Original Article

Nomograms to predict overall and cancer-specific survival in patients with penile cancer

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Background: To develop and validate prognostic nomograms for predicting overall survival (OS) and cancer-specific survival (CSS) in patients with penile cancer (PC).

Methods: Based on the Surveillance, Epidemiology, and End Result (SEER) database, patients diagnosed with PC from 2010 to 2015 were enrolled in this study. For each patient, clinical characteristics and survival results were respectively collected. With the method of random-number generation, included patients were divided into the training cohort and the validation group. Subsequently, nomograms were constructed to predict 3- and 5-year OS and CSS based on the results of multivariate analyses. Kaplan-Meier (KM) method and the log-rank test were used to estimate survival curves of each variables. Finally, the calibration plots, concordance index (C-index), area under the receiver operating characteristic (ROC) curves were used to evaluate nomograms performance.

Results: Totally, 1,418 patients were eventually enrolled in the study, including 994 patients in the training cohort and 424 patients in the validation cohort. No significant difference was detected in the baseline characteristics between two cohorts. According to results of the uni- and multivariate analysis in the training cohort, 7 factors (including age, race, T stage, N stage, M stage, histology codes, and the use of surgery) for OS and 7 factors (including race, T stage, N stage, M stage, histology codes, the use of surgery and lymph node removal) for CSS were selected for constructing the nomograms. The C-indices for OS and CSS were 0.755 and 0.805 in the training cohort and 0.711, 0.737 in the validation cohort. In addition, the 3- and 5-year area under the ROC curve (AUC)s for OS were 0.792 and 0.771 in the training cohort, and 0.687 and 0.695 in the validation group. When it came to CSS, it was 0.83 and 0.826 in the training cohort and 0.758 and 0.746 in the validation cohort. Lastly, the calibration curves indicated a good consistency between the actual survival and the predictive survival.

Conclusions: We firstly established survival models to predict OS and CSS in PC patients with good predictive ability. Further studies are needed to validate our results before clinical application in the future.

Keywords: Cox; survival; nomogram; Surveillance, Epidemiology, and End Result (SEER); penile cancer (PC)

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Introduction

Penile cancer (PC) is a relatively rare malignancy with 2080 estimation new cases in 2019 in the United States, representing 0.24% of all men's new cancer cases (1). The incidence and mortality of PC in developed countries have been low and stable (1-3). However, in South America, Asia, and parts of Africa, the morbidity is much higher, accounting for up to 1–2% of malignant tumors in men (4). In some poor areas, the incidence is as high as (6–7)/100,000 (5). The present paradigm for PC management includes pathological biopsy and immediate excision for highly suspicious lesions (6). Early resection is indeed beneficial to survival, unfortunately, patients who undergo inguinal lymphadenectomy are more likely to short- and long-term morbidity (7,8). In addition, the effects of chemotherapy and radiotherapy remained controversial because of their depressing results (9,10).

As far as we known, prognostic factors such as higher histological grade (11), growth pattern (superficial) (12), perineural invasion (13), venous and/or lymphatic embolization (14), marital status (15), age, race, tumor size, and treatment can influence patient outcomes. For instance, inguinal lymph node involvement is the most important prognostic factor and surgical management of the inguinal region is needed even when the clinical disease is absent (16). However, Lopes found that the T stage had not a significant relationship with the patient's overall survival (OS) (17). Previous studies had shown that histology codes of PC were controversial in predicting cancer progression (18,19). Radiation therapy has significant effects on the management of penile squamous cell carcinoma, which enables sustained local control of the primary tumor while retaining functional anatomy (20). Therefore, we sought to develop a prognostic model incorporating include patient status, tumor characteristics and therapeutic methods based on large samples.

The nomograms are accurate and convenient clinical outcomes prediction tool, which are used to predict the prognosis of patients with malignancy (21,22). As far as we know, this method has been widely used in renal cell carcinoma, prostate cancer and bladder cancer (23-25). Our study aimed to establish nomograms based on the Surveillance, Epidemiology, and End Result (SEER) database to effectively evaluate and predict prognosis in PC patients. For this reason, clinicians can better counsel patients and tailor personalized treatment based on easily accessible clinical variables.

Methods

Data source and Study population

Patients diagnosed with PC from 2010 to 2015 were identified and extracted from SEER database using the SEER*Stat software (Version 8.3.6; National Cancer Institute, Bethesda, USA). The National Cancer Institute's SEER program is the largest population-based cancer database in the United States, which collects and publishes information of cancer patients in 18 registries, covering nearly 30% of the USA population (26). Patients included in our study should meet the following criteria: (I) diagnosed as PC (International Classification of Diseases for Oncology: 8,000/3, 8,010/3, 8,033/3, 8,051/3, 8,052/3, 8,070/3, 8,072/3, 8,073/3, 8,074/3, 8,076/3, 8,081/3, 8,083/3, 8,090/3, 8,092/3, 8,094/3, 8,097/3, 8,120/3, 8,140/3, 8,255/3, 8,403/3, 8,413/3, 8,480/3, 8,542/3, 8,940/3) with positive histology; (II) diagnosed from 2010 to 2015 to ensure a relatively long follow-up period; (III) complete data were available with active follow-up. Meanwhile, the exclusion criteria were as follows: (I) the first primary malignancy was not PC; (II) data on included variables were missing, such as race, age, sex, TNM stage, treatment methods and so on. The TNM stage were defined according to the 7th edition American Joint Committee on Cancer (AJCC) staging system (27). For each patient, we then collected the following information, including demographic characteristics (age race, and marital status), clinicopathological features (histology codes and TNM stage), use of surgery/lymph node removal (LNR)/radiation/chemotherapy, and survival outcomes (survival months, cancer-specific death, and cause of death). Primary endpoints of this research OS and cancer-specific survival (CSS). No medical ethics review was sought because of the identified data from public-use data.

Statistical analyses

To develop and validate the survival nomograms, patients were divided into two cohorts (the training cohort and the validation cohort) randomly at a ratio of 7:3 with the method of random-number generation (28,29). Comparisons of clinical information between two groups were made using the chi-square test. Uni- and multivariate Cox regression analysis were used to find the significant variables for OS and CSS. Based on the results of the multivariate analysis, nomograms models were constructed to predict 3-and 5-year OS and CSS. Furthermore, survival

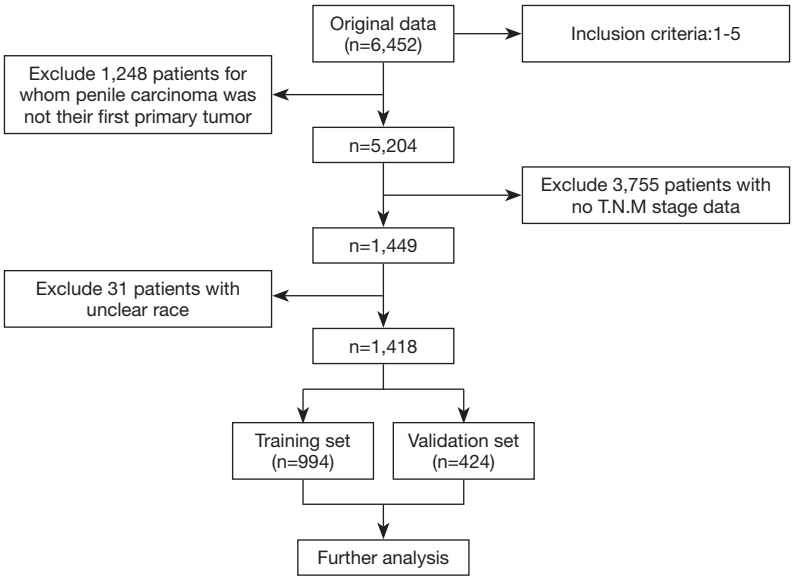

Figure 1 The study flow diagram of the selection process.

curves developed by Kaplan-Meier (KM) analysis and were compared utilizing the log-rank test among different variables.

Lastly, predictive performance of the nomograms was evaluated both internally (training set) and externally (validation set) with the calibration curve, Harrell's concordance index (C-index) (30) and the receiver operating characteristic (ROC) curve (31,32). Generally, area under the ROC curve (AUC) and the C-index range from 0.5 to 1.0, with 1.0 suggesting a perfect discrimination ability and 0.5 indicating the total chance (33). Consistency between the actual survival and the predicted survival was explored by calibration curves.

Chi-square test and Cox analysis were developed by SPSS 23.0 software (SPSS Inc, Chicago, IL, USA). Development and validation of the nomograms were performed using R version 3.6. 1 (http://www.r-project.org/) with rms, foreign, survival, survival ROC, and caret packages. During the whole analysis process, P<0.05 was considered to be statistically significant (two-sided).

Results

Demographic and characteristics of patients

A total of 1,418 patients were enrolled in the study. A flow diagram of data selection was present in *Figure 1*. All eligible cases were randomly regrouped into training (n=994) and validation (n=424) cohorts. The demographic characteristics, clinicopathological features, and treatment methods of participants were shown in *Table 1*. No significant differences were detected between two cohorts in all variables (all P>0.05) except histology (P=0.038). Patients with squamous cell carcinoma (SCC) in the validation cohort were more than those in the training cohort significantly (P=0.038). We thought it was because of the relatively fewer patients of other types of PC patients, which led to the selection bias.

Cox regression analyses and KM curve analyses

Uni- and multivariate Cox regression analyses were constructed to pick out key factors for OS and CSS. As shown in *Table 2* and *Table 3*, 7 factors (including age, race, T stage, N stage, M stage, histology codes, and surgery, all P<0.05) were tightly associated with OS and 7 factors (including race, T stage, N stage, M stage, histology codes, surgery, and LNR, all P<0.05) were closely related to CSS. Subsequently, Finally, KM survival curves for OS and CSS were generated to learn the actual effect of different variables (*Figures 2,3*).

Table 1 Clinical characteristics of included patients in the study

	Total (n=1,418), n (%)	Training cohort (n=994), n (%)	Validation cohort (n=424), n (%)	P
Age				0.993
<40	60 (4.3)	42 (4.2)	18 (4.2)	
40–59	419 (29.5)	292 (29.4)	127 (30.0)	
60–79	696 (49.1)	488 (49.1)	208 (49.1)	
≥80	243 (17.1)	172 (17.3)	71 (16.7)	
Race				0.739
White	1,187 (83.7)	832 (83.7)	355 (83.7)	
Black	146 (10.3)	105 (10.6)	41 (9.7)	
Other	85 (6.0)	57 (5.7)	28 (6.6)	
T stage				0.529
Ta	19 (1.3)	13 (1.3)	6 (1.4)	
T1	805 (56.8)	573 (57.7)	232 (54.7)	
T2	320 (22.5)	219 (22.0)	101 (23.8)	
T3	232 (16.4)	164 (16.5)	68 (16.1)	
T4	42 (3.0)	25 (2.5)	17 (4.0)	
N stage				0.726
N0	1,128 (79.6)	790 (79.5)	338 (79.7)	
N1	84 (5.9)	56 (5.6)	28 (6.6)	
N2	98 (6.9)	68 (6.9)	30 (7.1)	
N3	108 (7.6)	80 (8.0)	28 (6.6)	
M stage				0.796
M0	1,364 (96.2)	957 (96.3)	407 (96.0)	
M1	54 (3.8)	37 (3.7)	17 (4.0)	
LNR				0.349
No/Biopsy only	1,139 (80.3)	792 (79.7)	347 (81.8)	
Yes	279 (19.7)	202 (20.3)	77 (18.2)	
Surgery				0.841
NO/unknown	104 (7.3)	72 (7.2)	32 (7.5)	
Yes	1,314 (92.7)	922 (92.8)	392 (92.5)	
Histology				0.038
Other	128 (9.0)	100 (10.1)	28 (6.6)	
SCC	1,290 (91.0)	894 (89.9)	396 (93.4)	
Radiation				0.285
No/Unknown	1,299 (91.6)	914 (92.0)	385 (90.8)	
Yes	119 (8.4)	80 (8.0)	39 (9.2)	

Table 1 (*Continued*)

Table 1 (*Continued*)

	Total (n=1,418), n (%)	Training cohort (n=994), n (%)	Validation cohort (n=424), n (%)	P
Chemotherapy				0.582
No/Unknown	1,230 (86.7)	859 (86.4)	371 (87.5)	
Yes	188 (13.3)	135 (13.6)	53 (12.5)	
Marital status				0.623
Married	747 (52.7)	530 (53.3)	217 (51.2)	
Never married	403 (28.4)	275 (27.7)	128 (30.2)	
Previously married	268 (18.9)	189 (19.0)	79 (18.6)	

LNR, lymph nodes removal; SCC, Squamous cell carcinoma.

Table 2 Univariate and multivariate Cox regression analyses for OS in patients with PC

Characteristic	Univariate Cox			Multivariate Cox		
	HR	P	95% CI	HR	P	95% CI
Age (year)		0.000			0.000	
<40	REF			REF		
40–59	1.96	0.066	0.957–4.017	1.774	0.181	0.767–4.106
60–79	2.292	0.021	1.132–4.639	2.159	0.068	0.945–4.936
≥80	5.802	0.000	2.849–11.818	7.08	0.000	3.07–16.331
Race		0.003			0.000	
White	REF			REF		
Black	1.333	0.039	1.014–1.751	1.999	0.000	1.467–2.725
Others	1.056	0.768	0.733–1.522	0.949	0.826	0.593–1.518
T stage		0.000			0.000	
T1	REF			REF		
Ta	0.29	0.217	0.04–2.07	0.603	0.625	0.079–4.586
T2	1.957	0.000	1.511–2.535	1.45	0.009	1.098–1.915
T3	2.716	0.000	2.08–3.548	2.059	0.000	1.535–2.762
T4	4.895	0.000	2.958–8.099	3.697	0.000	2.099–6.514
N stage		0.000			0.000	
N0	REF			REF		
N1	2.167	0.000	1.571–2.988	1.741	0.011	1.134–2.674
N2	2.72	0.000	2.027–3.649	1.93	0.002	1.272–2.926
N3	3.607	0.000	2.79–4.665	2.267	0.000	1.528–3.364
M stage		0.000			0.000	
M0	REF			REF		
M1	5.807	0.000	4.24–7.953	3.552	0.000	2.359–5.348

Table 2 (*Continued*)

Table 2 (*Continued*)

Characteristic	Univariate Cox			Multivariate Cox		
	HR	P	95% CI	HR	P	95% CI
Histology		0.000			0.012	
SCC	REF			REF		
Others	0.347	0.000	0.22–0.549	0.507	0.012	0.299–0.859
Surgery		0.000			0.017	
No/unknown	REF			REF		
Yes	0.454	0.000	0.342–0.603	0.638	0.017	0.441–0.922
LNR		0.350				
No/Biopsy only	REF					
Yes	1.043	0.707	0.837–1.299			
Radiation		0.001			0.449	
No/unknown	REF			REF		
Yes	1.689	0.000	1.287–2.217	0.868	0.446	0.604–1.248
Chemotherapy		0.000			0.873	
No/unknown	REF			REF		
Yes	1.911	0.000	1.525–2.395	0.962	0.823	0.686–1.349
Marital status		0.002			0.078	
Married	REF			REF		
Previously married	1.492	0.000	1.194–1.864	1.253	0.104	0.955–1.644
Never married	1.288	0.022	1.037–1.599	1.309	0.042	1.01–1.698

OS, overall survival; HR, Hazard ratio, CI, confidence interval; SCC, squamous cell carcinoma; LNR, lymph node removal; REF, reference.

Table 3 Univariate and multivariate Cox regression analyses for CSS in patients with PC

	Univariate Cox			Multivariate Cox		
	HR	P	95% CI	HR	P	95% CI
Age(year)		0.131				
<40	REF					
40–59	1.413	0.421	0.609–3.28			
60–79	1.223	0.633	0.535–2.799			
≥80	1.901	0.145	0.802–4.507			
Race		0.019			0.009	
White	REF			REF		
Black	1.695	0.01	1.132–2.538	1.806	0.005	1.192–2.738
Others	0.68	0.319	0.319–1.452	0.617	0.219	0.285–1.334

Table 3 (*Continued*)

Table 3 (*Continued*)

	Univariate Cox			Multivariate Cox		
	HR	P	95% CI	HR	P	95% CI
T stage		0.000			0.000	
T1	REF			REF		
Ta	0	0.993	0–Inf	0	0.993	0–Inf
T2	2.867	0.000	1.982–4.147	1.942	0.001	1.306–2.888
T3	4.456	0.000	3.079–6.448	2.599	0.000	1.707–3.957
T4	11.706	0.000	6.711–20.417	4.732	0.000	2.475–9.047
N stage		0.000			0.000	
N0	REF			REF		
N1	4.189	0.000	2.571–6.824	3.678	0.000	2.112–6.406
N2	7.085	0.000	4.748–10.573	4.371	0.000	2.61–7.32
N3	8.15	0.000	5.688–11.678	4.604	0.000	2.724–7.784
M stage		0.000			0.000	
M0	REF			REF		
M1	10.013	0.000	6.613–15.163	3.091	0.000	1.927–4.957
Histology		0.001			0.012	
SCC	REF			REF		
Others	0.212	0.001	0.087–0.515	0.308	0.012	0.124–0.768
Surgery		0.000			0.028	
No/unknown	REF			REF		
Yes	0.32	0.000	0.214–0.479	0.603	0.029	0.384–0.949
LNR		0.002			0.031	
No/Biopsy only	REF			REF		
Yes	1.635	0.002	1.191–2.244	0.653	0.030	0.444–0.959
Radiation		0.000			0.619	
No/unknown	REF			REF		
Yes	2.51	0.000	1.697–3.712	0.892	0.608	0.576–1.381
Chemotherapy		0.000			0.765	
No/unknown	REF			REF		
Yes	3.51	0.000	2.573–4.787	0.936	0.75	0.625–1.403
Marital status		0.033			0.158	
Married	REF			REF		
Previously married	1.573	0.014	1.096–2.256	1.442	0.055	0.992–2.095
Never married	1.348	0.086	0.959–1.895	1.18	0.358	0.829–1.679

CSS, cancer-specific survival; HR, hazard ratio, CI, confidence interval; SCC, squamous cell carcinoma; LNR, lymph node removal; REF, reference.

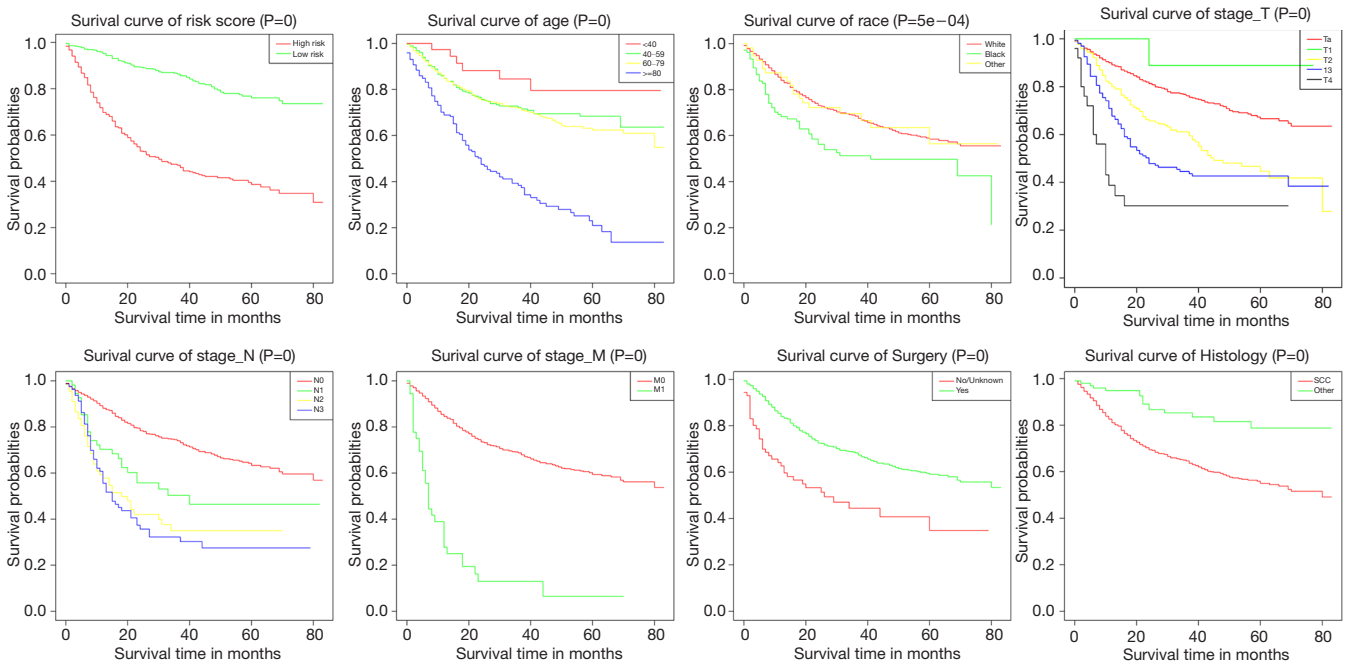

Figure 2 Kaplan-Meier curves of OS for risk stratification.

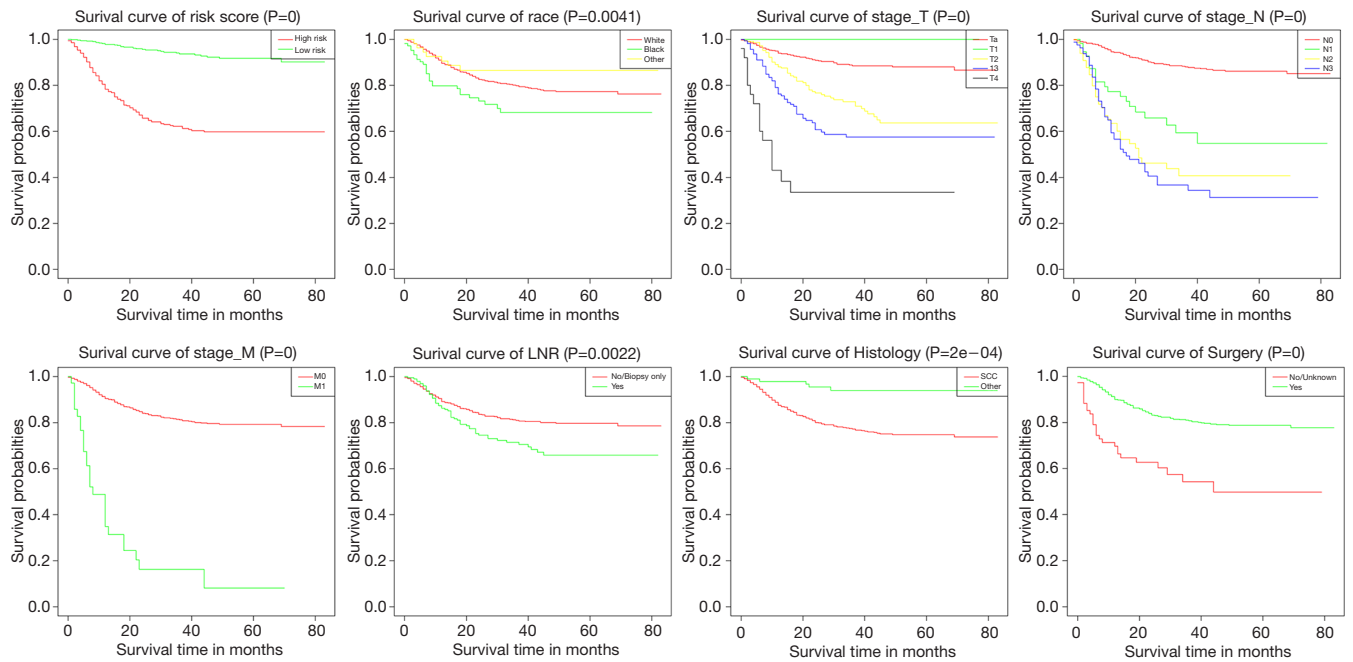

Figure 3 Kaplan-Meier curves of CSS for risk stratification.

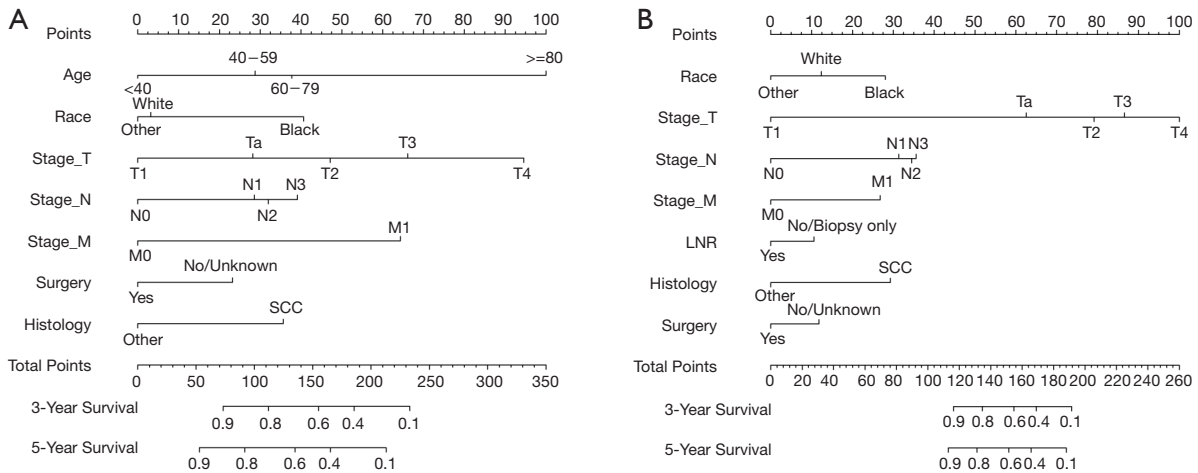

Figure 4 Prognostic nomograms of 3- and 5-year OS (A) and CSS (B).

Nomograms construction and validation

The nomograms were established for predicting OS and CSS, the OS (*Figure 4A*) nomogram revealed that age had the most important contributions to prognosis, followed by the T stage, M stage, race, N stage, histology codes, and surgery. As for CSS (*Figure 4B*), the nomogram demonstrated that the T stage contributed most to prognosis, followed by N stage, histology codes, race, M stage, surgery, and LNR.

C-index, calibration curve, ROC curve, and AUC were used to validate the accuracy of nomograms internally (training cohort) and externally (validation cohort). The C-indices for OS and CSS were 0.755 and 0.805 in the training cohort and 0.711 and 0.737 in the validation cohort. In addition, the 3- and 5-year AUCs for OS were 0.792 and 0.771 in the training cohort (*Figure 5A*), and 0.687 and 0.695 in the validation group (*Figure 5B*). When it came to CSS, it was 0.83 and 0.826 in the training cohort (*Figure 5C*) and 0.758 and 0.746 in the validation cohort (*Figure 5D*). Additionally, there were superb consistency between the calibration curves and the 45-degree reference lines in the calibration plots of 3 and 5-year OS (*Figure 6*) and CSS (*Figure 7*), which suggested that calibration curves for nomograms predicted 3 and 5-year OS and CSS performed pretty well with the ideal model.

Discussion

Nomograms are widely used to predict cancer survival because of their intuitive presentation of data, accuracy, and personalization (21). Combining different prognostic factors, we successfully developed and preliminarily validated nomograms to forecast 3- and 5-year OS and CSS of PC patients. The nomograms revealed favorable discrimination and good calibration both in internal and external validations. As a result, the nomogram of OS incorporated seven factors, including age at diagnosis, race, TNM stage, and histology codes, while the nomogram of CSS including seven factors, race, TNM stage, LNR, histology codes, and surgical treatment.

Previous studies have identified several risk factors to be independent prognostic factors for patients with PC (11-13,34-37). However, these studies focused on limited key factors but ignored some other significant risk factors and the sample of these was limited. In order to better predict prognosis for PC patients, we constructed a more synthetical model based on a large number of samples of 1,418 cases.

On the basis of the KM methods and log-rank analyses, survival rates were self-evidently affected by age and race. Of the eligible patients, it had been shown that getting older had a direct impact on OS. Previous research has suggested that marital status had protection on the OS and CSS of PC (15,29,34). However, our research found that marital status was not a significant predictor, probably because this research included only those patients who had poor physical conditions and a higher degree of cancer risk (15). Some studies also have examined the relationship between different races. Rippentrop *et al.* (38) found that notable differences could be detected in survival between African Americans and whites. Sharma *et al.* (36) described that

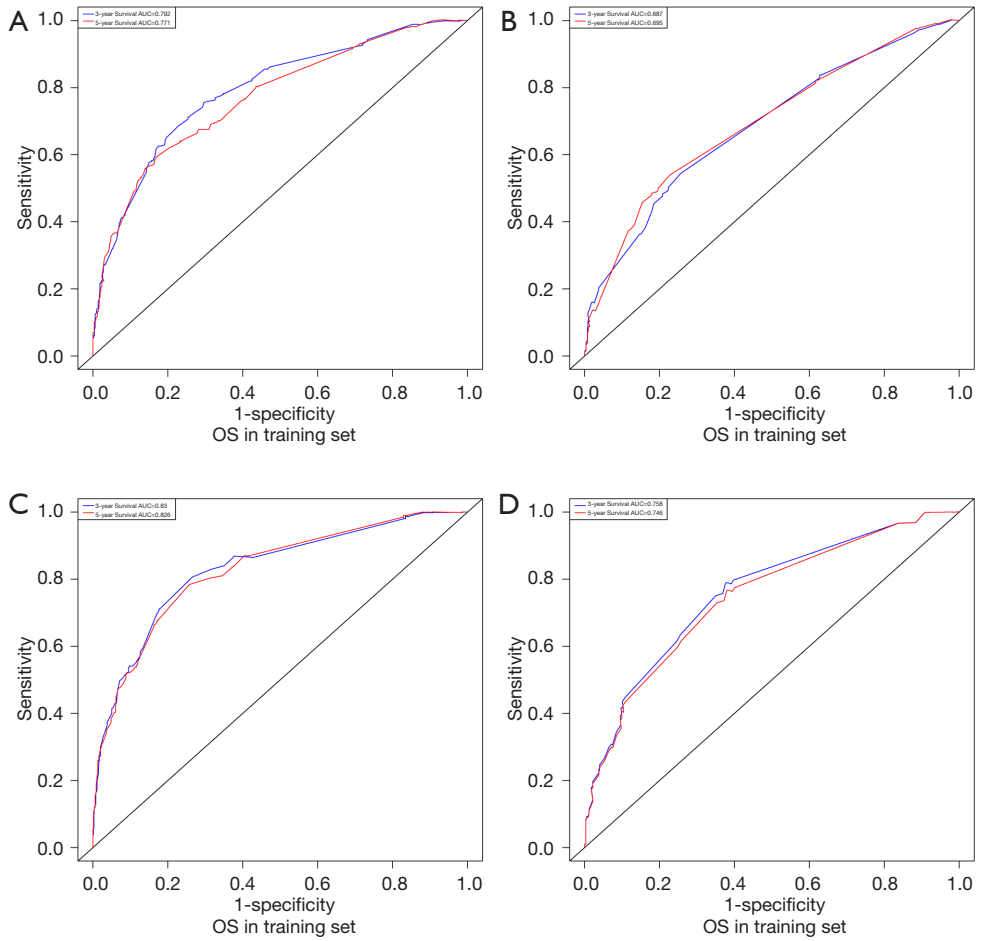

Figure 5 3- and 5-year ROC curves of OS and CSS in training (A, C) and validation (B, D) groups for validating nomogram model.

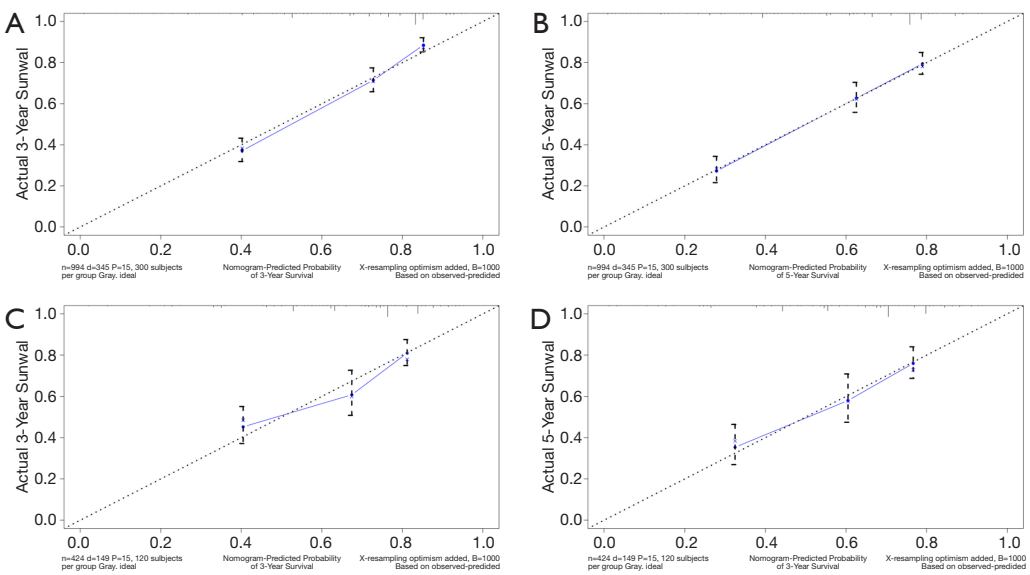

Figure 6 3- and 5-year calibration curves of OS in training (A,C) and validation (B,D) groups for validating nomogram model.

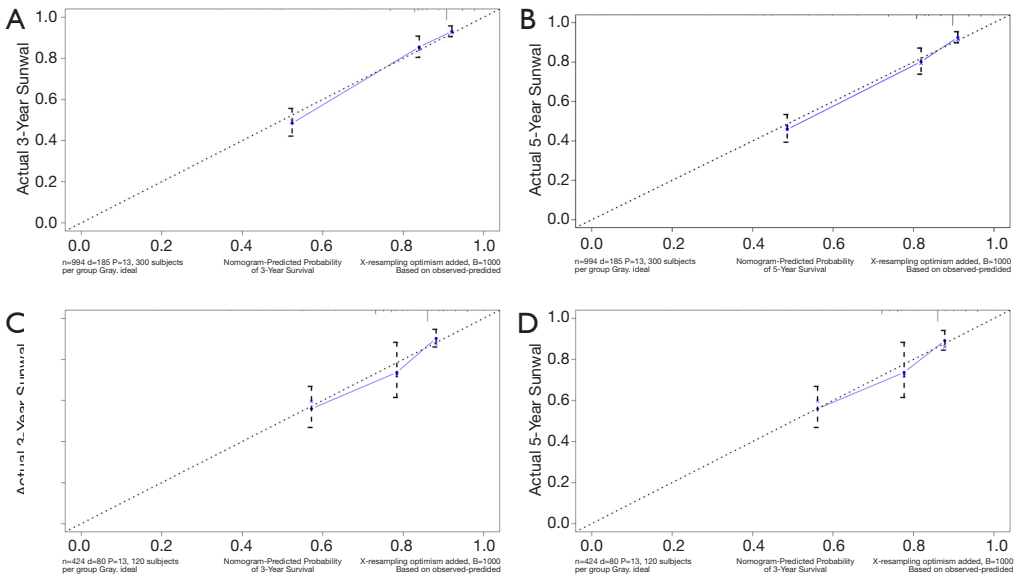

Figure 7 3- and 5-year calibration curves of CSS in training (A,C) and validation (B,D) groups for validating nomogram model.

being black was related to worse OS. Our study confirmed that the black race was associated with lower OS and CSS than white, which coincided with the former report.

As we all know, tumor characteristics play an important role in the prognosis of cancer patients. We established the first practical nomograms illustrated that SCC had a negative impact on patient survival than other pathological types, perhaps because patients with other pathological types of tumor which chosen more aggressive treatment, this finding needs further study to confirm. Our results shown that more advanced T, N and M stages meant potential predictors of PC patients. Based on the established nomograms, we could know that the T and N stages were great significant prognostic factors. The N stage was noticeably associated with OS and CSS according to our analysis, previous research found that lymph node dissection was one of the most important prognostic factors in men with PC (39-41), also, early lymph node dissection is recommend by many guidelines (35,42).

Previous studies have shown that LNR was positively associated with CSS (36,37), which was also confirmed by our study. However, OS of patients were not reelevate to the LNR in our study. This might be related to the incorrect clinical examination of the nodal staging (43,44), or the lymphadenectomy complication rate was relatively high. Hakenberg *et al.* (35) confirmed that surgical resection represented a prognostic factor for survival, which was consistent with our results. Furthermore, chemotherapy and radiotherapy were not independently correlated with OS or CSS in our study. Previous studies also suggested that chemotherapy was frustratingly ineffective in PC (9). In addition, the 2014 European Association of Urology (EAU) guidelines did not advocated radiation because the results of patients who received radiotherapy were discouraging (35). A lack of detailed information about chemotherapy and radiotherapy in the database might also lead to an inability to accurately identify prognostic factors. Interestingly, recent study established a competing-risks analysis model for PC patients (45), however, our research seems to be more suitable for the practical needs of clinical work, because our nomograms could visually and make individualized predictions.

Although these two nomograms performed well, we acknowledged that our study had some shortcomings. First of all, it was important to note that only a third of the patients were enrolled in our study, we excluded other patients because of the lack of necessary clinical data. Second, the nomograms lacked of some key indicators which were missing in the SEER database, such as biological markers, genetic mutation, site of involvement, and specific types of surgery. Furthermore, since all patients included in our study were from the same SEER dataset, our nomograms cannot be verified from another database.

Conclusions

It was the first time to conduct survival models for PC patients with predictive performance. It might be valuable of clinical application and further exploration with more studies in the future.

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Footnote

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