



Development and validation of a nomogram for predicting the overall survival of prostate cancer patients: a large population-based cohort study

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Background: Prostate cancer (PC) is the second most common malignant tumor, and its survival is of great concern. However, the assessment of survival risk in current studies is limited. This study is to develop and validate a nomogram for the prediction of survival in PC patients using data from the Surveillance, Epidemiology, and End Results (SEER) database.

Methods: A total of 153,796 PC patients were included in this cohort study. Patients were divided into a training set (n=107,657) and a testing set (n=46,139). The 3-, 5- and 10-year survival of the PC patients were regarded as the outcomes. Predictors based on the demographic and pathological data for survival were identified by multivariate Cox regression analysis to develop the predictive nomogram. Internal and subgroup validations were performed to assess the predictive performance of the nomogram. The C-index, time-dependent receiver operating characteristic (ROC) curves, and corresponding areas under the ROC curves (AUCs) were used to estimate the predictive performance of the nomogram.

Results: Age at diagnosis, race, marital status, tumor node metastasis (TNM) stage, prostate specific antigen (PSA) status, Gleason score, and pathological stage were identified as significantly associated with the survival of PC patients ($P < 0.05$). The C-index of the nomogram indicated a moderate predictive ability [training set: C-index = 0.782, 95% confidence interval (CI): 0.779–0.785; testing set: C-index = 0.782, 95% CI: 0.777–0.787]. The AUCs of this nomogram for the 3-, 5-, and 10-year survival were 0.757 (95% CI: 0.756–0.758), 0.741 (95% CI: 0.740–0.742), and 0.716 (95% CI: 0.715–0.717), respectively. The results of subgroup validation showed that all the AUCs for the nomogram at 3, 5, and 10 years were more than 0.70, regardless of marital status and race.

Conclusions: We developed a nomogram with the moderate predictive ability for the long-term survival (3-, 5-, and 10-year survival) of patients with PC.

Keywords: Prostate cancer; survival; nomogram; SEER database

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Introduction

Prostate cancer (PC) is the second most common malignant tumor diagnosed among men and remains the fifth leading cause of cancer-related deaths worldwide (1,2). An

estimated 268,490 new cases and 34,500 cancer-related deaths are reported annually in the United States (1). The 5-year survival rate declines to 31% for PC patients with metastatic disease (3). Therefore, it is imperative to identify

PC patients with poor prognoses, so as to implement management regimens to improve their quality of life.

Previous research have identified the factors associated with the prognosis of PC, including expression of the prostate specific antigen (PSA) (4,5). Younger age at diagnosis and being married have also been associated with improved prognosis and survival in PC patients (6-10). To predict patient prognosis more accurately, several models incorporating multiple prognostic factors have been built. Hu *et al.* developed a prognostic prediction model based on 22 autophagy-related genes expressed in PC patients (11). Han *et al.* conducted a prognostic nomogram for progression-free survival of 255 PC patients (12). However, the clinical applicability of these models is limited by the need to collect clinical samples and predictive ability. Furthermore, the performance of these prediction models validated in different subgroups has not been investigated.

Herein, a nomogram was developed to predict the long-term survival (3, 5, and 10 years) in 152,796 individuals based on data from the Surveillance, Epidemiology, and End Results (SEER) database. Internal validation and subgroup validation based on marital status and race were performed to assess the predictive performance of the nomogram. We present the following article in accordance with the TRIPOD reporting checklist (available at <https://tau.amegroups.com/article/view/10.21037/tau-22-498/rc>).

Methods

Study design and population

This was the development and validation of the nomogram based on a retrospective cohort. Data of PC cases were obtained from the SEER 18 Regs Custom Data (with additional treatment fields) of the National Cancer Institute (<http://seer.cancer.gov/>), which included cases diagnosed between 2005 and 2010. The SEER registries collect data on patient demographics, primary tumor site, tumor morphology, stage at diagnosis, first course of treatment, and patient vital statistics at follow up (13). The diagnosis of PC was confirmed in accordance with the International Classification of Diseases-Oncology 3 (ICD-O-3) 2008 site codes C8000, C8010, C8012, C8014, C8015, C8021, C8032, C 8041, C8042, C8045, C8140, C8141, C8143, C8200, C8201, C8210, C8246, C8255, C8260, C8310, C8323, C8380, C8480, C8481, C8490, C8500, C8501, C8521, C8523, C8550, C8551, C8560, C8570, C8571, C8574. The study was conducted in accordance with the

Declaration of Helsinki (as revised in 2013).

The inclusion criteria of this study were as follows: (I) PC patients; and (II) age more than 18 years old. The exclusion criteria were as follows: (I) unknown baseline characteristics (age, race, and marital status); (II) unknown American Joint Committee on Cancer (AJCC) stage [tumor/node/metastasis (T/N/M)], Gleason score, and PSA status; (III) missing or unknown survival status and survival months; and (IV) patients diagnosed with more than one primary cancer.

Data extraction

Demographic data from the SEER database were collated, including age at diagnosis, race (white, black, and others), and marital status (married and un-married). The pathological data collected included the following: pathological stage (distant/localized/regional), AJCC T stage (T1–T4), N stage (N0 and N1), M stage (M0, and M1), PSA levels (ng/mL), Gleason score, and bone metastasis. The survival months and survival status were obtained. The 3-, 5-, and 10-year survival of the PC patients were regarded as the outcomes. The follow up duration was 10 years, and follow-up was terminated when death occurred.

Statistical analysis

All statistical analyses were performed using the R (4.0.3) software. Tests for normality were conducted using the Kolmogorov-Smirnov test. Measurement data were described as mean \pm standard deviation (mean \pm SD) or median [interquartile range (IQR)]. The *t*-test or Mann-Whitney U test was used for intergroup comparisons. The statistical significance levels were all two-sided. A P value <0.05 was considered statistically significant.

The patients were randomly divided into a training set (n=107,657) and a testing set (n=46,139). In the training set, univariate and multivariate Cox regression analyses were conducted to identify predictive factors and develop the predictive nomogram. Internal validation was performed using the testing set. The C-index was calculated to assess the predictive performance of the presented nomogram. Subgroup validations based on marital status and race were conducted. The hazard ratio (HR) and 95% confidence interval (CI) were calculated. The time-dependent receiver operating characteristic (ROC) curves at different time

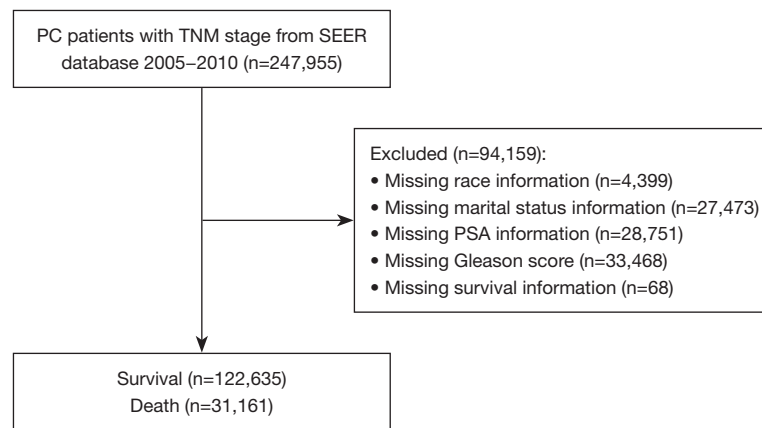


Figure 1 A flow chart of screening of prostate cancer patients. PC, prostate cancer; TNM, tumor node metastasis; PSA, prostate-specific antigen; SEER, Surveillance, Epidemiology, and End Results.

points (3, 5, and 10 years) in the whole population and subgroups based on marital status and race were drawn, and the corresponding areas under the ROC curve (AUC) were calculated to assess the predictive effect of the nomogram.

Results

Patient characteristics

A total of 153,796 patients were eventually included in this study, with an average age of 64.99 ± 9.10 years. The patients were divided into a training cohort ($n=107,657$) and a testing cohort ($n=46,139$). The detailed procedure for patient selection is presented in *Figure 1*. There was no significant difference in any of the variables between the training and testing sets ($P > 0.05$), suggesting that the data from the two groups were comparable (*Table 1*). Regarding ethnicity, there were 23,052 (14.99%) blacks, 122,449 (79.62%) whites, and 8,295 (5.39%) patients of other ethnicities. Of the 153,796 patients, 118,051 (76.76%) were married at diagnosis and 35,745 (23.24%) patients were unmarried. The mean follow-up time of the whole patient cohort was 101.52 ± 29.44 months. There were 31,161 (20.26%) deceased patients and 122,635 (79.74%) patients were alive at last follow-up.

Selection of predictive factors and construction of a predictive nomogram

Univariate Cox regression analyses of the training dataset revealed that age at diagnosis, race, marital status, TNM

stage, PSA, Gleason score, pathological stage, and bone metastasis were significant predictive factors ($P < 0.05$; *Table 2*). Furthermore, multivariate Cox stepwise regression analyses demonstrated that age at diagnosis, race, marital status, TNM stage, PSA, Gleason score, and pathological stage were significantly associated with the survival of patients with PC ($P < 0.05$; *Figure 2*). Based on these predictors, a nomogram for survival prediction in PC patients was established (*Figure 3*).

Predictive performance of the nomogram

The C-indexes of the nomogram in the training and testing sets were 0.782 (95% CI: 0.779–0.785) and 0.782 (95% CI: 0.777–0.787), respectively. In the training set, the AUCs for the prognostic nomogram at 3, 5, and 10 years were 0.757 (95% CI: 0.756–0.758), 0.741 (95% CI: 0.740–0.742), and 0.716 (95% CI: 0.715–0.717), respectively. In the testing set, the AUCs for the prognostic nomogram at 3, 5, and 10 years were 0.743 (95% CI: 0.741–0.745), 0.726 (95% CI: 0.724–0.728), and 0.716 (95% CI: 0.714–0.717), respectively. These results demonstrated that the nomogram exhibited a good predictive performance (*Figure 4*).

Validation for the predictive performance of nomogram in different subgroups based on marital status and race

For subgroup validation based on marital status, the C-index of the nomogram was 0.784 (95% CI: 0.778–0.790) among married patients and 0.757 (95% CI: 0.747–0.767) among

Table 1 The characteristics of PC patients

Variables	Total (n=153,796)	Training set (n=107,657)	Testing set (n=46,139)	Statistics	P
Age at diagnosis (year)	64.99±9.10	64.97±9.09	65.04±9.12	t=1.450	0.147
Race				$\chi^2=0.245$	0.885
Black	23,052 (14.99)	16,168 (15.02)	6,884 (14.92)		
White	122,449 (79.62)	85,683 (79.59)	36,766 (79.69)		
Others	8,295 (5.39)	5,806 (5.39)	2,489 (5.39)		
Marital status				$\chi^2=0.096$	0.756
Married	118,051 (76.76)	82,612 (76.74)	35,439 (76.81)		
Un-married	35,745 (23.24)	25,045 (23.26)	10,700 (23.19)		
Pathological stage				$\chi^2=0.001$	0.977
Distant	3,654 (2.38)	2,557 (2.38)	1,097 (2.38)		
Localized/regional	150,142 (97.62)	105,100 (97.62)	45,042 (97.62)		
T stage				$\chi^2=7.184$	0.066
T1	56,679 (36.85)	39,691 (36.87)	16,988 (36.82)		
T2	81,134 (52.75)	56,639 (52.61)	24,495 (53.09)		
T3	14,278 (9.28)	10,117 (9.40)	4,161 (9.02)		
T4	1,705 (1.11)	1,210 (1.12)	495 (1.07)		
N stage				$\chi^2=0.492$	0.483
N0	150,734 (98.01)	105,496 (97.99)	45,238 (98.05)		
N1	3,062 (1.99)	2,161 (2.01)	901 (1.95)		
M stage				$\chi^2=0.034$	0.854
M0	150,196 (97.66)	105,142 (97.66)	45,054 (97.65)		
M1	3,600 (2.34)	2,515 (2.34)	1,085 (2.35)		
PSA (ng/mL)	62 [46, 97]	62 [46, 97]	62 [46, 96]	Z=-1.107	0.268
Gleason score	6.74±0.95	6.74±0.95	6.73±0.94	t=-1.84	0.065
Bone metastasis				$\chi^2=0.007$	0.934
No	151,279 (98.36)	105,897 (98.37)	45,382 (98.36)		
Yes	2,517 (1.64)	1,760 (1.63)	757 (1.64)		
Survival month	101.52±29.44	101.49±29.50	101.60±29.29	t=0.710	0.479
Survival status				$\chi^2=0.082$	0.775
Alive	122,635 (79.74)	85,865 (79.76)	36,770 (79.69)		
Dead	31,161 (20.26)	21,792 (20.24)	9,369 (20.31)		

The data are expressed as mean ± SD or n (%) or M [Q₁, Q₃]. PC, prostate cancer; SD, standard deviation; T, tumor; N, node; M, metastasis; PSA, prostate-specific antigen.

Table 2 Univariate Cox regression analysis

Variables	β	Z	SE	P	HR (95% CI)
Race					
Black	Ref				
White	-0.211	-11.706	0.018	<0.001	0.810 (0.782–0.839)
Others	-0.257	-7.455	0.034	<0.001	0.774 (0.723–0.828)
Marital status					
Married	Ref				
Un-married	0.527	36.274	0.015	<0.001	1.693 (1.646–1.742)
Age at diagnosis	0.098	122.220	0.001	<0.001	1.103 (1.102–1.105)
T stage					
T1	Ref				
T2	-0.453	-31.341	0.014	<0.001	0.636 (0.618–0.654)
T3	-0.240	-9.792	0.025	<0.001	0.786 (0.749–0.825)
T4	1.158	28.677	0.040	<0.001	3.183 (2.940–3.445)
N stage (N1)	1.330	43.694	0.030	<0.001	3.780 (3.561–4.012)
M stage (M1)	2.510	108.407	0.023	<0.001	12.301 (11.756–12.872)
PSA	0.003	113.714	<0.001	<0.001	1.003 (1.003–1.003)
Gleason score	0.515	80.333	0.006	<0.001	1.674 (1.653–1.695)
Pathological stage					
Distance	Ref	–	–	–	–
Localized/regional	-2.494	-108.33	0.023	<0.001	0.083 (0.079–0.086)
Bone metastasis (yes)	2.498	92.462	0.027	<0.001	12.160 (11.533–12.821)

SE, standard error; HR, hazard ratio; CI, confidence interval; T, tumor; N, node; M, metastasis; PSA, prostate-specific antigen; Ref, reference.

non-married patients. In the married group, the AUCs for the nomogram at 3, 5, and 10 years were 0.747 (95% CI: 0.745–0.749), 0.739 (95% CI: 0.737–0.741), and 0.713 (95% CI: 0.710–0.715), respectively. In non-married patients, the AUCs for the nomogram at 3, 5, and 10 years were 0.730 (95% CI: 0.726–0.734), 0.725 (95% CI: 0.721–0.728), and 0.711 (95% CI: 0.707–0.715), respectively. These results demonstrated that the nomogram had a good predictive performance in populations with different marital status (Figure 5).

For subgroup validation based on ethnicity, the C-index of the nomogram was 0.788 (95% CI: 0.782–0.794) among whites, 0.750 (95% CI: 0.738–0.762) in blacks, and 0.783 (95% CI: 0.761–0.805) in other races. In the white population, the AUCs for the nomogram at 3, 5, and 10 years were 0.746 (95% CI: 0.745–0.748), 0.739

(95% CI: 0.737–0.741), and 0.716 (95% CI: 0.714–0.718), respectively. Among the black population, the AUCs for the nomogram at 3, 5, and 10 years were 0.739 (95% CI: 0.734–0.743), 0.733 (95% CI: 0.728–0.737), and 0.707 (95% CI: 0.702–0.712), respectively. In other races, the AUCs for the nomogram at 3, 5, and 10 years were 0.782 (95% CI: 0.775–0.789), 0.760 (95% CI: 0.753–0.767), and 0.739 (95% CI: 0.731–0.747), respectively. These results suggested that the nomogram had a good predictive performance regardless of ethnicity (Figure 6).

Example

To further validate the nomogram, we examined a divorced white patient who was diagnosed with PC at the age of 46 years. He had a pathological stage classification of

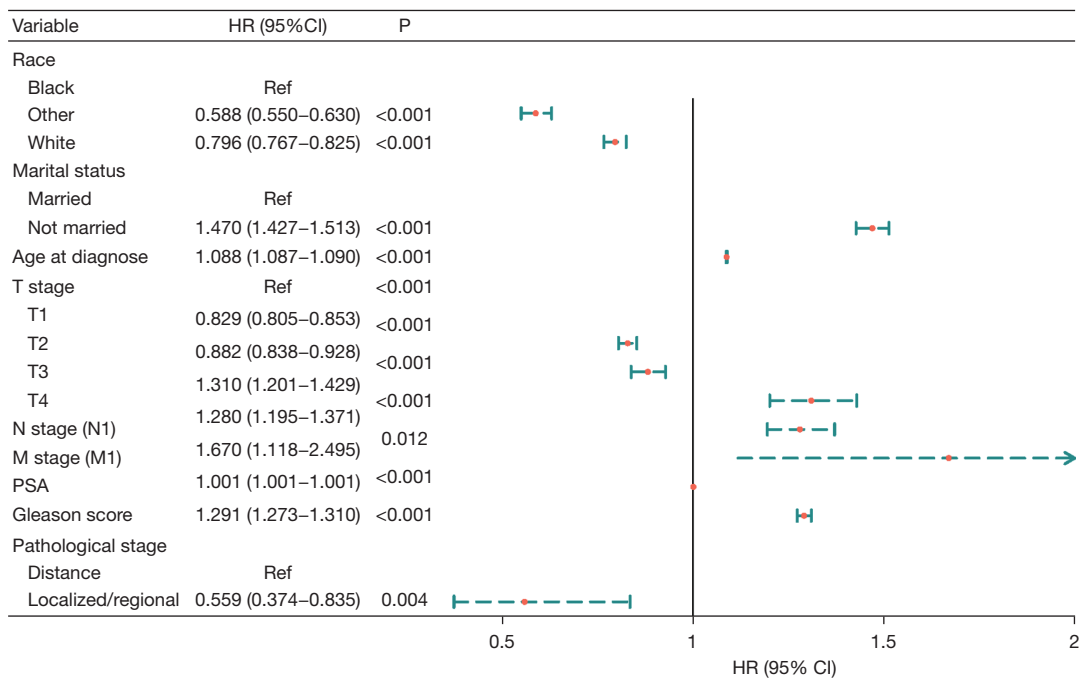


Figure 2 Predictors of the survival in PC patients. HR, hazard ratio; T, tumor; N, node; M, metastasis; PSA, prostate specific antigen; PC, prostate cancer.

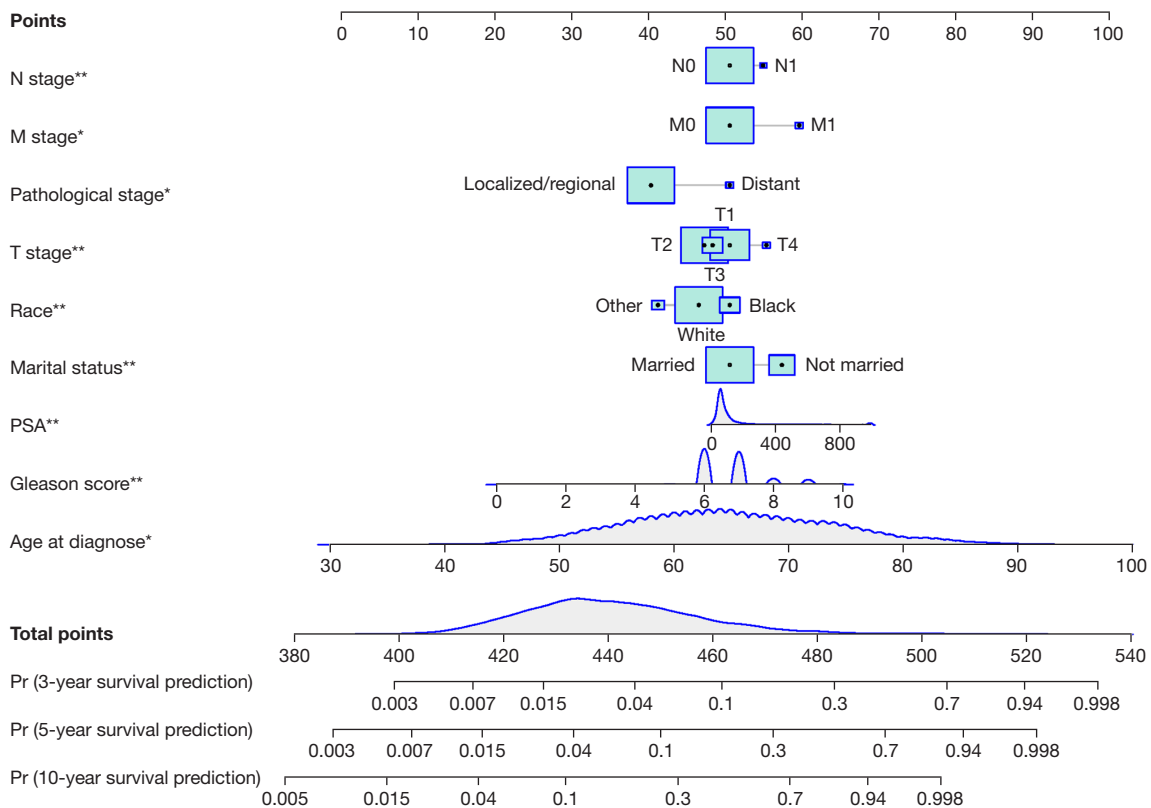


Figure 3 A nomogram for predicting the survival of PC patients. *P<0.05; **P<0.001. T, tumor; N, node; M, metastasis; PSA, prostate specific antigen; Pr, probability; PC, prostate cancer.

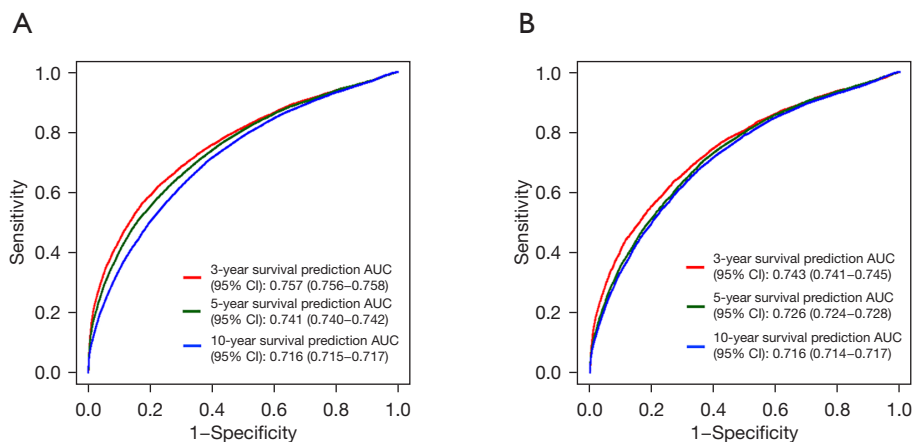


Figure 4 Time-dependent ROC curves and the corresponding AUC for the 3-, 5-, and 10-year survival. (A) Training set and (B) testing set. ROC, receiver operating characteristic; AUC, area under the curve.

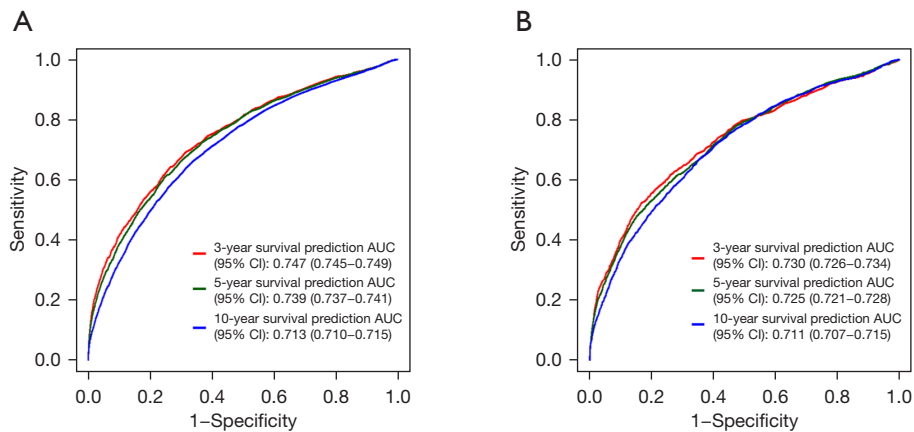


Figure 5 Time-dependent ROC curves and the corresponding AUC for the 3-, 5-, and 10-year survival of subgroups according to marital status. (A) Married and (B) unmarried. ROC, receiver operating characteristic; AUC, area under the curve.

localize/regional, a PSA level of 13 ng/100 mL, a Gleason score of 5, and T2/M0/N0 stage tumor. According to our nomogram, the patient had a total score of 406 points, and the predicted risk of death within 3, 5, and 10 years were 0.0045, 0.00875, and 0.0244, respectively. The patient’s actual survival time was 137 months, which was consistent with the prediction from the nomogram (Figure 7).

Discussion

In this study, a novel prediction nomogram for the long-term survival (3-, 5-, and 10-year survival) of PC patients was developed and validated. The selected predictive factors included age at diagnosis, race, marital status, TNM stage,

PSA levels, Gleason score, and pathological stage. The predictive tool for survival in PC patients was established based on the above predictors, with a C-index of 0.782 (95% CI: 0.779–0.785) and validation with the testing set showed a C-index of 0.782 (95% CI: 0.777–0.787). The AUCs of the model at 3, 5, and 10 years were 0.757 (95% CI: 0.756–0.758), 0.741 (95% CI: 0.740–0.742), and 0.716 (95% CI: 0.715–0.717), respectively. Validation with the testing set showed AUCs of 0.743 (95% CI: 0.741–0.745), 0.726 (95% CI: 0.724–0.728), and 0.716 (95% CI: 0.714–0.717) for the 3-, 5-, and 10-year survival, respectively. Additionally, subgroup validations based on marital status and race showed good predictive performances of the nomogram.

This research showed that patients in the state of

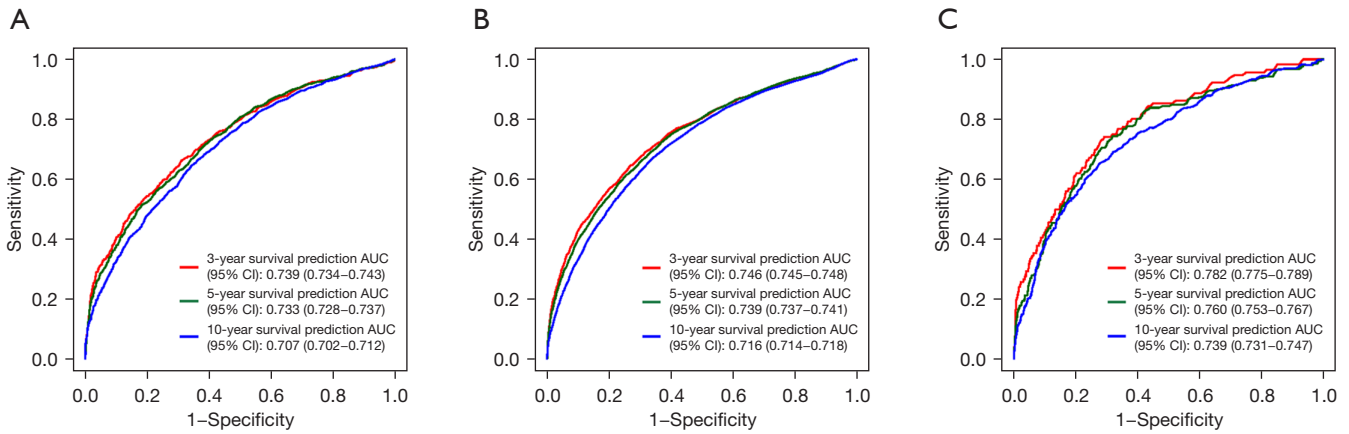


Figure 6 Time-dependent ROC curves and corresponding AUC for the 3-, 5-, and 10-year survival of subgroups according to race. (A) Black, (B) White, and (C) other races. ROC, receiver operating characteristic; AUC, area under the curve.

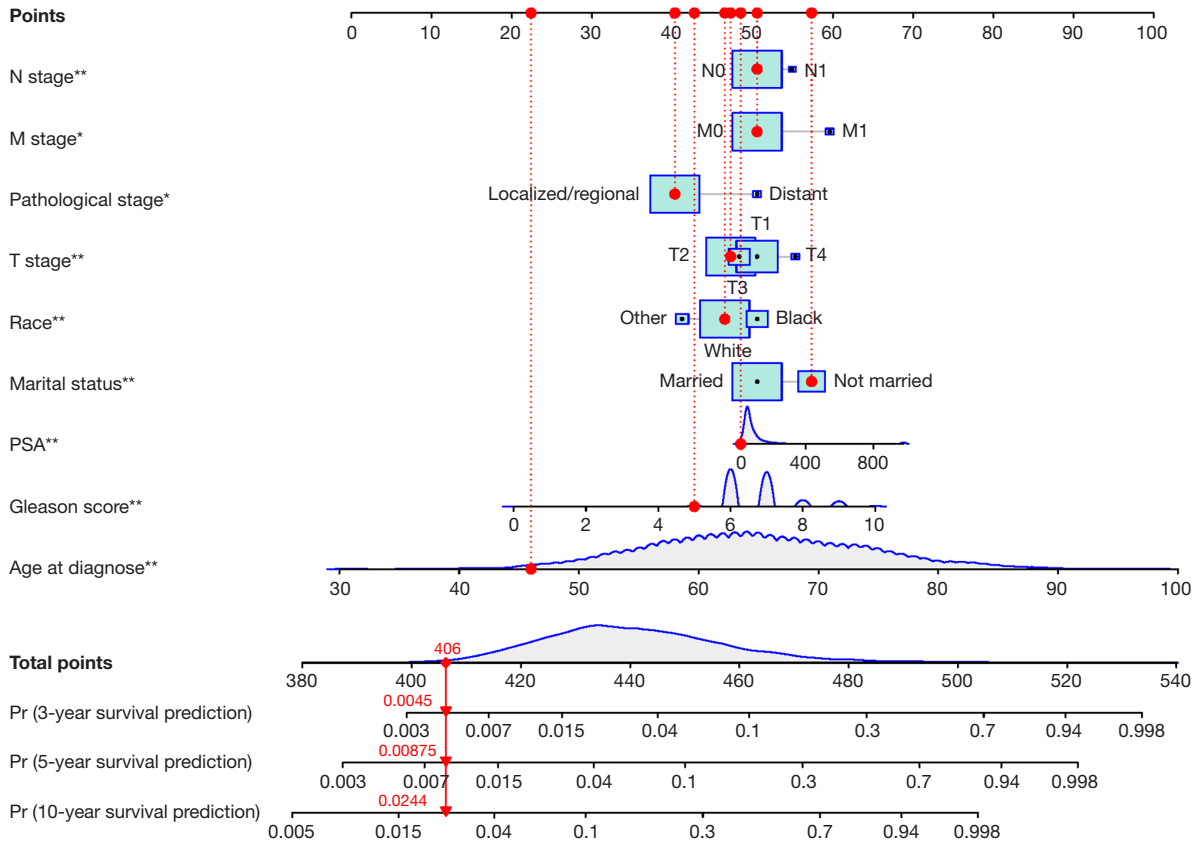


Figure 7 An example using the nomogram for predicting the survival of PC patients. * $P < 0.05$; ** $P < 0.001$. PSA, prostate specific antigen; T, tumor; N, node; M, metastasis; Pr, probability; PC, prostate cancer.

being married had a better prognosis than patients who were un-married. The association between marital status and survival may be attributed to the following plausible explanations: (I) married cases are likely to be in a better economic situation and have a higher degree of education compared to unmarried patients, and this may be associated with improved adherence to treatments (14); (II) unmarried patients are more likely to develop metastatic disease compared to married cases (15); and (III) there is a positive relationship between marriage and the possibility of early diagnosis of all types of cancer, and indeed, unmarried patients diagnosed with cancer are at higher risk of progression to advanced cancer and typically present with a shorter life expectancy compared to married patients (16). Hence, more effort should be focused on improving the long-term survival of unmarried individuals. Our results showed that increased age at diagnosis is associated with poor prognosis among PC patients, which is consistent with a previous study (6). It was noted that black patients had poorer prognosis compared to white patients. A previous study found that the CAG repeat length was shorter in black patients compared to white patients, and this was thought to be the reason for their higher risk of death (17).

This investigation demonstrated that PSA, Gleason score, TNM stage, and pathological stage were associated with long-term survival among PC patients. The TNM staging system has been widely used to assess the prognosis of cancer patients (18). It is worth noting that PC patients with T4 stage tumors have a higher risk of death than those with T1 stage tumors, while patients with T2 or T3 stage tumors have a better prognosis compared to those with T1 stage tumors. Some studies indicated that shortened overall survival may be related to the presence of bone metastasis among PC patients (19-21). Indeed, Lu *et al.* have mentioned that PC patients with stage T4 cancer have the highest risk of bone metastasis, and T2 or T3 patients have a lower risk of being diagnosed with bone metastasis than T1 patients (22). Further in-depth studies are warranted to explore the underlying reasons behind the differences in survival. PSA is a sensitive indicator for the evaluation of the therapeutic effect or even for the prognostic assessment of PC patients (23,24). Previous studies suggested that there is a negative correlation between PSA levels and risk of death (25,26), which is consistent with our results showing that higher levels of PSA is a risk factor for survival among PC patients. Consistent with a previous study (27), the results herein demonstrated that the Gleason scoring system, as the most widely used pathological grading criteria for PC, is

a prognostic predictor for survival in PC patients.

Several models have been developed to estimate the survival of PC patients. Schmidt *et al.* reported the success of using 4-miRNA [(miR-23a-3p × miR-10b-5p)/(miR-133a × miR-374b-5p)] for the prediction of outcomes in PC patients (28). However, the inconvenience of clinical collection of predictive indicators used in this latter model would increase the economic burden of patients and restrict its clinical application. Our nomogram was established using clinical features that are easily collected in the clinical setting. Another model proposed by Wang *et al.*, combines the method of treatment, hyperintensity within the prostate on diffusion-weighted imaging (DWI), and the metastasis burden of pelvic lymph nodes to assess the survival of PC patients (29). However, the predictive performance of this system was not evaluated and the small sample size (n=121) may weaken the reliability of this model. In contrast, the model constructed herein, was based on a larger sample size (n=16,775) and had a moderate predictive power after internal validation and subgroup analysis.

The nomogram designed in this report may be used effectively in predicting the long-term survival of PC patients. However, there were several limitations to this study. First, specific information of patients related to the survival of PC, such as certain biological indicators and behavioral habits, could not be collected from the SEER database. Second, long-term survival predicted by this nomogram may be affected by new treatment approaches, and more rigorously designed studies are needed to validate this model in the future. Third, there was no external validation in our study and future investigations should include this to verify the predictive ability of the presented model.

Conclusions

This study demonstrated that age, race, marital status, TNM stage, PSA, Gleason score, and pathological stage are associated with the survival of PC patients. Based on these predictors, a nomogram for the long-term survival (3-, 5-, and 10-year survival) of PC patients was developed and validated, with good predictive performance. This nomogram may be useful in the management of PC patients.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at <https://tau.amegrouops.com/article/view/10.21037/tau-22-498/rc>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tau.amegrouops.com/article/view/10.21037/tau-22-498/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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