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Prognostic Factors and a Nomogram Predicting Overall Survival in Muscle-invasive Bladder Cancer

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Abstract: Muscle-invasive bladder cancer (MIBC) is a common type of bladder cancer characterized by a poor prognosis. The aim of this study was to establish a nomogram predicting the overall survival (OS) for patients with MIBC. All the 14,393 cased with MIBC were collected from the Surveillance, Epidemiology, and End Results (SEER) database. The patients were randomly divided into training group and testing group with a 1:1 ratio. Then, we used The Kaplan-Meier to estimate the over survival OS of these patients. The Univariate and multivariate Cox analysis were performed to identify the independent risk factors related with OS, which were then used to construct a nomogram model in training group. And then the nomogram evaluated by the time-concordance index (C-index) and calibration curves in testing group. The result of Univariate and multivariate Cox analysis revealed that sex, race, N stage, M stage, surgery, radiotherapy, and chemotherapy were independent prognostic factors associated with OS. A nomogram was established using these factors with good discrimination and calibration.

Keywords: Bladder Cancer, Nonagram, Prognosis, Risk Factor

Introduction

Bladder cancer is the commonly diagnosed cancer worldwide, with approximately 573,000 new cases and 213,000 deaths in 2019 [1]. Muscle invasive bladder cancer (MIBC) is one of the most life-threatening cancers in elderly individuals [2]. Statistics showed that has high progression and recurrence rates [3]. Although radical cystectomy (RC) combined with pelvic lymph node dissection is widely used, the prognosis of MIBC is still poor [4]. MIBC can be treated with systemic chemotherapy and immunotherapy, but the overall 5-year survival rate of these patients remains less than 5% [5]. Many scholars have proposed some models for predicting prognosis of bladder cancer. The models were based on bioinformatics information data. These models [6] have not been verified by clinical trials, and need the support of biological sequencing technology. In general, these models have an effect in managing patients' prognosis. In addition, these prediction models were targeted at bladder cancer, and the MIBC prognosis model remains blank. Therefore, urologists urgently need to establish an accurate prognostic model to evaluate the prognosis of MIBC patients, so as to accurately know their long-term survival. In our work, a prognostic nomogram was developed to predict OS for patients with MIBC.

Method

Study Population

We conducted a retrospective cohort study based on SEER database that is a population-based cancer database in the United States (http://seer.cancer.gov). The data set of patients in this study were accessed by SEER*Stat version 8.3.9.2. Patients diagnosed with BLCA (histological diagnostic code 8120/03 in the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3)) from 2010–2015. Patients with incomplete information on baseline characteristics and follow-up were excluded. The considered variables were as follows: year of diagnosis, age, sex, race, marital status, TNM stages based on the AJCC 7th edition, radiotherapy, chemotherapy, vital status, and survival months. Finally, 14,393 patients were included for further analysis.

Variable Coding and Statistical Analysis

Patient age was divided into four classes: '<60'years, '60-69'years, '70-79'years,'≥80'years. Marital status of patients was recoded as unmarried, married, and SDW that represent separated, divorce, or widowed. The classes in T stage (AJCC 7th edition) was recoded as 'T2','T3', and 'T4'.The surgical type, radiotherapy and chemotherapy was recorded as 'YES' or 'NO'. The outcome of this research was the OS, which was defined as the time interval between the days from diagnosis to death of any other cause. The whole analysis set was randomly separated into training group and testing group. We calculated the number and proportion of cases in each category in two data sets. In training group, univariate and multivariate Cox regression analyses were used to find independent prognostic factors for OS in patients with MIBC. We also used the Kaplan-Meier method to estimate the OS by categorical variables via survival R package in the training cohort. Subsequently, the selected independent factors were incorporated to the nomogram for predict the 1-, 3-, and 5-year OS probability using the rms R package. For validation, the discrimination and calibration of the nomogram was estimated by the concordance index (C-index) and calibration curve in both training group and testing group. C-index >0.6 was considered significant classification. In the calibration curve, point and error

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bar distributed closer to the diagonal line implied the nomogram was considered more accuracy. All tests were two-sided, and P < 0.05 was considered statistically significant.

Results

A total of 14,393 patients from the SEER database were identified and included in this study and then spilt into training group (n=7196), and testing group (n=7197).The characteristics of MIBC patients were listed in table 1. As can be seen from the table, male patients account for the majority, accounting for 10270 (71.4%), much higher than 4123 (26.8%) of female. In addition, 2986 (20.7%) and 1635 (11.4%) patients had lymph node metastasis and distant metastasis. The proportion of chemotherapy is higher than that of radiotherapy, 6628 (46.1%) and 2486 (17.3%) respectively.

Table 1| The clinicpathologic characteristics of patients

Variable	level	Overall	testing	training
n		14393	7197	7196
Age (%)	<60	1968(13.7)	979(13.6)	989(13.7)
	60-69	4504(31.3)	2245(31.2)	2259(31.4)
	70-79	3458(24.0)	1736(24.1)	1722(23.9)
	≥80	4462(31.0)	2236(31.1)	2226(30.9)
Sex (%)	Female	4123(28.6)	2040(28.3)	2083(28.9)
	Male	10270(71.4)	5157(71.7)	5113(71.1)
Race (%)	Black	1026 (7.1)	493 (6.9)	533 (7.4)
	White	759 (5.3)	372 (5.2)	387 (5.4)
	Other	12608 (87.6)	6332(88.0)	6276(87.2)
T (%)	T2	8242 (57.3)	4122(57.3)	4120(57.3)
	T3	3876 (26.9)	1949(27.1)	1927(26.8)
	T4	2275 (15.8)	1126(15.6)	1149(16.0)
N (%)	N0	11407 (79.3)	5685(79.0)	5722 (79.5)
	N1	1289 (9.0)	667 (9.3)	622 (8.6)
	N2	1407 (9.8)	695 (9.7)	712 (9.9)
	N3	290 (2.0)	150 (2.1)	140 (1.9)
M (%)	M0	12758(88.6)	6368(88.5)	6390(88.8)
	M1	1635(11.4)	829(11.5)	806(11.2)
Surgery (%)	NO	812(5.6)	431(6.0)	381(5.3)
	YES	13581(94.4)	6766(94.0)	6815(94.7)
Chemotherapy (%)	NO	7765(53.9)	3862(53.7)	3903(54.2)
	YES	6628(46.1)	3335(46.3)	3293(45.8)
Radiation (%)	NO	11907(82.7)	5969(82.9)	5938(82.5)
	YES	2486(17.3)	1228(17.1)	1258(17.5)
Marital (%)	Unmarried	8455(58.7)	4229(58.8)	4226(58.7)
	Married	4175(29.0)	2103(29.2)	2072(28.8)
	SDW	1763(12.2)	865(12.0)	898(12.5)

Independent Prognostic Factors

The univariate and multivariate COX regression were performed to analyze all variables in predicting OS using the training set to identify the independent prognostic factors in patients with MIBC (table2). The results revealed that sex, race, N stage, M stage, surgery, radiotherapy, and chemotherapy were independent prognostic factors associated with OS. For instance, higher N stage (HRs >1, P <0.001), married or SDW status (HRs >1, P <0.001), were associated with poor survival rates. Compared with female patients, although male patients show a high prevalence, they were reported better survival (HR=0.87, P <0.001). Interestingly, T stage did not show a significant difference in the prognosis of MIBC (HR=1.01, p= 0.659). The result of Kaplan–Meier analyze (Figure 1A) with log-rank tests were alike to above Cox regression. The survival rate of patients with MIBC who chosed surgical treatment improved significantly compared with those who did not undergo surgery.

Table| Univariate and multivariate Cox regression models associated with overall survival

Variable	Multivariate analysis			Univariate analysis		
	HR	p	95%CI	HR	95%CI	P
Age						
60-69	2.37	<0.001	2.16-2.6	2.3	2.08 - 2.54	<0.001
70-79	1.1	0.062	0.99 - 1.22	1.16	1.05 - 1.29	0.004
≥80	1.42	<0.001	1.29 - 1.57	1.5	1.36 - 1.65	<0.001
Sex						
Male	0.87	<0.001	0.82 - 0.92	1	0.94 - 1.07	0.96
Race						
White	0.8	0.005	0.69 - 0.93	0.79	0.67 - 0.92	0.003
Other	0.86	0.003	0.77 - 0.95	0.88	0.79 - 0.98	0.016
T stage						
T3	1.01	0.659	0.95 - 1.08	0.98	0.92 - 1.05	0.541
T4	1.73	<0.001	1.61 - 1.86	1.44	1.33 - 1.55	<0.001
N stage						

N1	1.36	<0.001	1.24 - 1.5	1.39	1.26 - 1.53	<0.001
N2	1.7	<0.001	1.57 - 1.86	1.52	1.38 - 1.67	<0.001
N3	2.01	<0.001	1.68 - 2.4	1.7	1.41 - 2.05	<0.001
M stage						
M1	3.32	<0.001	3.07 - 3.59	2.96	2.71 - 3.23	<0.001
Surgery YES	0.4	<0.001	0.36 - 0.45	0.71	0.63 - 0.8	<0.001
Chemotherapy YES	0.68	<0.001	0.65 - 0.72	0.64	0.61 - 0.68	<0.001
Radiation YES	1.23	<0.001	1.15 - 1.32	1.16	1.08 - 1.24	<0.001
Marital						
Married	1.49	<0.001	1.4 - 1.58	1.27	1.2 - 1.36	<0.001
SDW	1.28	<0.001	1.18 - 1.39	1.34	1.23 - 1.46	<0.001

Nomogram Development and Validation

With the above-mentioned independent prognostic factors, we developed a nomogram (Figure2) in the training set to predict the 1-, 3-, and 5-year OS for MIBC. Values for each variable incorporating to nomogram points, and we can add them up to calculate total points. Then, the value of total points corresponds vertically to survival chances at 1-, 3-, and 5-year time points. Time-Concordance index (C-index) plot revealed accuracy discrimination in nomogram using both training group (0.65-0.86) and testing group (0.64-0.81), in (Figure1B). Moreover, calibration plot exhibited favorable prediction accuracy of the nomogram at multiple time points in both group (Figure 1C-D).

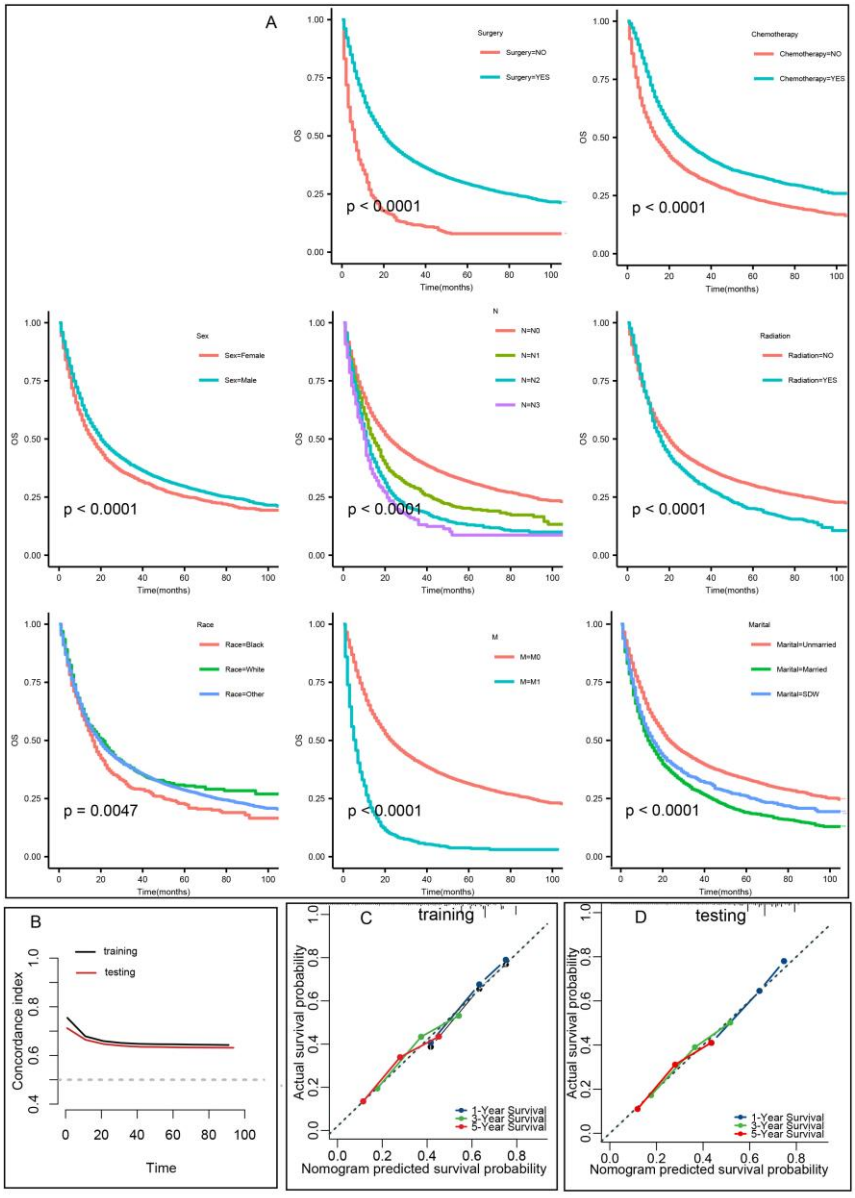

Figure1| Kaplan-Meier survival curves of overall survival and validation of nonogram

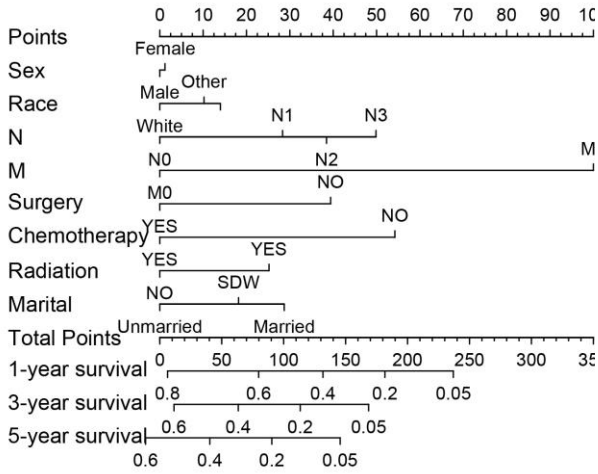

Figure2| The nomogram to predict overall survival

Discussion

Our study indicated that race, sex, marital status, N stage, M stage with AJCC 7th edition, additional chemotherapy, and radiotherapy were independent prognostic factors for OS in MIBC. Using these factors, we developed a nomogram with prediction accuracy in both the training and test group.

The MIBC has an aggressive biological behavior compared to other type bladder cancer [7], reflecting the prognostic heterogeneity [8] [9]. Accurate prognosis is essential to tell patients of their long-term risks and guide follow-up management. In this study, a nomogram was established using SEER database, which can predict the individual OS of MIBC patients according to clinicopathological parameters and treatment methods. In comparison to unmarried patients and SDW, married patients have worse survival. The aggressive factor of married marital status have been reported. Thus, the established nomograms help clinicians better evaluate the prognosis of patients with MIBC. Because of aggressive biological behavior, the treatment of MIBC is relatively difficult. At present, surgery is still the main measure for most urologists, especially for patients without lymph node metastasis. From previous studies[10, 11] have shown that people without surgery have worse survival than those who underwent surgery, which is consistent with our results, In addition, many studies have shown that patients with CDC can also benefit from chemotherapy[5, 12, 13]. In our study, chemotherapy was an independent protective factor associated with OS. Interestingly, according to multivariable Cox regression, radiation appears to have an adverse effect on overall survival. Likewise, the previous study also did not suggested the independent prognostic value of radiation therapy [4]. Several prognostic models have been established to predict the prognosis of patients with bladder cancer [14]. However, these [15] models were not focused on the muscle invasive bladder cancer that generally has poor prognosis. Therefore, our study establish a predictive nomogram of the MIBC, involving not only clinicopathological features, but also treatment methods. The nomogram shown good prediction accuracy in both training and testing group. We hope that the established nomogram can provide a comprehensive prognostic assessment of this aggressive cancer.

This study remained many limitations. Firstly, the dataset is collected from the secondary analysis of the public database. Firstly, preoperative laboratory results, centralized pathology review, blood parameters, and comorbidity were not accessible in the SEER database, which may also be associated with patients' prognosis. Secondly, the selection bias was Unavoidable during this study.

Conclusions

In conclusion, this study investigated the patient cohort using SEER database and analyzed the prognostic factors related to prognosis. Finally, we are the first to propose the nomogram of patient survival prediction, which can predict the OS and of patients individually. This finding can help clinicians better manage the prognosis.

Data Availability

All the data in the current study are publicly available in the Surveillance, Epidemiology, and End Results database (https://seer.cancer.gov/).

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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