Development and Validation of a Prognostic Nomogram in Patients with Bladder Cancer after Radical Cystectomy: A Study Based on the Chinese Population

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Research

Abstract

Purpose

To develop and validate a prognostic nomogram in patients with bladder cancer who underwent radical cystectomy based on the Chinese population.

Methods

The nomogram was built on a retrospective study included 191 patients with bladder cancer who underwent radical cystectomy between January 2010 to December 2019 at the authors' hospital. The primary cohort was divided into the training cohort and the validation cohort randomly. The endpoints in the study were disease-free survival and overall survival. The ability of distinguishing and predicting of the prognostic nomogram were determined by calibration plot and concordance index in the training cohort. Moreover, the results were also verified in the validation cohort internally.

Results

Multivariate analysis of the training cohort showed that hydronephrosis, Stage_T, Stage_N, PNI and EGFR were significantly associated with overall survival. Meanwhile, Stage_T, Stage_N, PNI and EGFR were independent risk factors for disease-free survival. The calibration plot agreed well between prediction and actual observation in survival possibility. The concordance index of the nomogram in the training cohort of overall survival and disease-free survival were 0.834 (95%CI: 0.785-0.833) and 0.823 (95%CI: 0.772-0.873), respectively. In the validation cohort, the nomogram also showed high predictive accuracy.

Conclusion

The proposed nomogram showed high accuracy in predicting survival for bladder cancer patients after radical cystectomy.

Introduction

Bladder cancer (BC) is reported to be one of the most common malignant tumors with estimated 549,000 new cases and 200,000 deaths yearly in the world[1]. At first diagnosis, approximately 75% of patients with BC were non-muscle invasive bladder cancer (NMIBC)[2, 3], and about 20% of patients were muscle-invasive bladder cancer (MIBC) and the other 5% was metastatic disease. For patients diagnosed with MIBC and high risk NMIBC, radical cystectomy and pelvic lymph node dissection (PLND) are recommended as the gold standard treatment[4].

Unfortunately, the prognosis of BC remains poor even if patients underwent radical cystectomy, especially with positive lymph node or metastasis. A previous study have reported that the recurrence-free survival (RFS) and overall survival (OS) rate were 68% and 60% at 5 years and 66% and 43% at 10 years after

radical cystectomy[5], respectively. Therefore, it is meaningful to estimate survival after radical cystectomy for patients with BC who might benefit from further adjuvant therapy.

Previously, clinicians mainly depended on the American Joint Committee on Cancer (AJCC) staging system[6], which includes primary tumor (T), regional lymph node (N), and distant metastasis (M) to predict survival status of patients. Nowadays, a lot of clinicopathological characteristics and preoperative index have been uncovered to influence the prognosis of BC. A retrospective study performed by Peng et al. found that prognostic nutritional index (PNI) was associated with OS and progression-free survival (PFS) for patients with BC after radical cystectomy irrespective of tumor stage[7]. Moreover, Oh et al. found that the presence of preoperative hydronephrosis in BC patients was also significantly associated with worse survival after radical cystectomy[8]. One study also revealed that the overexpression of epidermal growth factor receptor (EGFR) was an independent risk factor of bladder tumor recurrence[9]. Many reporters suggested other prognostic indicators such as lactate dehydrogenase (LDH), albumin count and relative platelet and blood indication levels, such as neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and lymphocyte to monocyte ratio (LMR)[10–13]. Given the fact of different risk factors were found about the prognosis of BC, lots of prognostic models have been established[14–16].

The nomogram is a graphical representation of multivariate results which can integrate many prognostic factors in the model to evaluate the possibility of individual survival at certain time[17]. Currently, nomograms have been developed in many different types of cancers[18–20]. Compared to the traditional TNM staging system, nomograms have been promoted or even as an alternative because of its convenience and accuracy. Therefore, it is necessary to develop a unique prognostic nomogram which is access especially to patients with BC after radical cystectomy.

This study aims to develop an effective prognostic nomogram for BC after radical cystectomy based on Chinese population. Meanwhile, the predictive accuracy of the nomogram was validated simultaneously.

Patients And Methods

Study design

This study was approved by the institutional review board of Zhongda hospital affiliated to Southeast University and owing to its retrospective nature, no written informed consents were request.
The study was retrospectively conducted on patients who underwent radical cystectomy for BC between January 2010 and December 2019 at authors' hospital. The inclusion criteria were as follows: older than 18 years; non-metastatic disease at the time of diagnosis of BC; without other malignant tumor; and histopathologically proven urothelial carcinoma; complete resection of bladder tumors in surgery with standard or extended pelvic lymph node dissection. Exclusion criteria included the following: tumors of uncertain origin or probable metastatic bladder tumor; upper tract urothelial carcinoma. Patients who lacked enough clinicopathological data or lost in the follow-up were also excluded. This study was censored on December 31, 2020. The flow chart of protocol was shown in Fig. 1.

Diagnosis and treatment

After a thorough medical history collection and a careful physical examination, relevant laboratory test results were recorded such as serum albumin, lactate dehydrogenase (LDH), and count of platelet, neutrophil, lymphocyte, and monocyte. The calculation of PNI was albumin level + 5 × lymphocyte count[21]. We also calculated PLR, NLR and LMR concomitantly. Baseline characteristics included age, gender, body mass index (BMI), American Society of Anesthesiologists (ASA) and previous medical history of (smoking, hypertension and diabetes). Urinary cytology was analyzed routinely on each patient. Radiological imaging like ultrasound (US), computed tomography urography (CTU) or magnetic resonance imaging (MRI) were optionally performed to evaluate the location of the lesion and to determine whether there is hydronephrosis preoperatively. The final diagnosis of BC before surgery is decided by histological evaluation of tissue achieved by transurethral resection of bladder tumor (TURBT).

For patients with MIBC and high risk NMIBC, radical cystectomy and standard or extended PLND were performed by two experienced surgeons in our center.

Histopathological research of the resected specimens was conducted by experienced pathologists in Department of Pathology of Zhongda hospital affiliated to Southeast University. The pathological features of tumor, such as size, grade, number, lymphovascular invasion, lymph node metastasis and infiltration depth were documented. The expression of EGFR was identified with immunohistochemisty.

Follow-up

All patients were routinely followed-up after surgery according to the guidelines. The schedule of follow-up is every 6 months in the first 2 years, and then yearly. The endpoints included DFS and OS. The definition of DFS was time interval between date of surgery to disease recurrence and OS was the period between surgery to death for any cause.

Statistical analysis

The decisions on the groups of categorical variables were made before developing the model. X-tile software version 3.6.1 (Yale University) was introduced to decide the optimal cutoff values of continuous variable of NLR, PLR, LMR and PNI. In univariate analysis, if P value < 0.05 by Log-rank test, it will be acknowledged as statistically significant. Then significant variables were entered into Cox proportional hazards regression model to determine the independent risk factors of OS and DFS.

A prognositic model was constructed including all significant variables in multivariate analysis and it was developed by R software version 4.0.2 (http://www. r-project.org/). The agreement between the predicted survival rate and the observed survival rate was measured by a calibration plot generated from our nomogram. Bootstraps with 1000 resamples were used for these evaluations. Validation of the nomogram was carried out in the validation cohort internally.

Results

Baseline characteristics of included patients

According to the inclusion and exclusion criteria, 191 patients including 166 (86.9%) males and 25 (13.1%) females with BC who received radical cystectomy were finally included in the study. The median follow-up time was 43.23 months (interquartile range, 27.03 to 74.77 months) of whole cohort. A total of 191 patients were then divided into the training cohort (n = 135) and the validation cohort (n = 56) randomly. The median age was 71 years and 69 years in the training cohort and the validation cohort. The clinicopathological characteristics of patients in the study are listed in Table 1. For the results acquired from X-tile software, the optimal cutoff values were 3.1, 202.2, 3.4 and 46.5 for NLR, PLR, LMR and PNI (Fig. 2).

Table 1
Clinicopathological characteristics of patients

Variable	Training cohort (n = 135)	Validation cohort (n = 56)
	No. of patients (%)	No. of patients (%)
Gender		
Male	116 (85.9)	50 (89.3)
Female	19 (14.1)	6 (10.7)
Age		
Median	71	69
Range	38−85	37−85
ASA		
≤ 2	119 (88.1)	9 (16.1)
> 2	16 (11.9)	47 (83.9)
Hydronephrosis		
Yes	33 (24.4)	22 (39.3)
No	102 (75.6)	34 (60.7)
Grade		
High	119 (88.1)	48 (85.7)
Low	16 (11.9)	8 (14.3)
History of smoking	21 (15.6)	14 (25.0)
hypertension	51 (37.8)	30 (53.6)
diabetes	23 (17.0)	15 (26.8)
Multiplicity		
Yes	84 (62.2)	32 (57.1)
No	51 (37.8)	24 (42.9)
Stage_T		
T1/a/is	70 (51.9)	27 (48.2)
T2	37 (27.4)	16 (28.6)

Abbreviations: ASA, American society of anesthesiologists; EGFR, epidermal growth factor receptor; LVI, lymphovascular invasion.

Variable	Training cohort (n = 135)	Validation cohort (n = 56)
T3	17 (12.6)	10 (17.9)
T4	11 (8.1)	3 (5.3)
Stage_N		
Positive	20 (14.8)	14 (25.0)
Negative	115 (85.2)	42 (75.0)
EGFR		
Positive	54 (40.0)	19 (33.9)
Negative	81 (60.0)	37 (66.1)
LVI		
Yes	41 (30.4)	19 (33.9)
No	94 (69.6)	37 (66.1)
Abbreviations: ASA, American society of anesthesiologists; EGFR, epidermal growth factor receptor; LVI, lymphovascular invasion.		

Tumor recurrence and OS in the training cohort

In the training cohort, the median OS time was 63.5 months, and postoperative 1-, 3-, 5-year OS rates were 87.7%, 63.9% and 55.8%. The median DFS was 63.3 months, and the 1-, 3-, and 5-year DFS rates were 84.6%, 64.3%, and 58.7%, respectively. Univariate analysis showed that preoperative hydronephrosis, Stage_T, Stage_N, PNI, EGFR, tumor size, LVI, NLR, PLR and LMR were associated with OS. Meanwhile, hydronephrosis, Stage_T, Stage_N, ASA, EGFR, LVI, PNI, diabetes were associated with DFS (Table 2).

Table 2
Univariate analysis of variables for OS and DFS in the training cohort

Variable	OS			DFS		
	HR	95%CI	P value	HR	95%	P value
Gender (male vs female)	0.740	0.248−2.203	0.588	2.382	0.851−6.667	0.098
Age (> 65 vs ≤ 65 years)	1.037	0.991−1.085	0.116	1.015	0.760−1.358	0.916
ASA (> 2 vs ≤ 2)	2.207	0.873−5.581	0.094	2.108	1.014−4.379	**0.046**
Hydronephrosis (yes vs no)	4.767	2.007−11.323	**< 0.001**	2.578	1.395−4.765	**0.003**
Grade (high vs low)	6.500	0.873−48.388	0.068	2.081	0.645−6.716	0.220
Multiplicity (yes vs no)	0.678	0.305−1.508	0.341	0.883	0.488−1.597	0.680
Size (> 3 vs ≤ 3)	3.137	1.380−7.133	**0.006**	1.408	0.781−2.537	0.255
Smoke (yes vs no)	0.316	0.094−1.063	0.063	0.702	0.297−1.658	0.419
Hypertension (yes vs no)	0.950	0.431−2.094	0.899	0.618	0.328−1.166	0.138
Diabetes (yes vs no)	0.913	0.379−2.197	0.839	2.169	1.117−4.204	**0.022**
Stage_T (2 ≥ vs < 2)	2.826	1.848−4.322	**< 0.001**	2.301	1.740−3.042	**< 0.001**
Stage_N (positive vs negative)	7.792	3.410−17.806	**< 0.001**	6.599	3.509−12.410	**< 0.001**
EGFR (positive vs negative)	2.679	1.215−5.910	**0.015**	2.586	1.423−4.701	**0.002**

Variable	OS			DFS		
LVI (yes vs no)	27.269	7.838−94.876	**< 0.001**	5.643	3.071−10.370	**< 0.001**
PNI (high vs low)	0.040	0.005−0.299	**0.002**	0.133	0.056−0.314	**< 0.001**
NLR (high vs low)	2.541	1.156−5.587	**0.020**	1.322	0.701−2.492	0.389
PLR (high vs low)	3.142	1.378−7.163	**0.006**	1.854	0.984−3.491	0.056
LMR (high vs low)	0.368	0.166−0.815	**0.014**	0.699	0.389−1.256	0.231
ALB (high vs low)	0.688	0.302−1.568	0.374	0.602	0.329−1.103	0.101
LDH (high vs low)	2.059	0.748−5.670	0.162	0.741	0.312−1.760	0.497

Independent prognostic factors of survival in the training cohort

In multivariate analysis (Table 3), the results revealed that hydronephrosis, Stage_T, Stage_N, PNI and EGFR were independent risk factors for OS. While Stage_T, Stage_N, PNI and EGFR were significantly associated with DFS. The OS of patients was shown in Fig. 3.

Table 3

Multivariate analysis of variables for OS and DFS in the training cohort

Variable	OS			DFS		
	HR	95%CI	P value	HR	95%	P value
Hydronephrosis (yes vs no)	1.708	1.005−2.903	**0.048**	-	-	-
Stage_T T1/is/a	Reference			Reference		
T2	2.420	1.100−5.325	**0.028**	2.795	1.270−6.150	**0.011**
T3	3.923	1.734−8.877	**0.001**	2.514	1.029−6.140	**0.043**
T4	4.391	1.470−13.117	**0.008**	4.290	1.605−11.468	**0.004**
Stage_N (positive vs negative)	2.681	1.564−4.594	**0.003**	3.358	1.523−7.402	**0.003**
EGFR (positive vs negative)	1.947	1.072−3.534	**0.029**	2.381	1.261−4.497	**0.007**
PNI (high vs low)	0.310	0.136−0.707	**0.011**	0.242	0.098−0.599	**0.002**

Development of a prognostic nomogram

The prognostic nomogram of OS and DFS that included all significant independent factors in the training cohort were shown in Fig. 4. The C-index for OS and DFS prediction value was 0.834 (95% CI: 0.785−0.833), and 0.823 (95% CI: 0.772−0.873), respectively. A calibration plot of survival rate at 3 or 5 years after surgery showed a great agreement between prediction and actual observation (Fig. 5A-D).

Validation of a prognostic nomogram

In the validation cohort, the median OS time was 54.23 months and the postoperative 1-, 3-, 5-year OS rates were 79.3%, 56.1% and 47.8%, respectively. The median DFS was 54.23 months, and the 1-, 3-, and 5-year DFS rates were 75.4%, 58.3%, and 47.7%, respectively. The C-index of the nomogram for predicting OS and DFS was 0.834 (95% CI: 0.796−0.926) and 0.856 (95% CI: 0.787−0.925), Which showed a superiority compared to the AJCC staging system (0.812; 95% CI: 0.724-0.900 and 0.811; 95% CI: 0.727−

0.895). The calibration curve showed a good accordance between prediction and observation in the probability of 5-year survival of OS and DFS (Fig. 5E-F).

Discussion

BC is one of the major health problems worldwide, with both high morbidity and mortality. Although different treatment methods have been applied, radical cystectomy remains the recommended therapy in MIBC and high-risk NMIBC[4]. It is necessary to develop a prognostic model for predicting individual survival and scheduling follow-up in BC patients who underwent radical cystectomy. In this study, we constructed a preoperative prognostic nomogram on the basis of different variables including demographic, clinical, pathological characteristics and preoperative nutrition status for patients of BC who underwent radical cystectomy. Furthermore, we also validated this prognostic model internally in the validation cohort.

In our nomogram, stage T and stage N contributed considerably to OS and DFS. Undoubtedly, advanced T stage and positive lymph node have always been linked to unfavorable survival in BC patients. Meanwhile, preoperative nutrition status can not be ignored in patients' survival after radical cystectomy. Moreover, presence of preoperative hydronephrosis led to decreased DFS and OS. We also incorporated the expression of EGFR in our nomogram. Each variable in our model was independently associated with patients' survival and consistent with prior studies. Zhu et al.[22] found that preoperative hydronephrosis is significantly associated with poorer OS and CSS after radical cystectomy for patients with BC. Bartsch et al.[23]discovered that 133 patients (16.9%) had hydronephrosis before surgery when conducting a prognostic analysis on 788 patients who recieved radical cystectomy for BC. Their results demonstrated that presence of preoperative hydronephrosis was independently associated with poorer RFS. Besides, Peng et al.[7] showed that PNI was independent predictors of OS and PFS for patients with BC after radical cystectomy. Moreover, Hashmi et al.[24]found that while the expression of EGFR was not significant in patient OS, it was associated with tumor grade, depth of invasion and cancer recurrence. In a word, the variables in our study are not only statistically reliable but also consistent with previous research results.

Recently, several prognostic models about BC have been put forward. Welty et al.[25] introduced the Cancer of the Bladder Risk Assessment (COBRA) score based on Surveillance, Epidemiology, and End Results (SEER) database. The COBRA is a risk-stratification model to evaluate the patient prognosis after cystectomy which included age, T stage, and lymph node density. Compared to the COBRA model, the C-index in our nomogram was high both in the training cohort (0.834 vs. 0.712) and validation cohort (0.834 vs. 0.705). Tao et al.[26] indicated that marital status was an independent prognostic factor of OS in distant-metastatic BC patients, but its contribution to predicting OS was relative small. They constructed a prognostic models based on SEER population by utilizing eight variables, including marital status, age, tumor grade, histology type, primary surgery, chemotherapy and metastasis status. Our model also showed an advantage in predictive accuracy (0.834 vs. 0.722). With the discovery of immune checkpoint inhibitors, immunotherapy has achieved promising results in BC. More and more studies are

exploring the factors that affect the efficacy of immunotherapy in BC. Qiu et al. [27]reported a prognostic model based on immunerelated genes (IRGs). They obtained RNA-seq data and clinical information of patients on BC from the Cancer Genome Atlas (TCGA) and gene expression omnibus (GEO). Seven BC-specific prognostic IRGs were identified and the survival outcomes of an IRG-based prognostic signature that stratified BC patients into two different subgroups was significantly different. The results showed that the increased infiltration of CD4 + T cells, CD8 + T cells, macrophage, neutrophil, and dendritic cells were associated with poorer survival outcomes. These nomograms mentioned above might not be applied to a broad population generally because most of studied were based on the SEER database, which is vulnerable to mistake in coding, data collection, and incomplete data. Meanwhile, lacking potential important factors, such as preoperative laboratory results and detailed pathological information led to the missing of important prognostic parameters which had been proved significant. Moreover, the complicated algorithm increased our calculation burden and the prognostic genes were not available conveniently, which limits the promotion of these nomograms. On the contrast, our nomogram is conveniently available and included variables were based on a population locally. Furthermore, our nomogram demonstrated to be not only clinically-relevant, but also pathological effective with great discriminative ability and predictive accuracy.

We admit that there remain some limitations in our work. First, this nomogram was developed based on data obtained from a single institution in China, and it was constructed retrospectively. The results should be taken carefully due to the retrospective nature. More resource of multi-center and prospective studies are needed to improve our model for clinical practice. Second, most patients had a relative low tumor stage in our training and validation cohort, which leads to lack of data on postoperative adjuvant treatment in our model. Third, it is obvious that our work on molecular subtypes and histopathology is not perfect. According to TCGA analytical platforms, five expression subtypes including luminal-papillary, luminal-infiltrated, luminal, basal/squamous, and neuronal were clustered by mRNA, long non-coding RNA, and miRNA expression[28]. It demostrated that different subtypes present heterogeneous clinical outcomes. Finally, whether this nomogram can be applied to patients who receive neoadjuvant therapy before radical cystectomy remains to be determined.

Conclusion

The nomogram we proposed in this study predicted the prognosis of patients with BC after radical cystectomy objectively and accurately. More clinical researches with high-level evidence are needed to externally validated our model.

Declarations

Ethics statement

This study was approved by the institutional review board of Zhongda hospital affiliated to Southeast University. No written informed consents were request.

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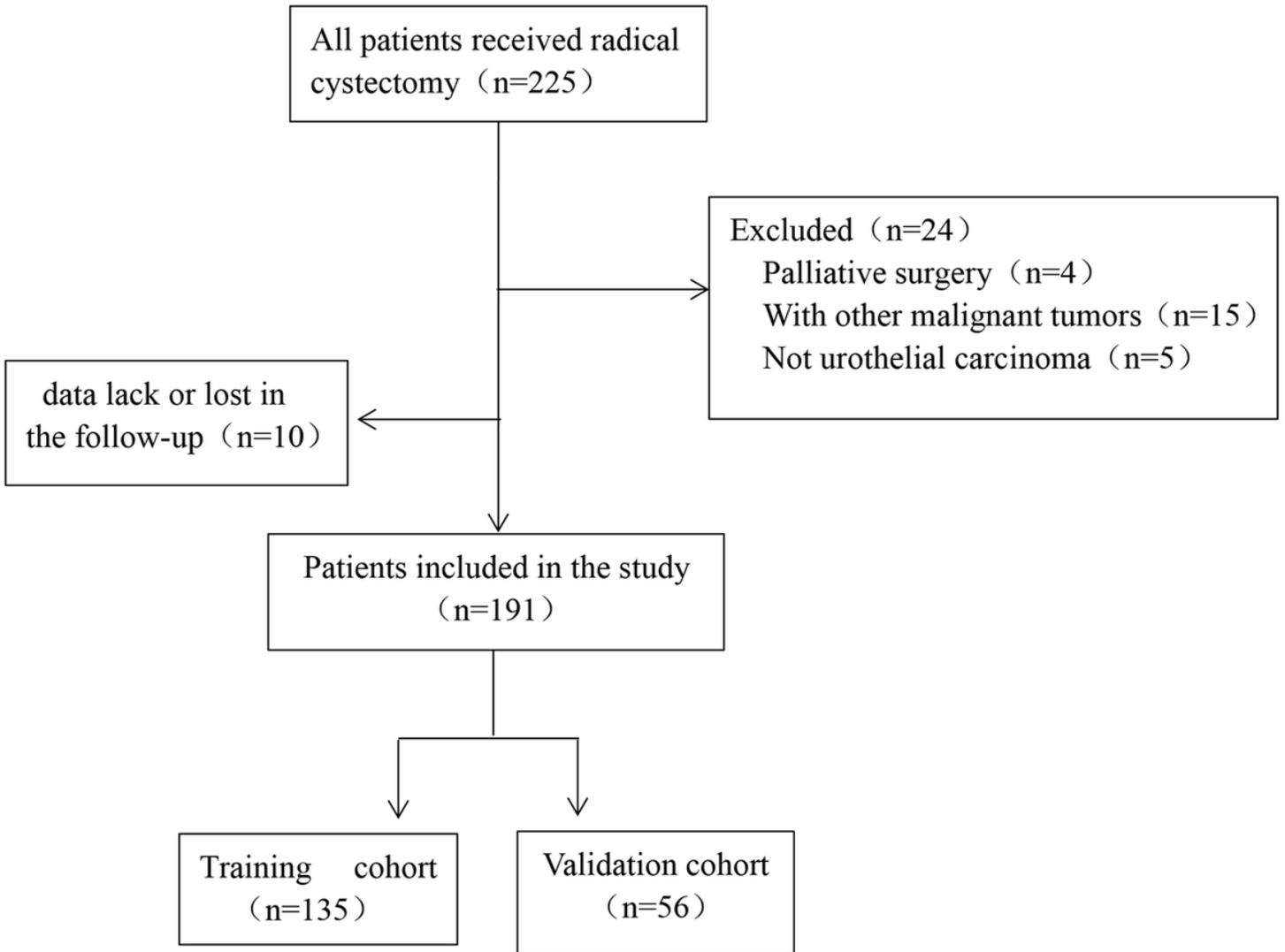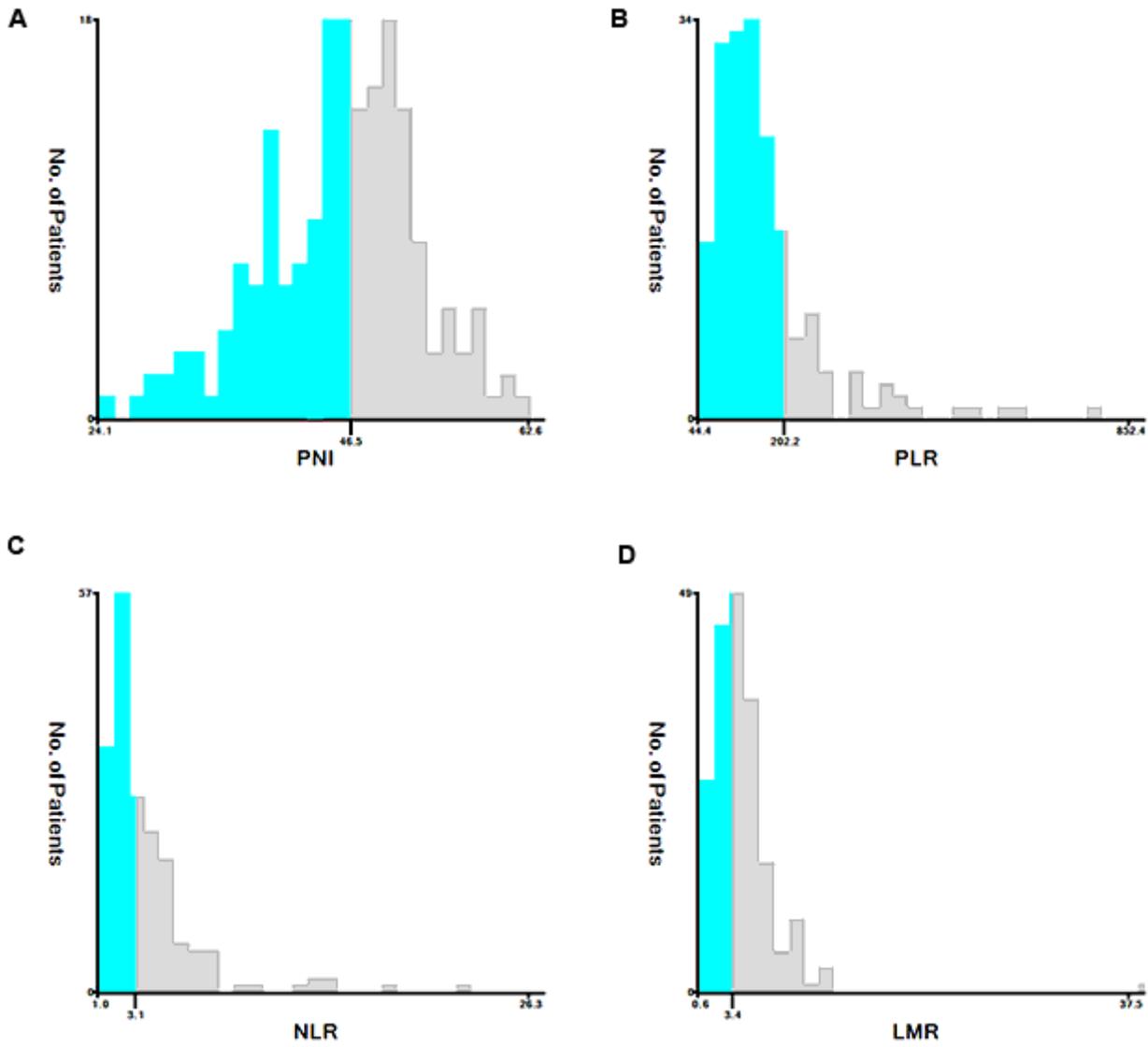
Figures

Figure 1

Flow chart of the study

Figure 2

Results of cutoff value by X-tile (A) the optimal cutoff value of PNI (B) the optimal cutoff value of PLR (C) the optimal cutoff value of NLR (D) the optimal cutoff value of LMR
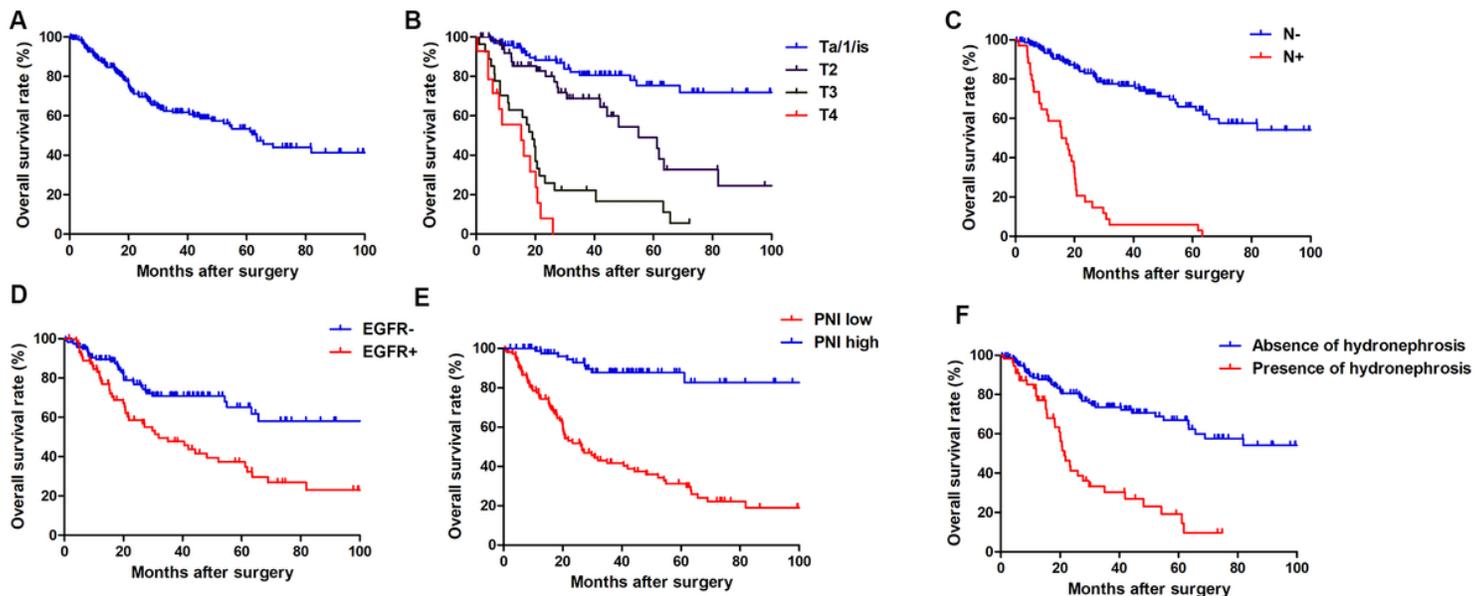
Figure 3

The OS of patients (A) the OS of all patients (B) the OS of Stage T (C) the OS of Stage N (D) the OS of EGFR (E) the OS of PNI (F) the OS of preoperative hydronephrosis
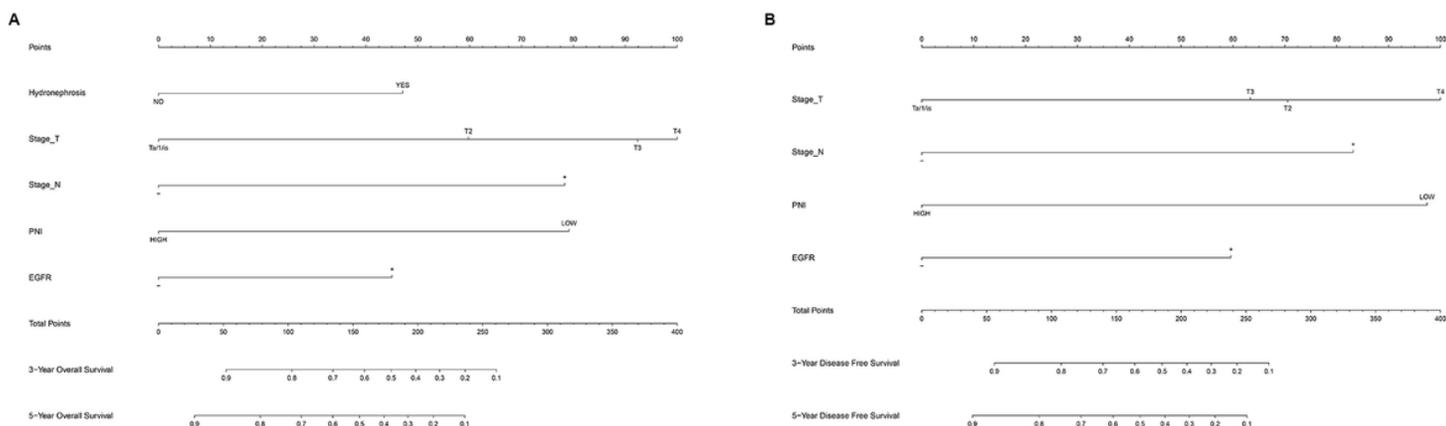

Figure 4

Prognostic nomograms of patients of BC after radical cystectomy (A) nomogram of OS (B) nomogram of DFS
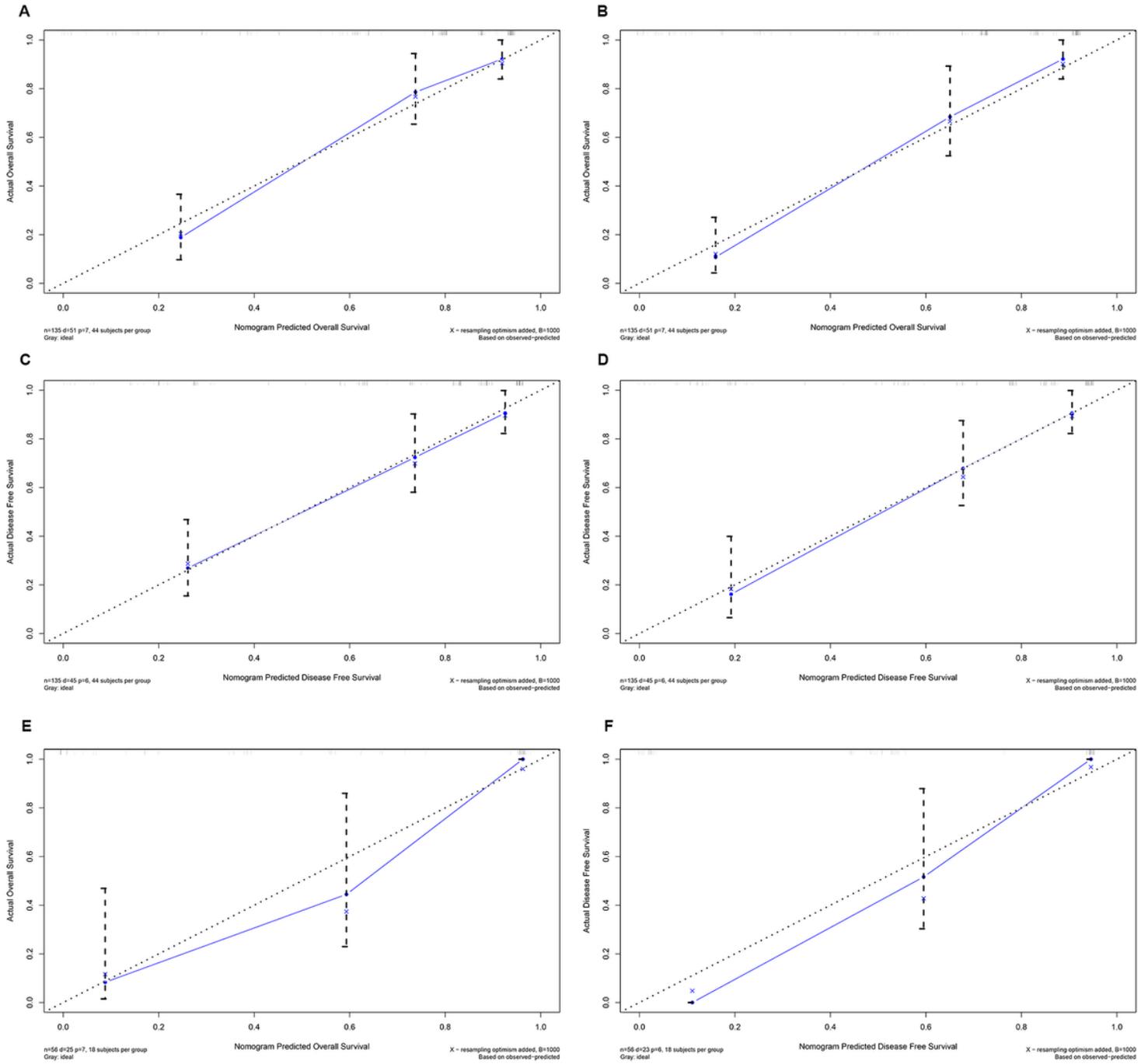
Figure 5

The calibration plot for predicting patient survival at (A) 3 years of OS (B)5 years of OS in the training cohort and at (C) 3 years of DFS (D) 5 years of DFS in the training cohort and at (E) 5 years of OS (F) 5 years of DFS in the validation cohort