, and (9) unknown Gleason score. The flowchart of patient inclusion and exclusion is shown in Figure 1.

We collected clinical information related to prostate cancer patients, including age, ethnicity, marital status, T stage, N stage, M stage, PSA Lab value recode, surgery, radiotherapy, bone metastasis, first malignant primary indicator, grade, Gleason score, median household income inflation, survival status, and survival time. In the SEER database, patient-related information

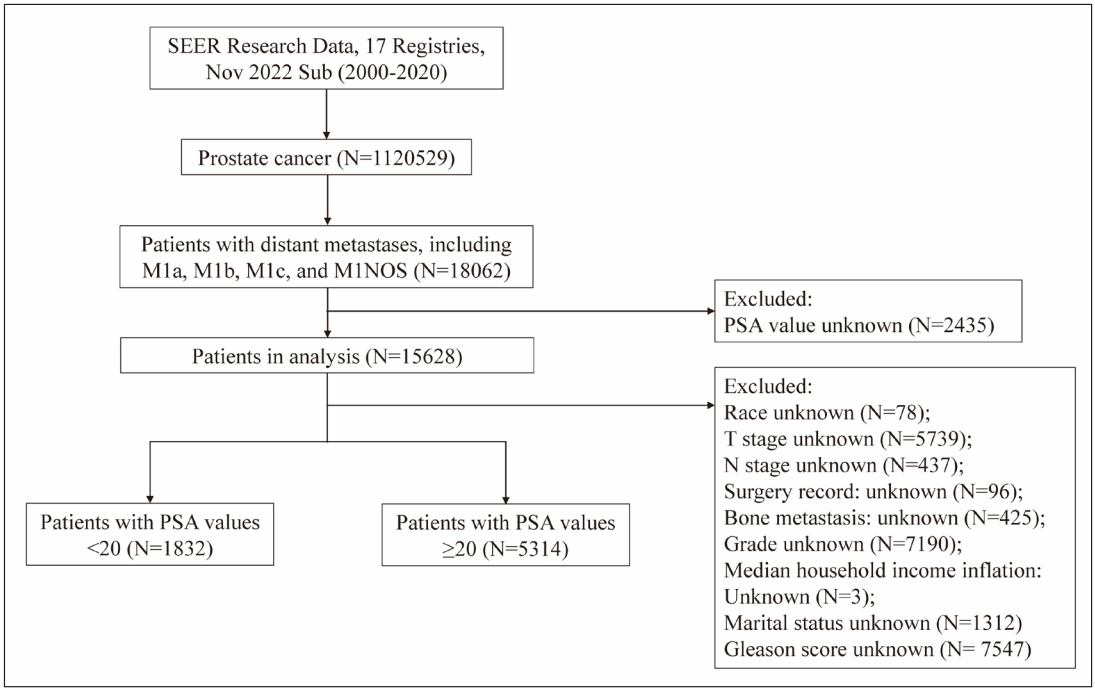

Figure 1. The flow chart of patient selection and data analysis.

is hidden, and each patient has only one ID for identification and labeling. The data in the SEER database are publicly available and, therefore, do not require ethical approval.

Construction of a Nomogram

First, we divided prostate cancer patients with distant metastases into two groups based on PSA values: PSA <20 ng/mL and PSA ≥20 ng/mL. Univariate and multivariate COX regression analyses were performed on the two groups of patients to determine the independent risk factors affecting OS and CSS in prostate cancer patients. A nomogram was constructed based on the patients' independent risk factors, which was used to predict OS and CSS at 5, 8, and 10 years in different subgroups of prostate cancer patients. Calibration curves and the Time-Dependent ROC Curve (timeROC) were constructed to evaluate the accuracy and judgmental ability of the nomogram. The "survival" and "rms" R packages are used to construct the nomogram and calibration curves. The "timeROC" R package is used to construct the Time-Dependent ROC curve.

Construction of the Kaplan-Meier Curve

The RiskScore derived after constructing the nomogram was divided into two groups, high and low, using the median as the cut-off. Kaplan-Meier curves were plotted to determine the nomogram's effect on OS and CSS for patients in different subgroups.

Statistical Analysis

SPSS 20.0 (IBM Corp., Armonk, NY, USA) and R version 4.0.5 software (R Foundation for Statistical Computing, Vienna, Austria) were employed for statistical analysis. Correlations between clinical and pathological parameters in different PSA value subgroups were tested using a Chi-square test using SPSS software version 20. Univariate and multivariate COX regression analyses were used to validate independent risk factors affecting patients' OS and CSS. Differences in OS and CSS between high- and low-risk groups were compared using Kaplan-Meier curves, and *p*-values were calculated using the log-rank test. We considered $p<0.05$ to be statistically significant.

Results

Patient Characteristics

First, we searched the SEER database for 1,120,529 patients diagnosed with prostate cancer. A total of 18,062 of these prostate cancer patients had distant metastases. After removing patients with missing PSA values, the patients were divided into two groups: the PSA >20 ng/mL group and the PSA ≥20 ng/mL group. Patient clinicopathologic information included age, ethnicity, marital status, T stage, N stage, M stage, surgery, radiotherapy, bone metastasis, first malignant primary indicator, grade, Gleason score, median household income inflation, OS, and CSS. Among them, there were significant differences ($p<0.05$) in ethnicity, maternal status, N stage, M stage, surgery, radiation, bone metastasis, first malignant primary indicator, grade, Gleason score, OS, and CSS among different PSA level groups (Table I). Among other things, the analysis suggested that patients in the PSA ≥20 ng/mL subgroup had a higher mortality rate.

COX Regression Analysis for PSA<20 ng/mL Group

Risk factors were validated using univariate COX regression analysis, and risk factors with $p<0.1$ were included in multivariate COX regression analysis to find independent risk factors in patients with distant metastatic prostate cancer with PSA <20 ng/mL. At the same time, the Hazard Ratio (HR) was calculated for each risk factor. The results showed that age [HR=1.029, 95% confidence interval (CI): 1.022-1.036, $p<0.001$], marital status (HR=1.302, 95% CI: 1.150-1.474, $p<0.001$), N stage (HR=1.239, 95% CI: 1.094-1.403, $p<0.001$), grade (HR=1.472, 95% CI: 1.130-1.918, $p=0.004$), Gleason score (HR=1.678, 95% CI: 1.385-2.033, $p<0.001$), and medical household income inflation (HR=0.861, 95% CI: 0.763-0.972, $p=0.015$) is associated with OS in prostate cancer patients in this group (Table II). The results suggest that in this subgroup, older age, unmarried, worse N-staging, higher grade, higher Gleason score, and lower household income are independent risk factors for OS in patients. In comparison, age (HR=1.018, 95% CI: 1.011-1.026, $p<0.001$), marital status (HR=1.311, 95% CI: 1.141-1.507, $p<0.001$), N stage (HR=1.311, 95% CI: 1. 134-1.516, $p<0.001$), bone metastasis (HR=0.774, 95% CI: 0.637-0.940, $p=0.01$), grade (HR=1.471, 95% CI: 1.045-2.069, $p=0.027$), and Gleason score (HR=2.265, 95% CI: 1.780-2.884, $p<0.001$) were associated with this group of prostate cancer patients' CSS (Table III). The results of the analysis suggest that in this subgroup, older age, being unmarried, worse N-staging, bone metastasis, higher grade, and higher Gleason score are independent risk factors for CSS in patients.

Table I. The clinicopathologic characteristics of patients in the PSA <20 ng/ml and PSA ≥20 ng/ml groups.

Characteristics	PSA<20	PSA≥20	*p*-value
n	1,832	5,314	
Age, mean±sd	69.221±9.34	69.09±10.591	0.618
Ethnicity, n (%)			<0.001
White	1,521 (21.3%)	3,968 (55.5%)	
Black	208 (2.9%)	1,013 (14.2%)	
Other	103 (1.4%)	333 (4.7%)	
Marital status, n (%)			<0.001
Married	1,353 (18.9%)	3,161 (44.2%)	
Unmarried	479 (6.7%)	2,153 (30.1%)	
T stage, n (%)			0.956
≤T2	1,314 (18.4%)	3,815 (53.4%)	
>T2	518 (7.2%)	1,499 (21%)	
N stage, n (%)			<0.001
N0	1,350 (18.9%)	3,432 (48%)	
N1	482 (6.7%)	1,882 (26.3%)	
Surgery, n (%)			<0.001
No	1,421 (19.9%)	4,661 (65.2%)	
Yes	411 (5.8%)	653 (9.1%)	
Radiotherapy, n (%)			<0.001
Yes	523 (7.3%)	1,187 (16.6%)	
No	1,309 (18.3%)	4,127 (57.8%)	
Bone metastasis, n (%)			<0.001
No	270 (3.8%)	543 (7.6%)	
Yes	1,562 (21.9%)	4,771 (66.8%)	
First malignant primary indicator, n (%)			0.004
Yes	1,656 (23.2%)	4,917 (68.8%)	
No	176 (2.5%)	397 (5.6%)	
Grade, n (%)			<0.001
Grade I and II	246 (3.4%)	417 (5.8%)	
Grade III and IV	1,586 (22.2%)	4,897 (68.5%)	
Gleason Score, n (%)			<0.001
Gleason score <8	434 (6.1%)	848 (11.9%)	
Gleason score ≥8	1,398 (19.6%)	4,466 (62.5%)	
Median household income inflation			0.102
<$75,000	1,230 (17.2%)	3,677 (51.5%)	
≥$75,000	602 (8.4%)	1,637 (22.9%)	
CSS, n (%)			<0.001
0	832 (11.6%)	1,855 (26%)	
1	1,000 (14%)	3,459 (48.4%)	
OS, n (%)			<0.001
0	568 (7.9%)	1,038 (14.5%)	
1	1,264 (17.7%)	4,276 (59.8%)	

Cancer-specific survival (CSS), Overall survival (OS).

Based on these results, we can tell that there are subtle differences in independent risk factors affecting OS and CSS in prostate cancer patients in this subgroup.

COX Regression Analysis for PSA ≥20 ng/mL Group

A total of 5,314 patients were included in this group for analysis. The results showed that age (HR=1.021, 95% CI: 1.018-1.024, $p<0.001$), ethnicity (HR=0.740, 95% CI: 0.647-0.846, $p<0.001$), marital status (HR=0.852, 95% CI: 0.800-0.907, $p<0.001$), bone metastasis (HR=0.760, 95% CI: 0.685-0.844, $p<0.001$), first malignant primary indicator (HR=1.132, 95% CI: 1.013-1.265, $p=0.028$), grade (HR=1.169, 95% CI: 1.001-1.366, $p=0.048$), Gleason score (HR=1.282, 95% CI: 1.151-1.428, $p<0.001$), and medical household income inflation (HR=0.878, 95% CI: 0.821-0.939, $p<0.001$) is associated with OS in prostate cancer patients in this group (Table IV). In this subgroup, older age, black ethnicity, unmarried, bone metastases, non-first malignant primary indicators, higher grade, higher Gleason score, and lower household income were independent risk factors for OS in prostate patients. In comparison, age (HR=1.031, 95% CI: 1.010-1.017, $p<0.001$), ethnicity (HR=0.722, 95% CI: 0.622-0.839, $p<0.001$), marital status (HR=0.896, 95% CI: 0.836-0.961, $p=0.002$), T stage (HR=1.088, 95% CI: 1. 010-1.171, $p=0.026$), radiotherapy (HR = 1.104, 95% CI: 1.019-1.195, $p=0.015$), bone metastasis (HR=0.708, 95% CI: 0.628-0.797, $p<0.001$), Gleason score (HR=1.360, 95% CI: 1.203-1.539, $p<0.001$), and median household income inflation (HR=0.911, 95% CI: 0.846-0.981, $p=0.013$) were associated with this group of prostate cancer patients' CSS correlation (Table V). Interestingly, in this PSA subgroup, patients with distantly metastasized prostate cancer who received radiotherapy did not appear to have a benefit for CSS. This may be related to the fact that patients who did not receive radiotherapy had less malignant tumors.

Construction of a Nomogram of OS and CSS for the PSA <20 ng/mL Group

Based on the results of COX regression analysis, we selected independent prognostic factors for nomogram construction. In this subgroup, for OS, we included 6 independent prognostic factors to construct nomograms for 5-, 8-, and 10-year OS (Figure 2A). In addition, we included 6 independent prognostic factors to construct nomograms for 5-, 8-, and 10-year CSS (Figure 2B). The corresponding scores for each indicator can be summed to calculate the likelihood of survival for each patient.

Construction of a Nomogram of OS and CSS for the PSA ≥20 ng/mL Group

For patients with distant metastatic prostate cancer with concomitant PSA ≥20 ng/mL, we similarly selected inclusion indicators for nomogram construction based on the results of COX

regression analysis. We included 8 independent prognostic factors to construct the nomogram for 5-, 8-, and 10-year OS (Figure 3A). For CSS, we included 8 independent prognostic factors to construct the nomogram (Figure 3B).

Evaluation of Nomogram

We first constructed a calibration curve to evaluate the accuracy of the nomogram. The results showed that in different PSA groups, the calibration curves of OS and CSS showed good consistency between nomogram prediction and actual observation results (Figure 4A-B). Further, we constructed timeROC curves to evaluate the predictive ability of nomograms. In the PSA <20 ng/mL group, the timeROC analysis results showed that the area under the curve (AUC) of nomogram of OS for predicting the 5-, 8-, and 10-year prognosis of prostate cancer patients were 0.678, 0.702, and 0.745, respectively (Figure 5A). The AUC of CSS

Table II. Univariate and multivariate analysis of risk factors for OS in PCa patients in the PSA <20 ng/ml group.

Characteristics	Total (N)	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Age	1,832	1.030 (1.024-1.037)	**<0.001**	1.029 (1.022-1.036)	**<0.001**
Ethnicity	1,832				
Black	208	Reference		Reference	
White	1,521	1.206 (1.008-1.442)	**0.041**	1.071 (0.891-1.288)	0.465
Other	103	0.853 (0.631-1.155)	0.304	0.805 (0.590-1.097)	0.169
Marital status	1,832				
Married	1,353	Reference		Reference	
Unmarried	479	1.276 (1.129-1.442)	**<0.001**	1.302 (1.150-1.474)	**<0.001**
T stage	1,832				
T≤2	1,314	Reference			
T>2	518	1.102 (0.975-1.245)	0.119		
N stage	1,832				
N0	1,350	Reference		Reference	
N1	482	1.282 (1.134-1.449)	**<0.001**	1.239 (1.094-1.403)	**<0.001**
Surgery	1,832				
No	1,421	Reference			
Yes	411	0.969 (0.848-1.108)	0.648		
Radiotherapy	1,832				
No	1,309	Reference		Reference	
Yes	523	0.858 (0.758-0.971)	**0.016**	0.957 (0.844-1.085)	0.491
Bone metastasis	1,832				
Yes	1,562	Reference			
No	270	0.909 (0.774-1.066)	0.241		
First malignant primary indicator	1,832				
No	176	Reference		Reference	
Yes	1,656	0.755 (0.629-0.905)	**0.002**	0.850 (0.706-1.024)	0.087
Grade	1,832				
Grade I and II	246	Reference		Reference	
Grade III and IV	1,586	2.318 (1.889-2.844)	**<0.001**	1.472 (1.130-1.918)	**0.004**
Gleason Score	1,832				
Gleason score <8	434	Reference		Reference	
Gleason score ≥8	1,398	2.127 (1.835-2.465)	**<0.001**	1.678 (1.385-2.033)	**<0.001**
Median household income inflation	1,832				
<$75,000	1,230	Reference		Reference	
≥$75,000	602	0.901 (0.800-1.014)	0.085	0.861 (0.763-0.972)	**0.015**

Overall survival (OS), Confidence interval (CI).

Table III. Univariate and multivariate analysis of risk factors for CSS in PCa patients in the PSA <20 ng/ml group.

Characteristics	Total (N)	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Age	1,832	1.020 (1.013-1.028)	**<0.001**	1.018 (1.011-1.026)	**<0.001**
Ethnicity	1,832				
Black	208	Reference		Reference	
White	1,521	1.213 (0.990-1.486)	0.062	1.080 (0.877-1.329)	0.468
Other	103	0.864 (0.614-1.216)	0.401	0.765 (0.542-1.080)	0.128
Marital status	1,832				
Married	1,353	Reference		Reference	
Unmarried	479	1.278 (1.114-1.466)	**<0.001**	1.311 (1.141-1.507)	**<0.001**
T stage	1,832				
T≤2	1,314	Reference		Reference	
T>2	518	1.193 (1.043-1.366)	**0.010**	1.060 (0.922-1.220)	0.412
N stage	1,832				
N0	1,350	Reference		Reference	
N1	482	1.353 (1.181-1.550)	**<0.001**	1.311 (1.134-1.516)	**<0.001**
Surgery	1,832				
No	1,421	Reference			
Yes	411	1.042 (0.899-1.208)	0.585		
Radiotherapy	1,832				
No	1,309	Reference		Reference	
Yes	523	0.887 (0.772-1.019)	0.091	0.990 (0.861-1.139)	0.888
Bone metastasis	1,832				
Yes	1,562	Reference		Reference	
No	270	0.824 (0.684-0.993)	**0.042**	0.774 (0.637-0.940)	**0.010**
First malignant primary indicator	1,832				
No	176	Reference			
Yes	1,656	0.894 (0.719-1.111)	0.312		
Grade	1,832				
Grade I and II	246	Reference		Reference	
Grade III and IV	1,586	3.157 (2.426-4.108)	**<0.001**	1.471 (1.045-2.069)	**0.027**
Gleason Score	1,832				
Gleason score <8	434	Reference		Reference	
Gleason score ≥8	1,398	2.887 (2.398-3.477)	**<0.001**	2.265 (1.780-2.884)	**<0.001**
Median household income inflation	1,832				
<$75,000	1,230	Reference			
≥$75,000	602	0.920 (0.806-1.051)	0.221		

Cancer-specific survival (CSS), Confidence interval (CI).

nomogram for predicting the 5-, 8-, and 10-year prognosis of prostate cancer patients were 0.690, 0.715, and 0.754, respectively (Figure 5B). For the PSA ≥20 ng/mL group, the AUC of the nomogram of OS predicting the 5-, 8-, and 10-year prognosis of prostate cancer patients were 0.630, 0.665, and 0.642, respectively (Figure 5C). The AUC of CSS nomogram for predicting the 5-, 8-, and 10-year prognosis of prostate cancer patients were 0.621, 0.642, and 0.624, respectively (Figure 5D). The above results suggest that the nomogram we constructed has a better predictive ability, which can help clinicians predict the survival time of prostate cancer patients more accurately.

Kaplan-Meier Analysis

Risk scores based on nomograms were categorized into two groups, high and low risk, using the median as the cutoff. The effect of risk scores in different PSA groupings on the prognosis of

Table IV. Univariate and multivariate analysis of risk factors for OS in PCa patients in the PSA ≥20 ng/ml group.

Characteristics	Total (N)	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Age	5,314	1.021 (1.018-1.024)	**<0.001**	1.021 (1.018-1.024)	**<0.001**
Ethnicity	5,314				
White	3,968	Reference		Reference	
Black	1,013	1.057 (0.980-1.141)	0.152	1.093 (1.010-1.183)	**0.028**
Other	333	0.726 (0.636-0.830)	**<0.001**	0.740 (0.647-0.846)	**<0.001**
Marital status	5,314				
Unmarried	2,153	Reference		Reference	
Married	3,161	0.855 (0.805-0.909)	**<0.001**	0.852 (0.800-0.907)	**<0.001**
T stage	5,314				
T≤2	3,815	Reference			
T>2	1,499	1.004 (0.939-1.073)	0.911		
N stage	5,314				
N0	3,432	Reference			
N1	1,882	0.970 (0.911-1.033)	0.343		
Surgery	5,314				
No	4,661	Reference		Reference	
Yes	653	1.133 (1.036-1.240)	**0.006**	1.078 (0.985-1.180)	0.101
Radiotherapy	5,314				
No	4,127	Reference			
Yes	1,187	1.028 (0.957-1.105)	0.452		
Bone metastasis	5,314				
Yes	4,771	Reference		Reference	
No	543	0.740 (0.667-0.821)	**<0.001**	0.760 (0.685-0.844)	**<0.001**
First malignant primary indicator	5,314				
Yes	4,917	Reference		Reference	
No	397	1.281 (1.148-1.429)	**<0.001**	1.132 (1.013-1.265)	**0.028**
Grade	5,314				
Grade I and II	417	Reference		Reference	
Grade III and IV	4,897	1.470 (1.299-1.663)	**<0.001**	1.169 (1.001-1.366)	**0.048**
Gleason Score	5,314				
Gleason score <8	848	Reference		Reference	
Gleason score ≥8	4,466	1.388 (1.274-1.512)	**<0.001**	1.282 (1.151-1.428)	**<0.001**
Median household income inflation	5,314				
<$75,000	3,677	Reference		Reference	
≥$75,000	1,637	0.877 (0.822-0.937)	**<0.001**	0.878 (0.821-0.939)	**<0.001**

Overall survival (OS), Confidence interval (CI).

prostate cancer patients was observed. The results showed a substantial decrease in survival for patients with high-risk scores, regardless of subgroup (Figure 6).

Discussion

Past studies[13] have shown that the overall incidence of prostate cancer has decreased since 2000, but the number of prostate cancer patients diagnosed with distant metastases has increased since 2010. The underlying cause may be the usual lack of early symptoms of prostate cancer, leading to the discovery of multiple organ metastases in mid- to late-stage[14]. Although the majority of prostate cancer patients will be treated accordingly, one-third develop advanced metastases, which is the terminal stage of the disease[15,16]. Most prostate cancer patients develop skeletal metastases,

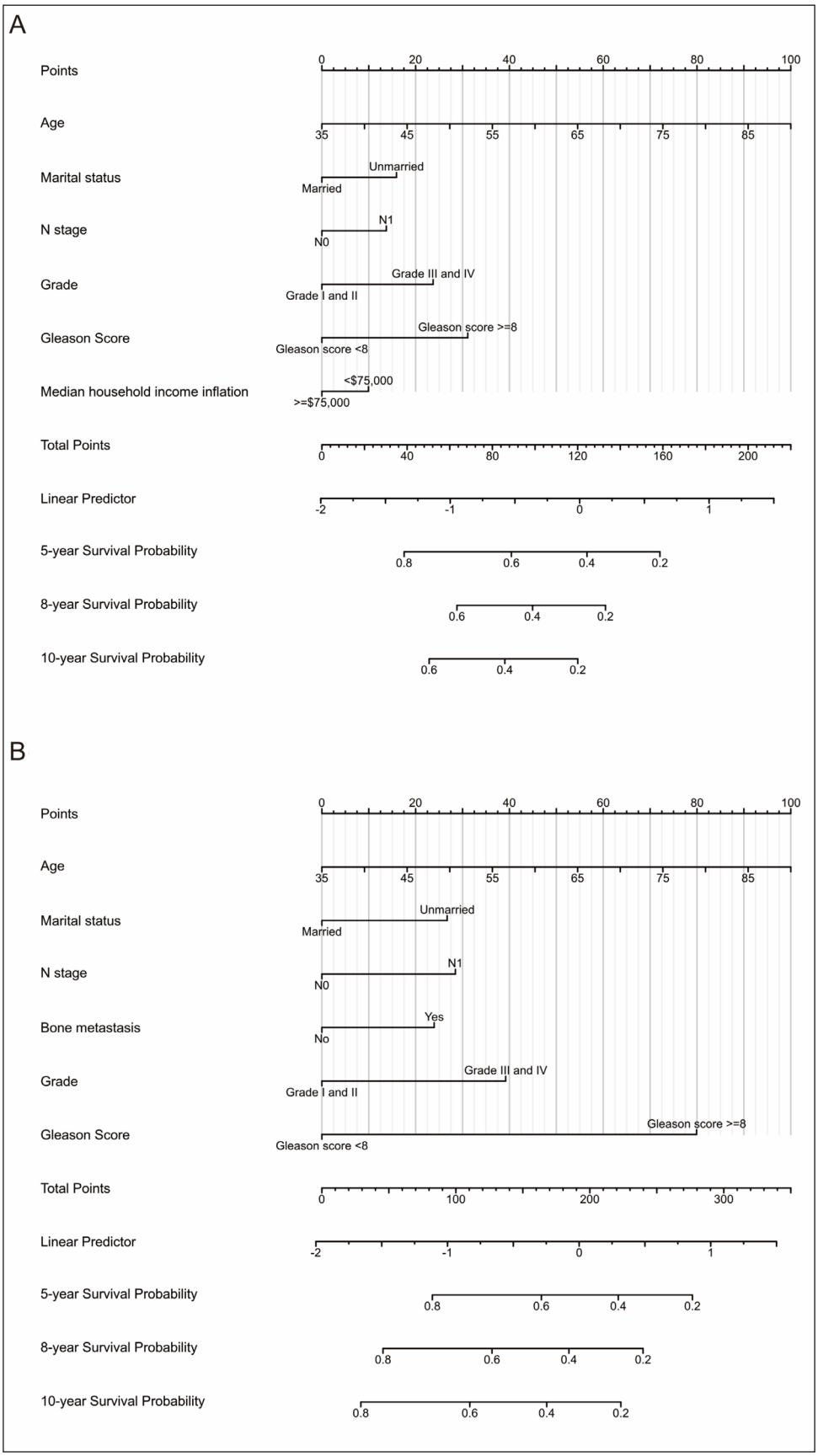

Figure 2. Nomograms predicting OS and CSS at 5, 8, and 10 years in PCa patients in the PSA <20 ng/ml group. **A**, Nomogram for OS; (**B**) Nomogram for CSS.

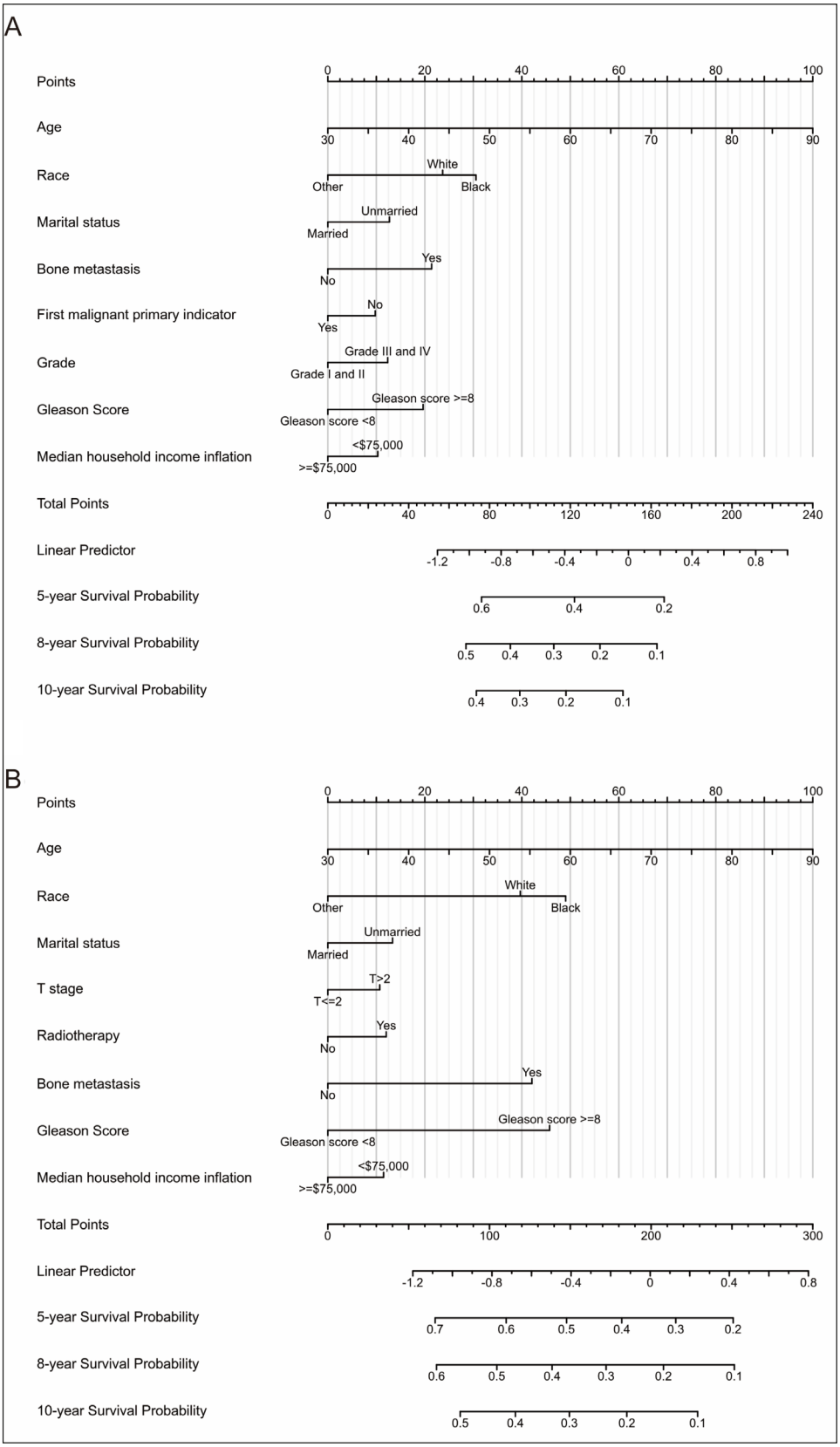

Figure 3. Nomograms predicting OS and CSS at 5, 8, and 10 years in PCa patients in the PSA ≥20 ng/ml group. **A**, Nomogram for OS; (**B**) Nomogram for CSS.

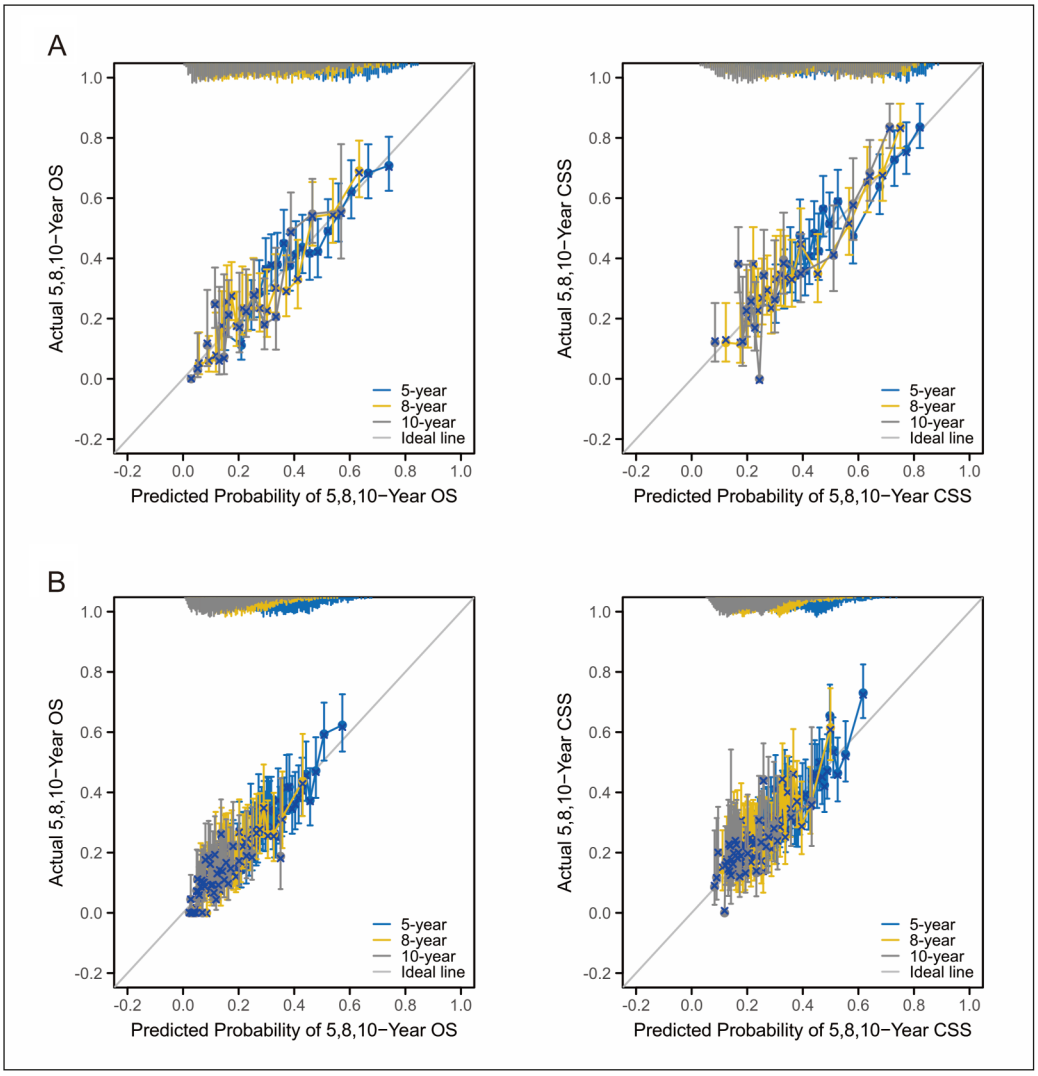

Figure 4. Calibration curves of 5-, 8-, and 10-year OS versus CSS in PCa patients. **A**, PSA <20 ng/ml group; (**B**) PSA≥20 ng/ml group.

leading to a range of adverse symptoms such as severe pain, impaired mobility, and pathologic fractures[17]. Therefore, the current aim for the treatment of metastatic PCa is mainly to eradicate or alleviate the side effects of bone metastases[18].

For the treatment of prostate cancer, in addition to surgical interventions, androgen deprivation therapy (ADT), radiation therapy (RT), ablation therapy, chemotherapy, and emerging immunotherapies[19]. The prognosis for localized prostate cancer is good, with a 5-year survival rate of 99% for this group of patients. However, the 5-year cancer-specific survival rate for metastatic prostate cancer is only 30%. For metastatic hormone-sensitive prostate cancer (mHSPC), the currently considered standard of care is to undergo ADT. This subset of patients initially responds to this treatment and then enters a period of castration-resistant[20]. Therefore, for patients with distantly metastatic prostate cancer, analyzing a large amount of patient clinical information is essential to more accurately predict patient prognosis.

Previous studies[21,22] have shown that PSA significantly improves the prediction of the final pathologic stage in patients with prostate cancer. In addition, PSA can be used to determine the success of treatment received by a patient and to predict the likelihood of metastasis and death in prostate cancer patients. In particular, serum PSA levels were associated with the risk of prostate cancer metastasis when PSA was >20 ng/mL[23].

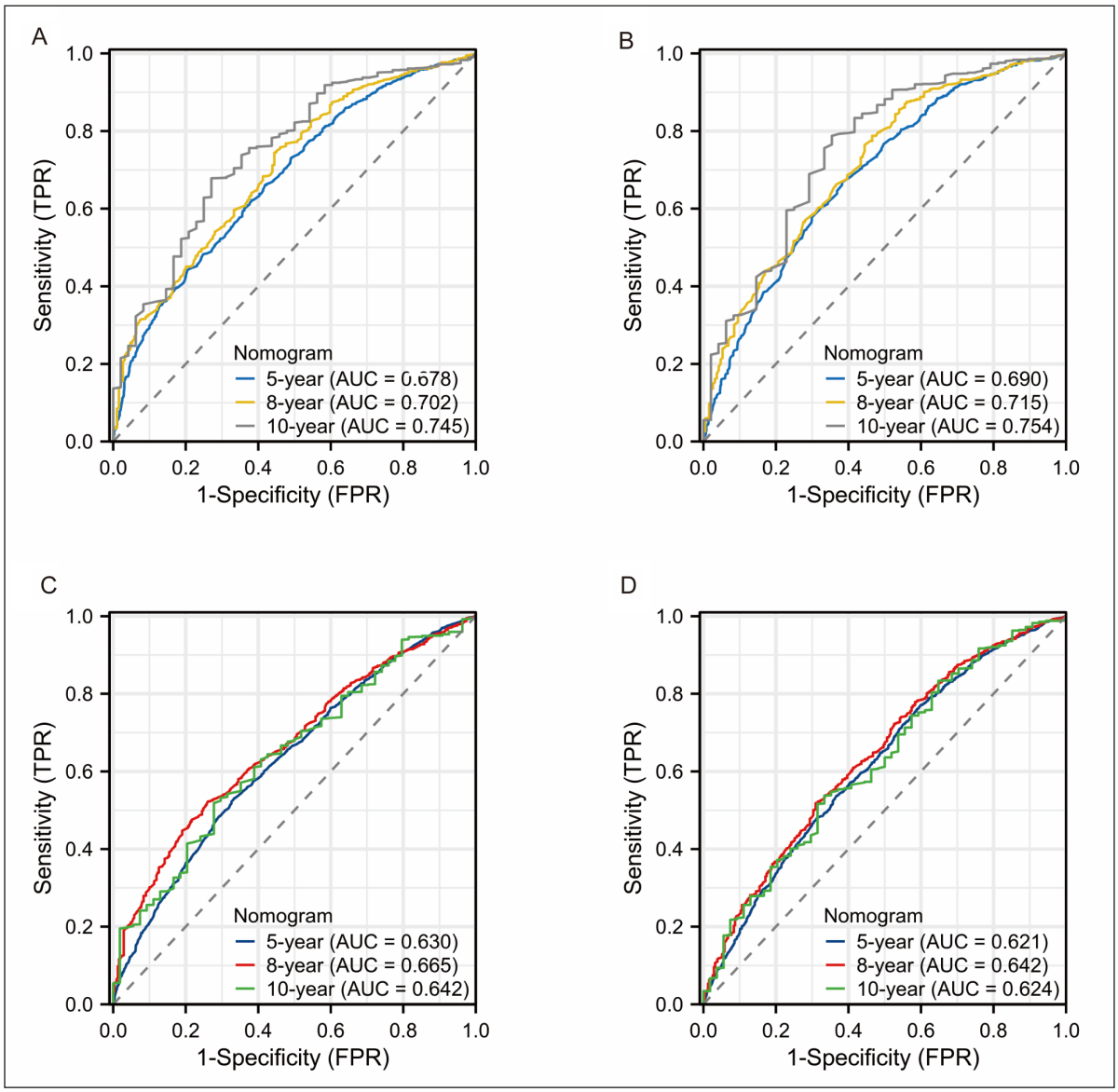

Figure 5. The timeROC curve analyzes the predictive power of the nomogram for 5-, 8-, and 10-year OS and CSS. **A**, In the PSA<20ng/ml group, timeROC curves were used to analyze the predictive ability of the nomogram for OS in PCa patients. **B**, In the PSA<20ng/ml group, timeROC curves were used to analyze the predictive ability of the nomogram for CSS in PCa patients. **C**, In the PSA≥20ng/ml group, timeROC curves were used to analyze the predictive ability of the nomogram for OS in PCa patients. **D**, In the PSA ≥20 ng/ml group, timeROC curves were used to analyze the predictive ability of the nomogram for CSS in PCa patients.

Such patients will be more likely to be diagnosed with locally advanced or metastatic disease[24]. In practice, however, the clinical use of PSA alone to determine a patient's prognosis is often less accurate due to age and other conditions (e.g., benign prostatic hyperplasia and prostatitis)[25]. In fact, because of the current increase in prostate biopsies, most physicians probably view PSA as a lower risk factor[26]. In this regard, determining the differences in risk factors among patients with different PSA levels in distant metastatic prostate cancer is particularly important to achieve accurate prediction of patient prognosis.

This study retrospectively analyzed data from patients with distantly metastatic prostate cancer based on the SEER database. Our findings showed that older age, unmarried, worse N stage, bone metastasis, worse grade, high Gleason score, and low income were independent risk factors affecting patient survival in the PSA <20 ng/mL subgroup.

Differently, in the PSA >20 ng/mL subgroup, older age, blacks, unmarried, worse T stage, radiotherapy, bone metastases, non-first malignant primary indicator, worse grading, higher Gleason score, and low income were the independent risk factors affecting patient survival.

Some of the prognostic factors identified in this study that are associated with patient survival have been explored in previous studies[27]. Older and unmarried PCa patients have a worse prognosis, which is consistent with previous studies[27,28]. Our study found that worse T stage, worse N stage, bone metastases, higher Grade and higher Gleason score were independent risk factors affecting the survival of prostate cancer patients. These findings are equally consistent with clinical experience[29-31]. In terms of the patients' household income, we consider the possibility that differenc-

Table V. Univariate and multivariate analysis of risk factors for CSS in PCa patients in the PSA ≥20 ng/ml group.

Characteristics	Total (N)	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Age	5,314	1.012 (1.009-1.016)	**<0.001**	1.013 (1.010-1.017)	**<0.001**
Ethnicity	5,314				
White	3,968	Reference		Reference	
Black	1,013	1.058 (0.972-1.151)	0.192	1.079 (0.989-1.179)	0.088
Other	333	0.716 (0.617-0.831)	**<0.001**	0.722 (0.622-0.839)	**<0.001**
Marital status	5,314				
Unmarried	2,153	Reference		Reference	
Married	3,161	0.890 (0.832-0.953)	**<0.001**	0.896 (0.836-0.961)	**0.002**
T stage	5,314				
T≤2	3,815	Reference		Reference	
T>2	1,499	1.068 (0.992-1.149)	0.079	1.088 (1.010-1.171)	**0.026**
N stage	5,314				
N0	3,432	Reference			
N1	1,882	1.045 (0.975-1.120)	0.209		
Surgery	5,314				
No	4,661	Reference		Reference	
Yes	653	1.108 (1.002-1.226)	**0.045**	1.065 (0.962-1.178)	0.227
Radiotherapy	5,314				
No	4,127	Reference		Reference	
Yes	1,187	1.084 (1.001-1.173)	**0.046**	1.104 (1.019-1.195)	**0.015**
Bone metastasis	5,314				
Yes	4,771	Reference		Reference	
No	543	0.701 (0.622-0.789)	**<0.001**	0.708 (0.628-0.797)	**<0.001**
First malignant primary indicator	5,314				
Yes	4,917	Reference		Reference	
No	397	1.121 (0.986-1.275)	0.081	1.031 (0.905-1.174)	0.650
Grade	5,314				
Grade I and II	417	Reference		Reference	
Grade III and IV	4,897	1.530 (1.330-1.759)	**<0.001**	1.157 (0.970-1.381)	0.105
Gleason Score	5,314				
Gleason score <8	848	Reference		Reference	
Gleason score ≥8	4,466	1.468 (1.332-1.618)	**<0.001**	1.360 (1.203-1.539)	**<0.001**
Median household income inflation	5,314				
<$75,000	3,677	Reference		Reference	
≥$75,000	1,637	0.903 (0.839-0.971)	**0.006**	0.911 (0.846-0.981)	**0.013**

Cancer-specific survival (CSS), Confidence interval (CI).

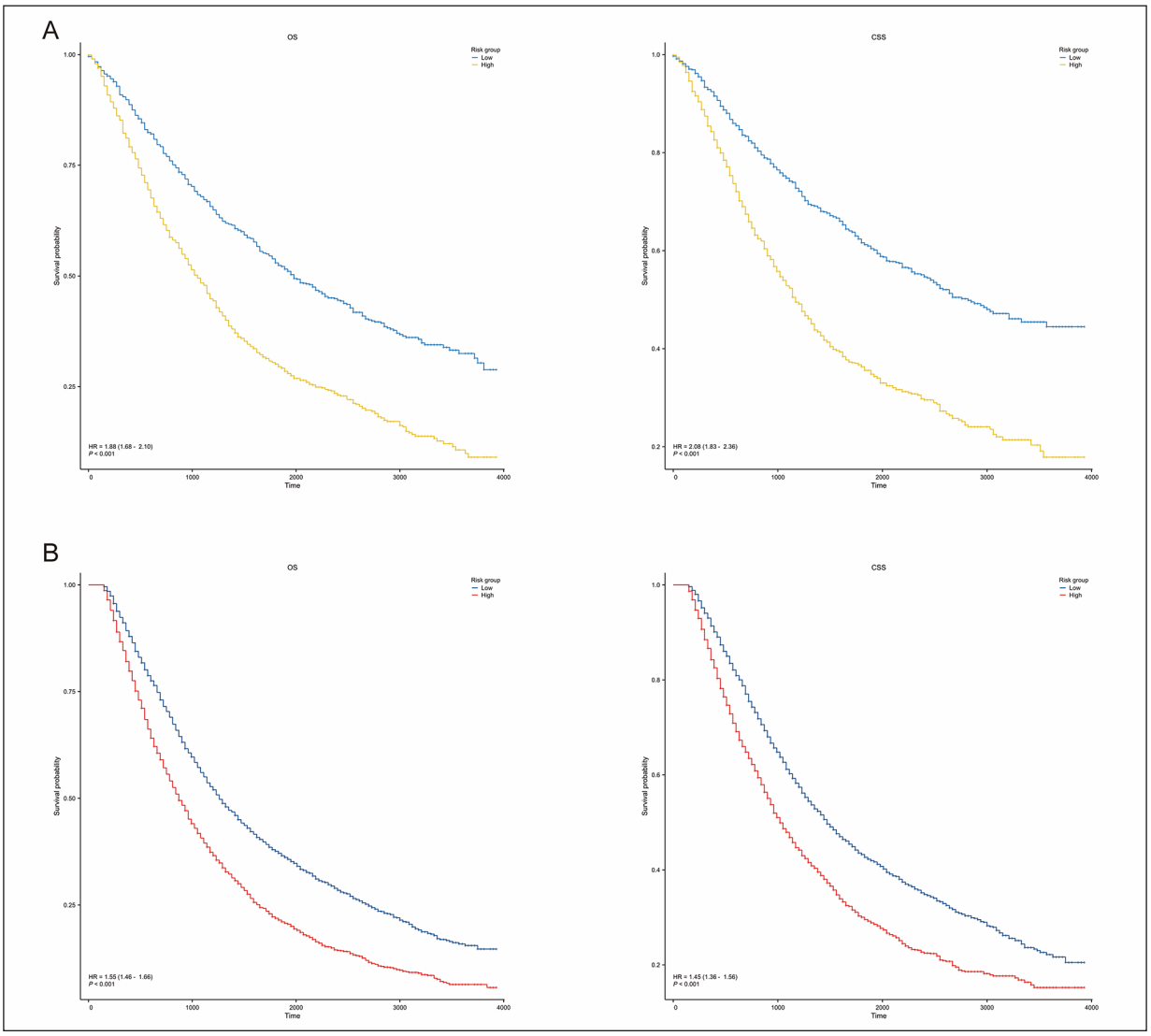

Figure 6. Kaplan-meier curves for OS and CSS in PCa patients with different risk levels. **A**, PSA <20 ng/ml group; (**B**) PSA≥20 ng/ml group.

es in treatment and care choices for low-income patients may lead to a poorer prognosis. Surprisingly, radiotherapy did not seem to have a beneficial effect on patients' CSS in the PSA ≥20 ng/mL subgroup. We considered the possible reasons to be that patients who did not receive radiotherapy had fewer malignant tumors of their own or had received better surgical treatment.

In recent years, the nomogram has become a commonly used prognostic assessment tool in clinical practice, which can synthesize a variety of prognostic factor variables as a means of predicting a patient's probability of survival[32]. Based on the independent prognostic factors of different subgroups, we constructed a nomogram to help clinicians accurately predict the survival time of prostate cancer patients to adjust clinical decisions. We further used calibration curves and timeROC curves to determine the accuracy and predictive power of the nomogram.

Limitations

There are some limitations to our study. First, this was a retrospective study, so there may be a possibility of selection bias that may need to be further verified by conducting a prospective study. Second, the patients were not divided into training and validation groups due to sample limitations. This study lacked

external validation, and external data may be needed in the future to validate the accuracy of the model further. Finally, the SEER database lacks necessary screening data and treatment information, such as tumor biomarkers, radiotherapy doses, and immunotherapy. Therefore, we were unable to perform a more comprehensive analysis. However, we have included most of the essential variables and therefore do not cause excessive bias.

Conclusions

Our study found that independent prognostic factors for OS and CSS were not the same when grouped according to different PSA values in prostate cancer patients who had developed distant metastases. Meanwhile, we developed a reliable nomogram in different groups, which can help clinicians more accurately predict the survival of prostate cancer patients who have developed distant metastases.

Conflict of Interest
The authors have declared that no competing interests exist.

Ethics Approval
The data for this study were obtained from the SEER database. Patient data were open and anonymized; therefore, ethical approval was not required for this study.

Informed Consent
Not applicable.

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Authors' Contributions
Authors Haodong Li and Siqi Fan contributed equally to this paper, including conceptualizing the concept, data collection, analyzing the data, and writing the paper. The other authors played a coordinating role in the above.

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Data Availability
The data used to support the findings of this study are available from the corresponding author upon reasonable request.

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