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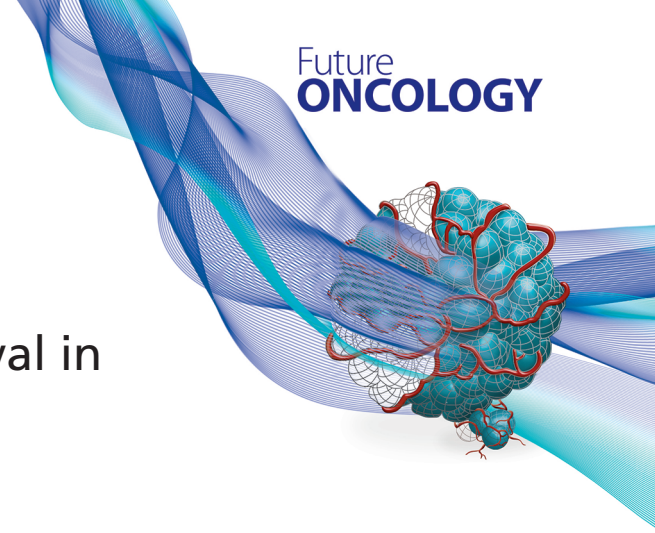

Nomogram to predict overall survival in patients with primary bladder neuroendocrine carcinoma: a population-based study

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Aim: To develop a prognostic model to predict the overall survival of primary bladder neuroendocrine carcinoma (BNEC) patients. **Methods:** Using univariate and multivariate Cox regression analyses, a nomogram was constructed. Calibration curves, receiver operating characteristic curves and C-index were utilized to evaluate the performance. **Results:** The study enrolled 906 BNEC patients. The following variables were incorporated in the nomogram: age, marital status, Tumor node metastasis (TNM) stage, chemotherapy and surgery. The nomogram had a C-index of 0.702 in the training cohort and 0.724 in the validation cohort. **Conclusion:** Compared with the TNM staging system, the proposed nomogram exhibits superior prognostic discrimination and survival prediction.

Plain language summary: Neuroendocrine bladder cancer accounts for <1% of all bladder cancers and has a poor prognosis. Due to its rarity, the best treatment still requires further exploration. A total of 906 patients with neuroendocrine bladder cancer were recruited from the SEER database. The three- and five-year survival rates were <40%. Combination therapy results in longer survival compared with a single therapy. Patients are advised to receive comprehensive treatment if their physical condition is tolerable. An accurate, easy-to-understand nomogram to predict overall survival in patients with neuroendocrine bladder cancer was developed. The nomogram will enable clinicians to assess a patient's risk and apply personalized treatment.

Tweetable abstract: An accurate and easily accessible prognostic model has been developed for a rare form of bladder cancer, bladder neuroendocrine carcinoma. This model can be used clinically to assess patient risk and to inform the adoption of individualized treatment.

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Keywords: bladder neuroendocrine carcinoma • nomogram • overall survival • prognosis • SEER

In the United States, bladder cancer is the second most common genitourinary cancer and the fourth most common cancer overall, with an estimated 81,400 new cases and around 17,980 new deaths in 2020 [1,2]. This includes urothelial carcinomas (UCs), squamous cell carcinomas, adenocarcinomas, neuroendocrine carcinomas and other less common neoplasms. Of these, bladder neuroendocrine carcinoma (BNEC), accounts for <1% of all bladder malignancies [3,4]. Reports are scarce and have mostly been based on retrospective studies. Therefore, researchers naturally have paid less attention to BNEC. Yet, it is more aggressive than UCs, resulting in worse survival rates [5,6]. Hence, it is necessary to better understand BNEC, especially in terms of prognosis. According to the 2016 WHO classification of tumors of the bladder, BNECs include small-cell neuroendocrine carcinoma (SCNEC), large-cell neuroendocrine carcinoma (LCNEC), paraganglioma (PGL) and well-differentiated neuroendocrine [3].

As BNEC only occurs in a very small percentage of patients, there is no accurate prognostic model for this disease. The tumor node metastasis (TNM) staging system was established by the American Joint Committee on Cancer (AJCC) and it is the most common method for predicting patient prognosis. Nevertheless, factors such as demographics and treatment are not considered in TNM staging and may also have a significant impact on prognosis, although some of these have not yet been thoroughly examined [7]. Radical surgery and radiotherapy had been reported to be associated with improved overall survival (OS) by Schreiber *et al.* [8]. In the National Cancer Data Base, Patel *et al.* [9] found a trend toward longer survival for patients undergoing radical surgery. However, one study included 856 patients from the National Cancer Data Base with cT1-T4aN0M0 SCNEC. There was no difference in OS between chemoradiotherapy and cystectomy plus chemotherapy [10]. Dong *et al.* [11] proposed nomograms to predict individual prognosis in patients with primary small-cell carcinoma of the bladder, but they do not apply to other types of neuroendocrine bladder cancer. All in all, it is crucial for clinicians that a convenient, comprehensive and accurate prognostic model be developed. A nomogram is a combination of important predictors used to predict a particular end point and is regarded as a practical tool in prognosis evaluations for cancer [12–15]. A predictive nomogram for patients with BNEC, however, has not yet been developed. Therefore, in the present study, a nomogram to predict survival in patients with BNEC was developed and validated. Furthermore, this study will facilitate the development of customized treatment options and medical decisions in patients with BNEC.

Materials & methods

Patients

The data used in this study were obtained from SEER Stat 8.4.0. As all SEER database information has been deidentified, institutional review board approval or informed consent was not required for this study. Among the inclusion criteria were the following: diagnosed between 2004 and 2015; primary site codes C67.0–C67.9; diagnosed based on positive histology; histological type limited to BNEC (ICD-O-3 codes: 8013/3: LCNEC; 8041/3: small-cell carcinoma; 8240/3: carcinoid tumor (well-differentiated neuroendocrine tumor); 8045/3: combined small-cell carcinoma; 8246/3: neuroendocrine carcinoma; 8680/3: PGL and 8700/3: pheochromocytoma; relatively adequate information on variables including demographics and clinicopathological characteristics like tumor size, TNM stage, treatment and so on. Exclusion criteria consisted of the following: not the first primary tumor (n = 647); complete dates for survival months unavailable (n = 68); T stage/N stage/M stage unknown (n = 134). A total of 906 eligible patients were enrolled in the cohort after selection.

Variables

Variables in the selected cohort were included demographic characteristics (sex, marital status, age at diagnosis, race), tumor characteristics (histology, American Joint Committee on Cancer Sixth Edition TNM stage, tumor size, grade) and therapy details (surgery, chemotherapy and radiotherapy). OS was the primary end point of this study, referred to as the interval from BNEC diagnosis to the last follow-up or death without restrictions on how the death occurred. In the analysis, some variables were regrouped. According to their age at diagnosis, patients were grouped into ≤64, 65–74 and ≥75. Races such as American Indian/Alaskan Native, Asian/Pacific Islander and Black were classified as 'Asian.al'. Those patients in the SEER database whose marital status was divorced, single, unmarried or widowed were regrouped into the unmarried' group. In light of the small sample size, grades I (well differentiated) and II (moderately differentiated) were grouped together with grade III (poorly differentiated). Histology types were classified into SCNEC, LCNEC and neuroendocrine carcinoma (NEC). T stages were divided into T1–T4; likewise, N stages were divided into N0, N1 and N2. According to the median tumor size, the cut-off point was set at 5 cm. Treatment details for the primary tumor included no treatment, local tumor ablation/transurethral resection of the bladder (TURB) and partial/radical cystectomy (P/R).

Statistical analyses

Statistical analysis was performed in three steps. In the first step, based on a ratio of 7:3, the study population was randomly divided into training and validation cohorts. $\chi 2$ tests and Mann–Whitney's U tests were applied, as appropriate, to compare baseline information between the groups. For categorical variables, whole numbers and proportions are reported, and for continuous variables, median values with interquartile ranges are reported unless otherwise noted. Second, in the training group, univariate Cox regression analysis was used to identify potential prognostic factors. When the p-value was <0.05, it was included in the multiple Cox proportional hazards regression model. Results are presented as hazard ratios (HR) and 95% CIs. Then, a nomogram was constructed by

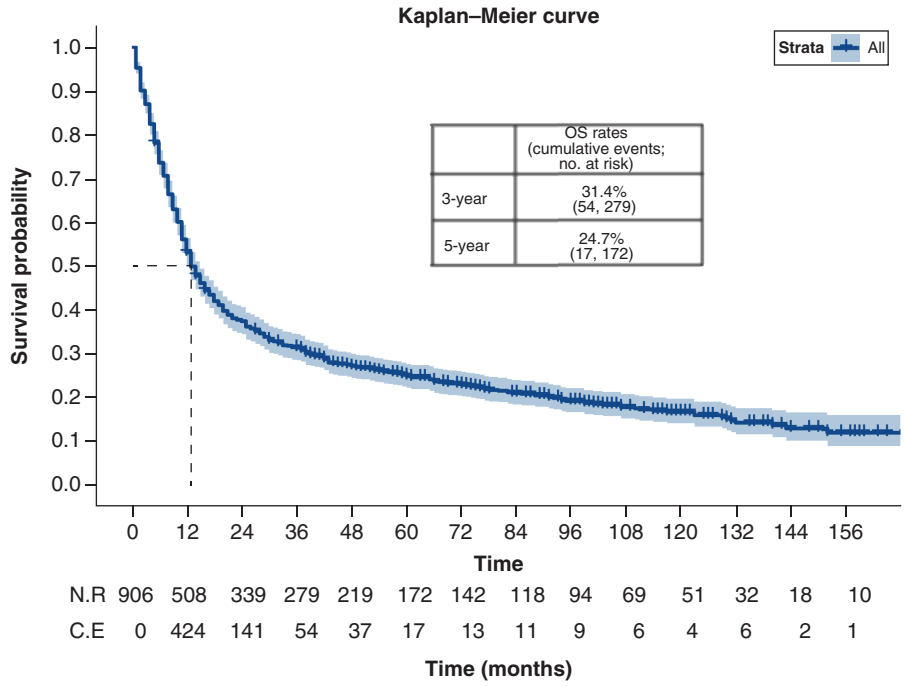

Figure 1. Kaplan–Meier curve showing overall survival rates in the overall patient population (n = 906).
C.E.: Cumulative event; N.R.: Number at risk; OS: Overall survival.

incorporating the meaningful variables ($p < 0.05$). The nomogram predicts 3- and 5-year survival probabilities in the training cohort. In the third step, Harrell's concordance indices (C-index) and the receiver operating characteristic (ROC) were calculated to estimate the discriminative accuracy of the model, which was used as the base for the nomogram. Calibration plots were then used to evaluate the consistency of predicted and actual outcomes of 3- and 5-year survival times. If the model is well-calibrated, the predictions should fall on the 45-degree diagonal. Statistical analyses were performed with SPSS 26 and R version 4.1.3. The significance level for all tests was set at 0.05 on a two-sided basis.

Results

Clinicopathological features

In Table 1, the demographics and clinical characteristics of the total cohort (n = 906), training cohort (n = 635) and validation cohort (n = 271) are presented. In the total cohort, the patients were mainly male (75.1%) and most were white (89.5%). A minority of patients had metastases (21.2%). With regard to treatment, most patients did not have P/R (68.9%) or radiotherapy (72.2%). Most patients had chemotherapy (64.1%). No statistical difference was observed between the two groups of variables except for survival time. The 3- and 5-year OS rates were 31.4% and 24.7% in the total cohort, respectively (Figure 1). In the total cohort, training cohort and validation cohort, the mean survival times were 32.4, 29.9 and 38.1 months, respectively (Table 1).

Nomogram construction

The findings from the univariate and multivariate analyses of Cox regression suggest that age, marital status, TNM stage, chemotherapy and surgery are strong prognostic factors. Moreover, no significant association was seen between sex, race, histology, grade or radiotherapy with OS (Table 2). On the basis of data from the training cohort, Figure 2 presents a prognostic nomogram based on all risk factors that may be associated with patients' OS. A score was assigned to each factor and the compounded score represented the 5- and 3-year OS rates. A higher overall score, based on all the factors in the nomogram summed up, indicates a worse prognosis.

Validation of nomogram for OS

In the training cohort, the C-index of the nomogram model to predict OS was 0.702 (95% CI: 0.680–0.724), while the C-index in the validation cohort was 0.724 (95% CI: 0.691–0.757). Both of these were higher than the

Table 1. Baseline demographic and clinicopathological characteristics.

Characteristics	Total (n = 906)	Training (n = 635)	Validation (n = 271)	p-value
Age				0.739
≤64	254 (28.0%)	175 (27.6%)	79 (29.2%)	
65–74	287 (31.7%)	206 (32.4%)	81 (29.9%)	
≥75	365 (40.3%)	254 (40.0%)	111 (41.0%)	
Sex				0.627
Male	680 (75.1%)	480 (75.6%)	200 (73.8%)	
Female	226 (24.9%)	155 (24.4%)	71 (26.2%)	
Marital				0.415
Married	518 (57.2%)	357 (56.2%)	161 (59.4%)	
Unmarried	388 (42.8%)	278 (43.8%)	110 (40.6%)	
Race				0.497
White	811 (89.5%)	572 (90.1%)	239 (88.2%)	
Black	57 (6.3%)	36 (5.7%)	21 (7.7%)	
Asian.al	38 (4.2%)	27 (4.3%)	11 (4.1%)	
Histology				0.999
LCNEC	37 (4.1%)	26 (4.1%)	11 (4.1%)	
SCNEC	686 (75.7%)	481 (75.7%)	205 (75.6%)	
NEC	183 (20.2%)	128 (20.2%)	55 (20.3%)	
Grade				0.304
≤III	286 (31.6%)	202 (31.8%)	84 (31.0%)	
IV	373 (41.2%)	269 (42.4%)	104 (38.4%)	
Unknown	247 (27.3%)	164 (25.8%)	83 (30.6%)	
T stage				0.529
T1	148 (16.3%)	108 (17.0%)	40 (14.8%)	
T2	496 (54.7%)	344 (54.2%)	152 (56.1%)	
T3	154 (17.0%)	111 (17.5%)	43 (15.9%)	
T4	108 (11.9%)	72 (11.3%)	36 (13.3%)	
N stage				0.342
N0	716 (79.0%)	496 (78.1%)	220 (81.2%)	
N1	79 (8.7%)	60 (9.4%)	19 (7.0%)	
N2	111 (12.3%)	79 (12.4%)	32 (11.8%)	
M stage				0.432
M0	714 (78.8%)	496 (78.1%)	218 (80.4%)	
M1	192 (21.2%)	139 (21.9%)	53 (19.6%)	
Tumor size				0.545
≤5	391 (43.2%)	276 (43.5%)	115 (42.4%)	
>5	196 (21.6%)	142 (22.4%)	54 (19.9%)	
Unknown	319 (35.2%)	217 (34.2%)	102 (37.6%)	
Surgery				0.947
TURB	592 (65.3%)	413 (65.0%)	179 (66.1%)	
P/R	282 (31.1%)	199 (31.3%)	83 (30.6%)	
No	32 (3.5%)	23 (3.6%)	9 (3.3%)	
Radiotherapy				0.818
No/unknown	654 (72.2%)	451 (71.0%)	203 (74.9%)	
Yes	252 (27.8%)	184 (29.0%)	68 (25.1%)	
Chemotherapy				0.150
No/unknown	325 (35.9%)	231 (36.4%)	94 (34.7%)	
Yes	581 (64.1%)	404 (63.6%)	177 (65.3%)	
OS				0.004
Mean (SD)	32.4 (38.9)	29.9 (36.4)	38.1 (43.9)	
Median (IQR)	13.0 (6.0,47.6)	13.0 (6.0, 39.5)	15.0 (6.0, 58.5)	

Asian.al: Asian, Pacific Islander and American Indian/Alaska; IQR: Interquartile range; LCNEC: Large-cell neuroendocrine carcinoma; NEC: Neuroendocrine carcinoma; OS: Overall survival; P/R: Partial/radical cystectomy; SCNEC: Small-cell neuroendocrine carcinoma; SD: Standard deviation; TURB: Local tumor ablation/transurethral resection of the bladder; Unmarried: Separated/divorced/widowed.

Table 2. Univariate and multivariate regression analyses for overall survival.

Characteristics	Univariate analysis HR (95% CI)	p-value	Multivariate analysis HR (95% CI)	p-value
Age				
≤64	ref.		ref.	
65–74	1.1 (0.88–1.4)	0.407	1.15 (0.91–1.45)	0.228
≥75	1.6 (1.25–1.9)	<0.001***	1.30 (1.10–1.74)	0.004**
Sex				
Male	ref.			
Female	1 (0.84–1.2)	0.826		
Marital				
Married	ref.		ref.	
Unmarried	1.5 (1.3–1.8)	<0.001***	1.29 (1.08–1.55)	0.005**
Race				
White	ref.		ref.	
Black	1.50 (1.05–2.1)	0.025*	1.15 (0.80–1.65)	0.450
Asian.al	0.76 (0.48–1.2)	0.231	0.79 (0.50–1.26)	0.326
Histology				
LCNEC	ref.			
SCNEC	1.1 (0.73–1.7)	0.586		
NEC	1.1 (0.69–1.7)	0.693		
Grade				
≤III	ref.		ref.	
IV	0.81 (0.66–0.99)	0.035*	0.96 (0.78–1.18)	0.706
Unknown	0.89 (0.71–1.11)	0.296	0.94 (0.75–1.19)	0.618
T stage				
T1	ref.		ref.	
T2	1.0 (0.79–1.3)	0.977	1.17 (0.92–1.50)	0.211
T3	1.0 (0.77–1.4)	0.825	1.45 (1.05–2.01)	0.026*
T4	1.6 (1.17–2.2)	0.004**	1.50 (1.05–2.13)	0.025*
N stage				
N0	ref.		ref.	
N1	1.5 (1.1–2.0)	0.008**	1.57 (1.16–2.13)	0.004**
N2	1.8 (1.4–2.3)	<0.001***	1.58 (1.19–2.11)	0.001**
M stage				
M0	ref.		ref.	
M1	2.8 (2.3–3.4)	<0.001***	2.48 (1.95–3.14)	<0.001***
Tumor size				
≤5	ref.		ref.	
>5	1.4 (1.1–1.8)	0.003**	1.23 (0.98–1.1.54)	0.078
Unknown	1.2 (1.0–1.5)	0.038*	1.05 (0.86–1.30)	0.618
Surgery				
TURB	ref.		ref.	
P/R	0.55 (0.45–0.67)	<0.001***	0.57 (0.45–0.71)	<0.001***
No	1.27 (0.81–2.00)	0.294	0.70 (0.43–1.15)	0.159
Radiotherapy				
No/unknown	ref.			
Yes	1.0 (0.83–1.2)	0.995		
Chemotherapy				
No/unknown	ref.		ref.	
Yes	0.58 (0.49–0.69)	<0.001***	0.49 (0.41–0.60)	<0.001***

Statistical significance: *p < 0.05; **p < 0.01; ***p < 0.001.
Asian.al: Asian, Pacific Islander and American Indian/Alaska; HR: Hazard ratio; LCNEC: Large-cell neuroendocrine carcinoma; NEC: Neuroendocrine carcinoma; P/R: Partial/radical cystectomy; SCNEC: Small-cell neuroendocrine carcinoma; TURB: Local tumor ablation/transurethral resection of the bladder; Unmarried: Separated/divorced/widowed.

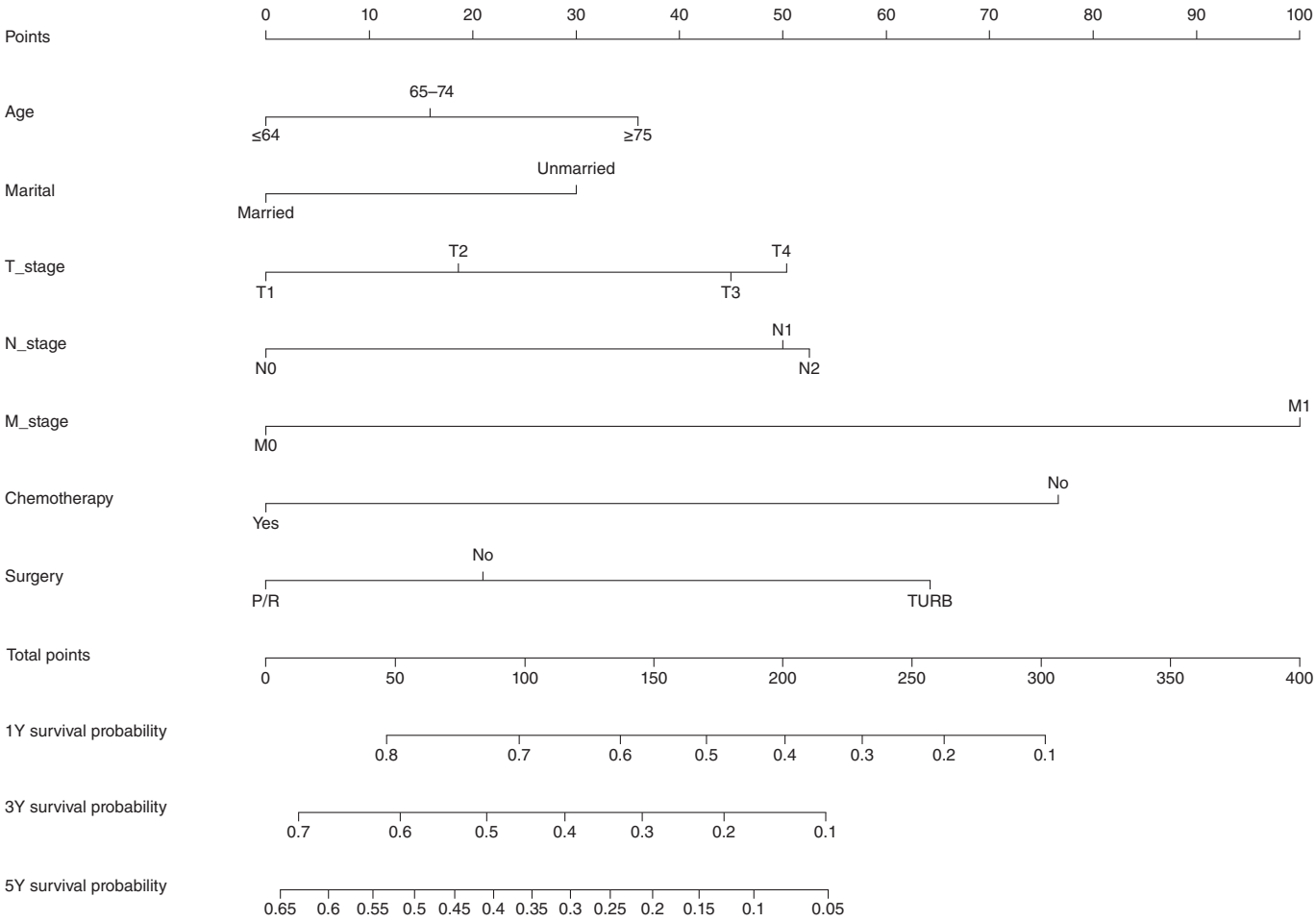

Figure 2. Nomogram for predicting 3- and 5-year overall survival. Position patient values on each axis. Draw a vertical line on the points axis to determine how many points each variable value has. Sums the points of all variables. Find the sum in the 'Total Score' row. Draw a vertical line toward 3Y survival probability and 5Y survival probability. The axes determine survival probabilities at 3 and 5 years, respectively.
P/R: Partial/radical cystectomy; TURB: Transurethral resection of the bladder.

TNM system, which was 0.610 (95% CI: 0.584–0.635) in the training cohort and 0.634 (95% CI: 0.594–0.673) in the verification cohort. The area under the curve (AUC) values for the model were 0.773 at 3 years and 0.771 at 5 years in the training cohort (Figure 3A) and 0.792 at 3 years and 0.768 at 5 years in the validation cohort (Figure 3B). Moreover, calibration plots for 3 and 5 years were generated to internally verify the model across the training and validation groups. All calibration plots fell near the 45-degree diagonal line (500 bootstrap resamples, Figure 4A–D).

Discussion

A rare and heterogeneous disease, BNEC has been difficult to manage due to a lack of gold standards [16]. Having the ability to accurately predict patients' OS would benefit clinicians in individualizing decision-making. A nomogram is a simple but visible and reliable statistical prediction tool that is widely used to provide customized individual prognostic information [17]. In this study, a nomogram was developed that computed BNEC individual OS from patient-related and tumor-related factors. These factors are useful in assessing the prognosis of patients and in making individualized decisions about their therapy and follow-up. Since the nomogram was developed using data from a large group of BNEC patients (n = 906), this study is important. In addition, we rigorously evaluated the nomogram and internally validated its performance. It also has an additional strength, namely that it uses a wide range of variables based on clinical relevance, scientific knowledge and predictors that have been described in the literature [11,18]. Through the process of developing the nomogram, we identified the following independent

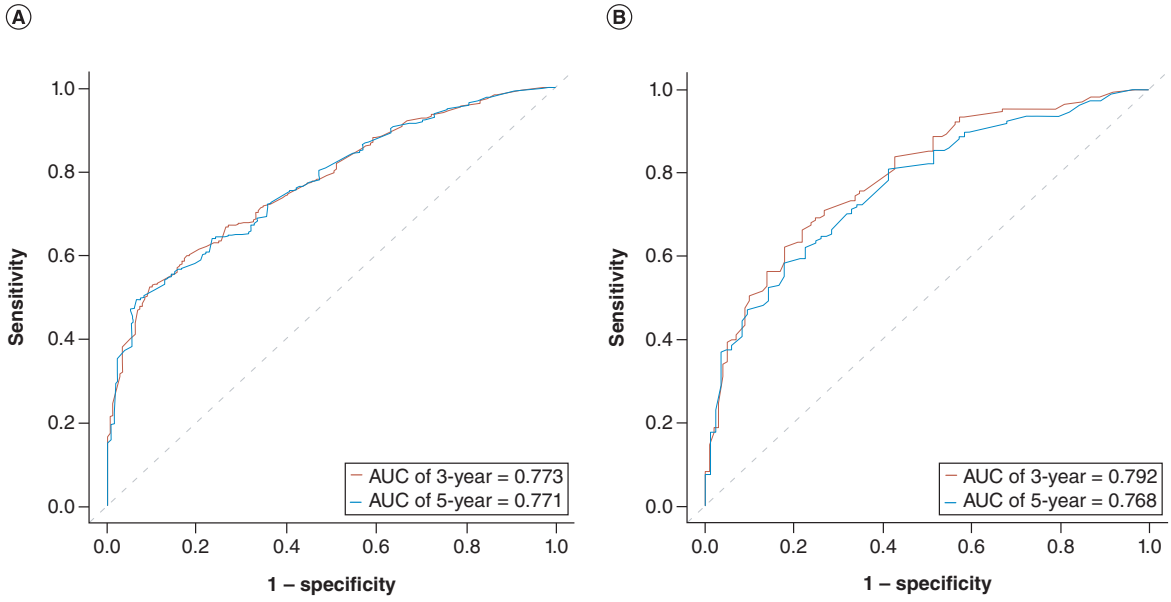

Figure 3. Receiver operating characteristic curves of the nomogram predicting (A) 3-year and 5-year overall survival in the training cohort and (B) validation cohort.
AUC: Area under curve.

prognostic factors that can predict survival among patients with BNEC: marital status, age at diagnosis, TNM stage, chemotherapy and surgery. Researchers have previously found that advanced age is usually associated with a poor prognosis in BNEC patients [11,18]. We also found that older patients (age ≥75; HR: 1.30; 95% CI: 1.10–1.74; p = 0.004) had higher scores on the nomogram, indicating a poorer prognosis. Marital status also affected prognosis, which is consistent with some research [19,20]. Both univariate and multivariate Cox regression analyses showed that marital status affected OS independently; 'unmarried' patients (HR: 1.29; 95% CI: 1.08–1.55; p = 0.005) with BNEC had worse survival than married patients. Marital status is associated with cancer survival through different mechanisms. A person's marital status is commonly used as a measure of social support. Married patients may have greater financial resources, have stronger social connections [21], may lead healthier lifestyles [22] and will receive better treatment [23]. In addition, it is controversial whether the TNM stage is also an independent prognostic factor for BNEC [11,18,24]. This study found that patients with advanced TNM stage have a higher risk of death than those with early-stage disease (Table 2). M stage was strongly linked to outcomes because the risk of death was 2.5-fold higher among patients with M1 stage disease. This is understandable because patients with metastases usually require more comprehensive treatments, such as radiotherapy and chemotherapy, but patients are often unable to tolerate side effects and have to discontinue treatment. Besides, a higher-grade TNM stage means local spread of the tumor, more likely to invade blood vessels and cause cancer cells to enter the bloodstream and metastasize. Furthermore, receiving partial/radical surgery (HR: 0.57; 95% CI: 0.45–0.71; p < 0.001) and chemotherapy (HR: 0.49; 95% CI: 0.41–0.60; p < 0.001) were shown as protective factors for patients with BNEC. Although surgery alone is not recommended [10,25,26], it plays a pivotal role in the correct management of these patients. Combining radical surgery with platinum-based neoadjuvant chemotherapy had been shown to improve outcomes [25]. Compared with monotherapy, radical cystectomy plus chemotherapy and chemoradiation are associated with improved survival, according to data from the National Cancer Database [10]. Concerning the surgical options, our data showed that only 31.1% of cases were initially treated with P/R and about 65.3% of cases were treated with TURB. This may be because most patients are diagnosed at an earlier pathological stage (T1–T2 stage accounts for 71%) and refuse radical cystectomy for a better quality of life. We suggest that partial/radical surgery could be recommended for BNEC patients with a life expectancy >5 years. Patients who received chemotherapy had a higher OS rate than those who did not in almost all retrospective studies involving bladder cancer patients with BNEC [11,16,18,24,27]. Chemotherapy regimens were mostly extrapolated from those used for the same pathological tumors of pulmonary types, so neoadjuvant or adjuvant etoposide and platinum were the therapy options of choice [25,28]. It is interesting that radiotherapy has been a critical factor in

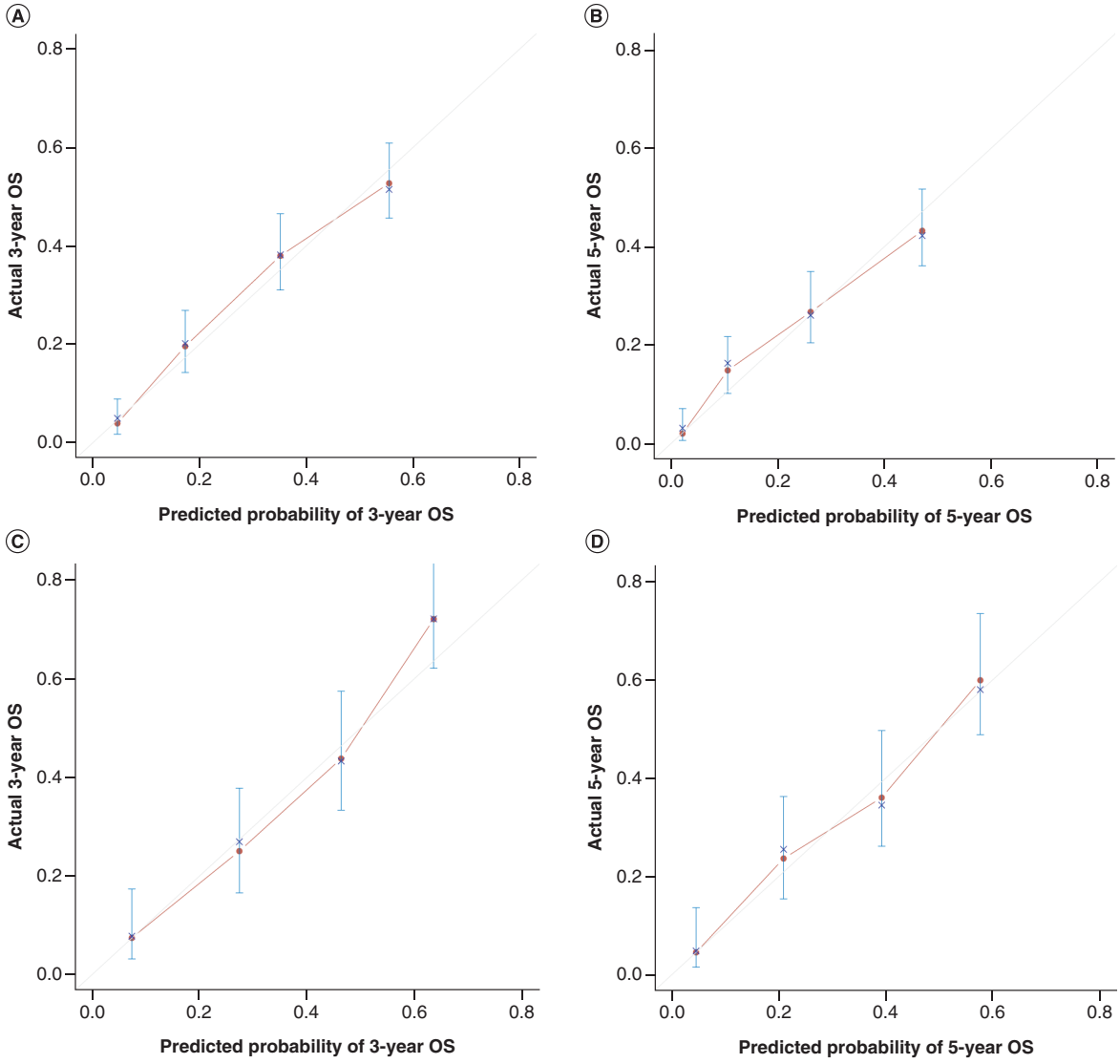

Figure 4. Calibration plots of the nomogram describing (A) 3- and (B) 5-year overall survival in the training cohort and (C) 3- and (D) 5-year overall survival in the validation cohort.
OS: Overall survival.

managing small-cell lung cancer, but radiotherapy was not regarded as an independent factor in the current analysis. Furthermore, Serussi *et al.* [16] also proposed that radiotherapy did not improve OS, but suggested that it might be a good alternative for strongly selected patients with locally advanced disease. However, it has been suggested that post-prostate-cancer external beam radiation therapy and high-dose brachytherapy may trigger this cancer [29]. These deserve further study with prospective experiments. Most importantly, the relatively high C-index and AUC of both the 3- and 5-year cohorts in the training and validation cohorts confirm that the nomogram performs well and has good discriminative power (Figure 3). Additionally, the calibration curves demonstrated perfect congruence between the prediction of the nomogram and the actual outcome (Figure 4). AJCC TNM stage and our nomogram were compared for clinical performance using the C-index. The AUC and C-index of our model were greater than those of the TNM system in the training cohort. All in all, these data strongly suggest that the proposed nomogram can be used to predict OS for patients with BNEC based on patient-specific information. During the study period, multimodal treatment was increasingly used in BNEC patients. Immunotherapy has shown promising results in the management of BNEC. Recent approvals of anti-PD-L1 and anti-PD-1 antibodies have allowed them to be used to treat metastatic cancer patients who cannot receive cisplatin, or patients after platinum-based chemotherapy failure [30]. Nonurothelial bladder cancer was also tested for dual checkpoint inhibition [31–33]. It

is becoming increasingly evident that immune checkpoint inhibition could play a role in nonurothelial bladder cancer, like UCs, where the use of PD-1/PD-L1 inhibitors is now considered standard in the first or subsequent lines of therapy [34].

This study does, however, have important limitations. First, this is a retrospective study using SEER datasets. Retrospective studies have inherent issues such as selection and information bias. To reduce the bias, we used a wide range of variables based on clinical relevance, scientific knowledge and predictors that had been described in the literature. Second, our nomogram was based on the AJCC Sixth Edition TNM staging system and requires further majorization based on the eighth edition of the AJCC staging system. Third, the SEER database collects a large amount of patient information from multiple regions and hospitals, and although the extent of tumor anatomy is very standardized across all treatment centers, differences in surgeon and pathologist attitudes and interindividual variability may affect TNM staging precision. Ultimately, although the validation cohort was internally validated, the results of this validation means were not perfect since the patients developed and validated came from an identical database. Further external validation is therefore needed to confirm the accuracy and dependability of the nomogram.

Conclusion

In this study, several demographic factors, clinicopathological characteristics and therapy strategies were significantly associated with the prognosis of BNEC patients. All of these factors could be readily obtained in most hospitals and the nomogram obtained good applicability. Additionally, an accurate and easy-to-understand nomogram was developed to predict the individual OS of patients with BNEC. The nomogram will allow clinicians to assess the risks of patients with BNEC and to apply personalized therapy. Nevertheless, future studies are needed to renew this nomogram to include more patients as well as more detailed information such as laboratory tests, immunotherapy regimens and so on.

Summary points

- Reports of bladder neuroendocrine carcinoma (BNEC) are scarce and have mostly been based on retrospective studies. Therefore, researchers naturally have paid less attention to BNEC.
- Nomograms combine important predictors used to predict a particular end point and are regarded as practical tools in prognosis evaluations of cancer.
- The 3- and 5-year overall survival (OS) rates were 31.4 and 24.7% in the total cohort, respectively.
- Both univariate and multivariate cox regression analyses showed that marital status affects OS independently; unmarried patients with BNEC had worse OS than married patients.
- M stage was strongly linked to outcomes; the risk of death was 2.5-fold higher among patients with stage M1 disease.
- Partial/radical surgery could be recommended for BNEC patients with a life expectancy >5 years.
- The nomogram also has an additional strength, namely that it uses a wide range of variables based on clinical relevance, scientific knowledge and predictors that have been described in the literature.
- All of these factors could be readily obtained in most hospitals and the nomogram obtained good applicability.
- Nevertheless, future studies are needed to renew this nomogram to include more patients as well as more detailed information such as laboratory tests, immunotherapy regimens and so on.

Author contributions

L Weipeng and B Fu contributed to the conception of the study; S Li and X Liu contributed significantly to the analysis and manuscript preparation.

Acknowledgments

The SEER database provides clinical data about cancer patients, which greatly facilitates clinical research.

Financial & competing interests disclosure

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