A Prognostic Nomogram for Patients with Stage II/III Rectal Cancer Undergoing Surgical Resection after Neoadjuvant Chemoradiotherapy

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Research Article

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Abstract

Background: The purpose of this study was to create a nomogram incorporated on log odds of positive nodes (LODDS) for predicting the overall survival (OS) of patients with stage II/III rectal cancer who underwent surgical resection after neoadjuvant chemoradiotherapy (NCRT).

Methods: The Surveillance, Epidemiology, and End Results database was used to collect information on patients diagnosed with stage II/III rectal cancer who underwent surgical resection after neoadjuvant chemoradiotherapy between 2010 and 2015. The Cox regression analyses were performed to determine the independent prognostic factors. In this study, LODDS was employed instead of American Joint Committee on Cancer (AJCC) 7th N stage to determine lymph node status. Then a nomogram integrating independent prognostic factors was created to predict the 24-, 36-, and 60-month overall survival of patients. The receiver operating characteristic (ROC) curves and calibration curves were used to evaluate the nomogram. Furthermore，patients were stratified into three risk groups(high-, middle-, and low-risk) based on the total points obtained from the nomogram using X-tile software. And Kaplan-Meier curves were plotted to compare OS of the three groups.

Results: A total of 3,829 patients were included in the study. Race, sex, age, marital status, T stage, tumor grade, tumor size, LODDS, CEA level, and postoperative chemotherapy were identified as independent prognostic factors. Then the prognostic nomogram was created and evaluated. The ROC curves and calibration curves showed good performance of the prognostic nomogram. The Kaplan-Meier curves showed that the three risk groups had significant differences in overall survival.

Conclusion: The LODDS-incorporated prognostic nomogram was created and showed satisfactorily discriminative and stable ability to predict the OS of patients with stage II/III rectal cancer undergoing surgical resection after NCRT. It is convenient to access the risk factors included in this nomogram in clinical practice. The nomogram is expected to be a useful tool in developing individualized treatment strategies and follow-up protocols.

1. Introduction

For patients with locally advanced rectal cancer (LARC), neoadjuvant chemoradiotherapy (NCRT) followed by surgical resection has become the standard therapy (1). NCRT can help to downstage tumors, increase the rate of curative resection, and decrease the rate of local recurrence. According to data from the Surveillance, Epidemiology, and End Results (SEER) database, about 35.7% of patients with rectal cancer in stages II/III received NCRT (2). The reason could be that the survival benefit of NCRT has so far been controversial (3, 4), and radiotherapy can make surgical dissection more difficult and increase the risk of postoperative complications, such as anastomotic leakage, wound infection, and pelvic abscess (5). Patients with stage II/III rectal cancer who have undergone surgical resection after NCRT form a distinct cohort with specific prognosis characteristics.

Nomograms have been routinely utilized to predict cancer outcomes In recent years (6). A nomogram integrating multiple prognostic factors can be used to estimate the probability of a particular result. Useful in individualized medicine, it has been applied to a wide range of malignancies (7, 8), For patients with rectal cancer, a number of nomograms have been created to date. However, nomograms for patients with stage II/III rectal cancer undergoing surgical resection after NCRT have rarely been reported. The aim of this study was to utilize SEER database to create a nomogram to predict these patients' prognosis.

The log odds of positive nodes (LODDS) was defined as the log of the ratio between the number of positive lymph nodes (PLN) and negative lymph nodes (NLN) (9). In recent years, it has been proposed and confirmed as a reliable indicator of prognosis in a variety of cancers, such as pancreatic cancer (10), colorectal cancer (11), and gastric cancer (12), and has proven to be a superior predictive factor in patients with colorectal cancer when compared to the American Joint Committee on Cancer (AJCC) N stage (13, 14). As a result, instead of AJCC N stage, we incorporated LODDS into this nomogram and attempted to provide a practical tool for clinicians and patients with stage II/III rectal cancer undergoing surgical resection after NCRT.

2. Methods

2.1. Patient selection

This population-based study was conducted using the SEER database. The SEER database collects statistical, oncological, diagnostic, treatment, and survival information from specific geographical regions representing roughly 28% of the US population. Database was obtained from the SEER*Stat software (version 8.3.6). Patients who were diagnosed after 2015 were not included in this study to ensure enough time for follow-up. In this study, only patients with stage II/III rectal cancer diagnosed between 2010 and 2015 were included. The following were the criteria for inclusion: (1) rectal cancer as the only primary tumor; (2) histologically confirmed as rectal adenocarcinoma; (3) stage II/III rectal cancer patients undergoing surgical resection after NCRT; and (4) patients with complete survival information, demographic data, and clinicopathologic features. Finally, we identified a total of 3829 patients. At a 7:3 ratio, study patients were randomly assigned to the training cohort and validation cohort.

2.2. Statistical Analysis. SPSS 26.0 was used for statistical analysis. The proportions between the training cohort and validation cohort were compared using Pearson's Chi-square test. The best tumor size cutoff was calculated using X-tile software (15), and tumor size was grouped as < 4.6, 4.6–7.0, and ≥ 7.0 cm. LODDS was calculated using the following formula: LODDS = log [(0.5 + PLN) / (0.5 + NLN)] (16). A P value of less than 0.05 was considered statistically significant. The univariate and multivariate Cox regression analyses were performed to determine the independent prognostic factors. The hazard ratio (HR, 95% confidence interval (CI)) was used to express the risk factors. A nomogram integrating independent prognostic factors was created to predict the 24-, 36-, and 60-month overall survival of patients and conducted with R software (version 4.1.0). Receiver operating characteristic (ROC) curves were constructed and the area under curve values (AUCs) were determined to evaluate the discrimination

of nomograms. To assess the consistency between actual and nomogram-predicted survival rates, calibration curves were plotted. Furthermore, X-tile software were used to stratify patients into three risk groups (high-, middle-, and low-risk) according to the total points obtained from the nomogram. And Kaplan-Meier curves were plotted to compare OS of the three groups.

3. Results

3.1. Clinicopathologic and demographic characteristics

3,829 rectal cancer patients were included and randomly assigned in a 7:3 ratio to a training cohort (n = 2,678) and validation cohort (n = 1,151). Table 1 showed the patients' clinicopathologic and demographic characteristics and no statistically significant differences were found between the two cohorts. Overall, patients of white ethnicity (80.9%) made up the majority of the entire population, and men (62.9%) accounted for more than half of the patients. Tumor grade II was the most common (80.6%). The majority of patients were classified as T3 by the AJCC (7th edition) tumor-node-metastasis (TNM) system (83.3%). LODDS between − 1.5 and − 0.4 were found in roughly 62.5 percent of patients. More than half (56.9%) of the patients received postoperative chemotherapy and only a small percentage of patients (3.4%) underwent postoperative radiotherapy.

Table 1
Demographic and clinicopathologic characteristics of the included patients.

Variables	Total number(n = 3829), n (%)	Training cohort(n = 2678) ,n (%)	Validation cohort(n = 1151), n (%)	P
Age				
60	2120(55.4)	1493(55.7)	627(54.5)	0.466
≥60	1709(44.6)	1185(44.3)	524(45.5)	
Race				
White	3096(80.9)	2176(81.2)	920(79.9)	0.624
Black	289(7.5)	199(7.4)	90(7.8)	
Other†	444(11.6)	303(11.3)	141(12.4)	
Sex				
Female	1419(37.1)	988(36.9)	431(37.4)	0.746
Male	2410(62.9)	1690(63.1)	720(62.6)	
Marital status				
No‡	1540(40.2)	1082(40.4)	458(39.8)	0.723
Yes	2289(59.8)	1596(59.6)	693(60.2)	
Grade				
I	282(7.4)	194(7.2)	88(76.5)	0.895
II	3088(80.6)	2157(80.5)	931(80.9)	
III	408(10.6)	290(10.8)	118(10.3)	
IV	51(1.3)	37(1.4)	14(1.2)	
T stage				
T1	33(0.9)	26(1.0)	7(0.6)	0.789
T2	181(4.7)	124(4.6)	57(5.0)	
T3	3190(83.3)	2233(83.4)	957(83.1)	
T4a	108(2.8)	77(2.9)	31(2.7)	
T4b	317(8.3)	218(8.1)	99(8.6)	
LODDS				
<-1.5	1020(26.6)	714(26.7)	306(26.6)	0.521

Variables	Total number(n = 3829), n (%)	Training cohort(n = 2678) ,n (%)	Validation cohort(n = 1151), n (%)	P
-1.5~-0.4	2394(62.5)	1664(62.1)	730(63.4)	
≥-0.4	415(10.8)	300(11.2)	115(10.0)	
Tumor size(mm)				
<46	1942(50.7)	1360(50.8)	582(50.6)	0.747
46–70	1349(35.2)	949(35.4)	400(34.7)	
≥70	538(14.1)	369(13.8)	169(14.7)	
CEA level				
Negative	2144(56.0)	1514(56.5)	630(54.7)	0.304
Positive	1685(44.0)	1164(43.5)	521(45.3)	
Postoperative chemotherapy				
No	1651(43.1)	1166(43.5)	485(42.1)	0.422
Yes	2178(56.9)	1512(56.5)	666(57.9)	
Postoperative Radiation				
No	3700(96.6)	2593(96.8)	1107(96.2)	0.308
Yes	129(3.4)	85(3.2)	44(3.8)	

3.2. Prognostic Factors Associated With Os

To determine the prognostic factors, the univariate and multivariate analyses were conducted included the patients from the training cohort. As shown in Table 2. in the univariate analysis, Race, sex, age, marital status, T stage, tumor grade, tumor size, LODDS, CEA level, and postoperative chemotherapy were statistically associated with OS ($P < 0.05$). The effects of postoperative radiation were not statistically significant ($P > 0.05$). Finally, race, sex, age, marital status, T stage, tumor grade, tumor size, LODDS, CEA level, and postoperative chemotherapy were all revealed to be independent predictive variables in the multivariate analysis. Advanced age, male sex, unmarried status, higher tumor grade, elevated CEA levels, and tumor size more than 70mm was related to a higher risk of mortality. T4b and LODDS greater than −0.4 were obviously detrimental to patient survival. Furthermore, as measured by a hazard ratio of 0.81 (95% CI: 0.693–0.947), patients who underwent postoperative chemotherapy showed a reduced mortality rate.

Table 2
Univariate and multivariate Cox analyses in rectal cancer patients

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Age						
<60	Reference			Reference		
≥60	1.282	1.094–1.502	0.002**	1.344	1.145–1.579	< 0.001***
Race						
Black	Reference			Reference		
White	0.682	0.531–0.877	0.003**	0.666	0.517–0.858	0.002**
Other	0.719	0.522-0.900	0.044*	0.682	0.492–0.944	0.021*
Sex						
Female	Reference			Reference		
Male	1.282	1.094–1.502	0.002**	1.344	1.145–1.579	< 0.001***
Marital status						
No	Reference			Reference		
Yes	0.790	0.680–0.916	0.002**	0.829	0.711–0.966	0.016*
Grade						
I	Reference			Reference		
II	1.081	0.797–1.465	0.618	1.129	0.831–1.534	0.438
III	1.718	1.212–2.436	0.002**	1.567	1.098–2.235	0.013*
IV	1.891	1.038–3.446	0.037	1.815	0.985–3.343	0.056
T stage						
T1	Reference			Reference		
T2	1.312	0.455–3.783	0.615	1.481	0.507–4.331	0.473

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
T3	1.730	0.647–4.625	0.275	1.866	0.688–5.064	0.221
T4a	2.360	0.821–6.783	0.111	2.252	0.774–6.550	0.136
T4b	3.254	1.194–8.870	0.021*	3.141	1.136–8.681	0.027*
LODDS						
<-1.5	Reference			Reference		
-1.5~-0.4	1.660	1.355–2.034	< 0.001***	1.678	1.368–2.059	< 0.001***
≥-0.4	3.466	2.716–4.423	< 0.001***	3.616	2.820–4.637	< 0.001***
Tumor size(mm)						
<46	Reference			Reference		
46–70	1.050	0.889–1.239	0.565	0.994	0.840–1.177	0.946
≥70	1.528	1.243–1.878	< 0.001***	1.309	1.056–1.623	0.014*
CEA level						
Negative	Reference			Reference		
Positive	1.567	1.351–1.817	< 0.001***	1.384	1.189–1.612	< 0.001***
Postoperative chemotherapy						
No	Reference			Reference		
Yes	0.797	0.685–0.928	0.003**	0.810	0.693–0.947	0.008**
Postoperative Radiation						
No	Reference					
Yes	1.397	0.969–2.013	0.073			

3.3. Creation and evaluation of prognostic nomogram.

A prognostic nomogram integrating independent prognositc factors for OS was created (Fig. 2). The predicted probability of 24-, 36-, and 60-month OS could be calculated by summing the points on the nomogram for each patient's matching factors. Figure 2 displayed the survival probability of a given patients was calculated using the nomogram.

In the evaluation of the nomogram, the AUCs of the nomogram for the 24-, 36-, and 60-month OS In the training cohort were 0.736, 0.720, and 0.688, respectively; and 0.691, 0.696, and 0.694 in the validation cohort, respectively. The AUCs demonstrated the satisfactory discriminative power of the model (Fig. 3). In both the validation and training cohorts, the calibration curves showed a high degree of consistency between actual and nomogram-predicted survival rates (Fig. 4).

3.4. Stratification Of Risk Groups

All patients were stratified into three risk groups based on the total points obtained from the nomogram using X-tile software: high-risk (total points ≥ 368), middle-risk (339 ≤ total points < 368), and low-risk (total points < 339). As shown in Fig. 5, the Kaplan-Meier curves indicated that the three risk groups had significant differences in overall survival. The mortality rates of patients in the high-risk group were significantly higher than those in the low-risk group.

4. Discussion

In this study, the data from 3,829 patients in the SEER database were used to create a prognostic nomogram. Although several nomograms have been established previously for patients with LARC undergoing surgical resection after NCRT, the study by Zhifang et al. covering 785 cases (17), has certain limitations as it is a single-center study and their results lacked externally validation. The study by Valentini et al. was based on five European randomized clinical trials (18), but the variables they employed differed greatly from those in our analysis, which included tumor size, CEA level, tumor grade, marital status, and, in particular, LODDS. To the best of our knowledge, this is the first nomogram based on the SEER database that incorporates LODDS to predict the OS of patients with stage II/III rectal cancer undergoing surgical resection after NCRT.

Through multivariable Cox regression analysis, ten parameters, including race, sex, age, marital status, T stage, tumor grade, tumor size, LODDS, CEA level, and postoperative chemotherapy were determined as independent prognostic factors. It was obvious that LODDS greater than − 0.4 contributed most to the poor prognosis, followed by T4b stage.

As we all know, lymph node status plays a significant role in rectal cancer patients’ prognosis. In recent years, in addition to AJCC N stage, many scholars have proposed and analyzed other parameters to evaluate the status of lymph nodes, such as LODDS and the lymph node ratio (LNR). Although AJCC N stage is currently the most widely used method for lymph node classification, many researchers have pointed out its limitation since it only considers the number of positive lymph nodes and ignores the total

number of lymph nodes (TLN) retrieved during surgery. In rectal cancer, TLN has been proven to be an independent prognosis-related factor (19–21). For accurate staging of colorectal cancer, removal of at least twelve lymph nodes was recommended by AJCC. LNR involves both TLN and PLN and has been claimed to be more accurate than AJCC N stage for rectal cancer (22, 23). However, other scholars have noticed that when TLN are either all non-metastatic or all metastatic, patients with the same LNR values might be extremely varied. LODDS, as a novel lymph node classification, can overcome the drawbacks of LNR and increase the accuracy for prognostic evaluation, and studies have shown its superiority to LNR in rectal cancer (16, 24, 25). For LARC, LODDS was confirmed to perform better than both AJCC N stage and LNR in terms of prognostic predictive value (13, 14, 26). Therefore, the nomogram wil be more convicing and effective if LODDS is incorporated into it.

In this study, 56.9% of patients who received postoperative chemotherapy, seemed to have a better outcome. On the other hand, several large randomized controlled trials concluded that postoperative chemotherapy could not improve the OS of rectal patients undergoing surgery after NCRT (27–29). These trials, however, had significant limitations, such as poor adherence in the European Organization for Research and Treatment of Cancer trial 22921. Therefore, it remains uncertain if these patients will benefit from postoperative chemotherapy. According to current National Comprehensive Cancer Network (NCCN) recommendations, rectal patients with tumors staged as T3 or N1 and higher should consider postoperative chemotherapy after neoadjuvant chemotherapy (30). However, experts convened by the European conference on rectal cancer concluded that there is currently insufficient evidence to demonstrate the benefits of receiving adjuvant chemotherapy after preoperative chemoradiotherapy; hence, postoperative chemotherapy cannot be recommended (31). In this way, more comprehensive and conclusive researches will be conducted in the future.

To summarize, the probability of 24-, 36-, and 60-month OS of patients with stage II/III rectal cancer undergoing surgical resection after NCRT can be simply calculated by summing the points on the nomogram for each patient's matching factors. The prognostic factors included in this nomogram can be quickly accessed in clinical work, making it as a practical tool. In additional, by employing risk group stratification, patients who are at high risk can be easily tracked down and treated with a more personalized approach in early intervention. Finally, the nomogram was validated and shown to be repeatable and reliable, with satisfactory discriminative power.

There are some limitations to this study. First, as this was a retrospective analysis based on the SEER database, there was bound to be some degree of selection bias. Second, the SEER database did not offer certain information that could have affected patient outcomes, such as surgical margins, lymph/vascular or perineural invasion, and chemotherapy/radiation regimen. Future predictive models could benefit from the use of molecular tumor markers as well as genetic data.

5. Conclusion

The prognostic nomogram incorporated LODDS was established and exhibited satisfactory and stable predictive power. All factors included in the model are easily obtained in clinical practice, making it as a convenient and practical tool for predicting the prognosis of patients with stage II-III rectal cancer treated with NCRT followed by surgical resection. The nomogram is expected to be useful to make individualized treatment strategies and follow-up protocols.

Declarations

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). The SEER database is an open access database, and all patient information has been de-identified, so individual consent for this retrospective analysis was waived.

Consent for publication: Not applicable.

Data Availability Statements: The datasets generated during and/or analysed during the current study are available in the SEER database repository, SEER Data & Software (cancer.gov).

Competing interests: The authors declare that they have no competing interests

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Figures

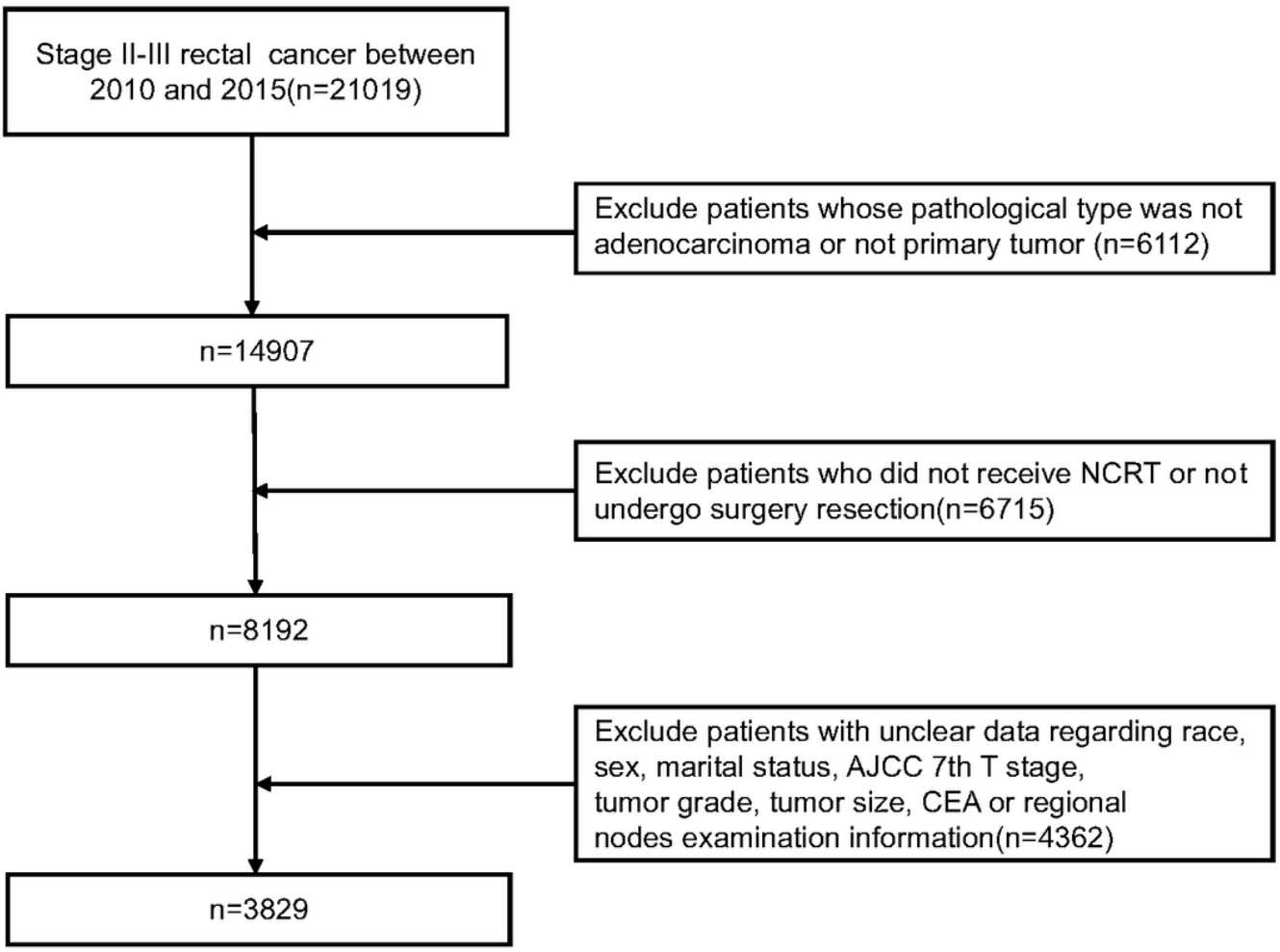

Figure 1

Flow diagram of the study selection process. NCRT, neoadjuvant chemoradiotherapy; CEA, carcinoembryonic antigen; AJCC, American Joint Committee on Cancer.

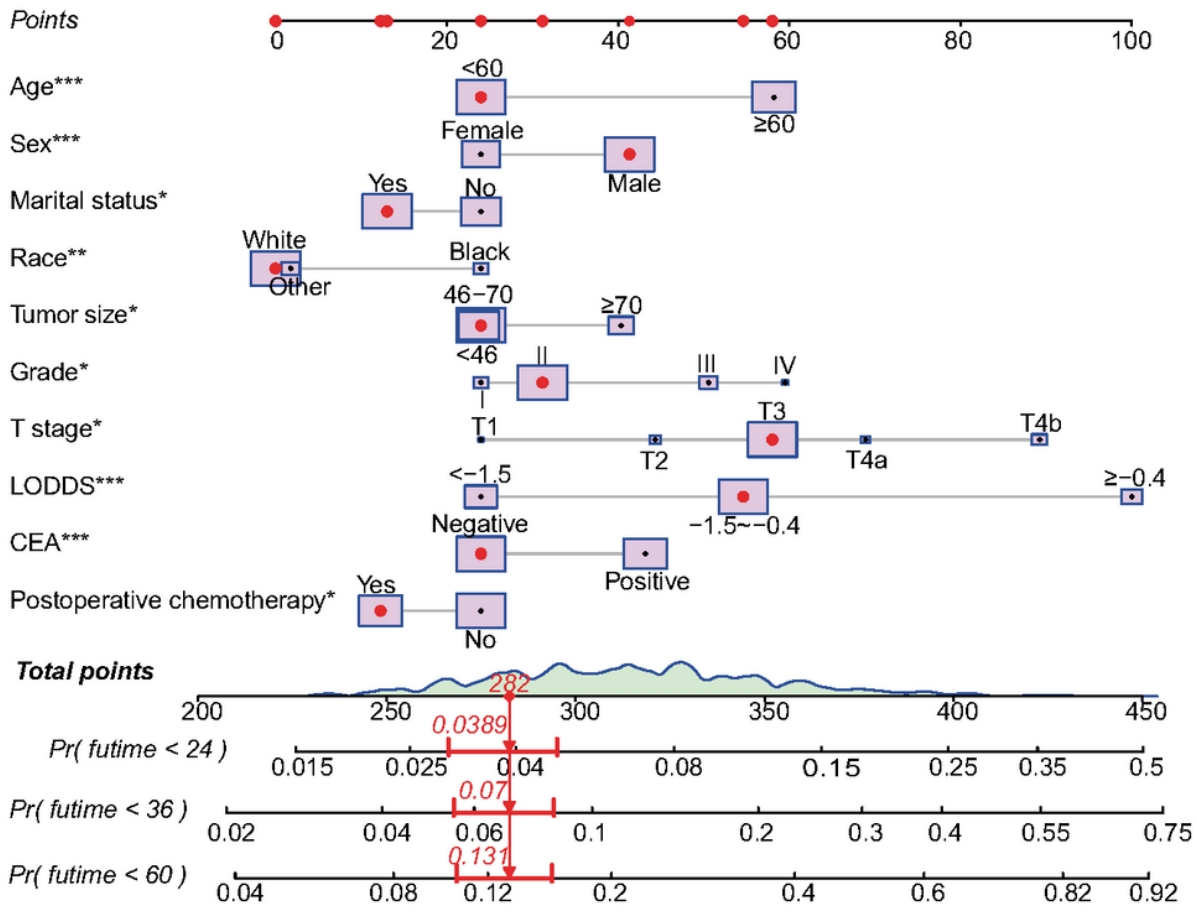

Figure 2

Nomogram for predicting the OS at 24、36 and 60 months. According to Nomogram's estimate the cumulative risk of OS in patients no.30 at 24、36 and 60 months is 0.0389, 0.07 and 0.131, respectively. *, P<0.05; **, P<0.01; ***, P<0.001. OS, overall survival; CEA, carcinoembryonic antigen; LODDS, log odds of positive lymph nodes.

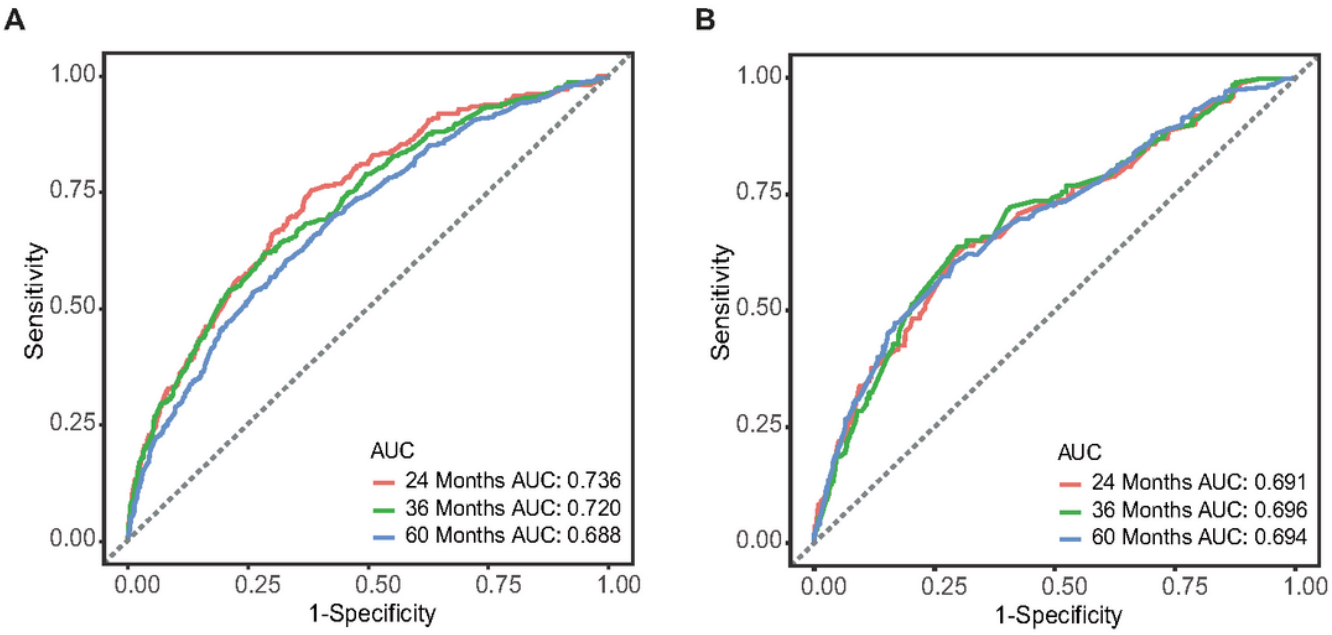

Figure 3

ROC curves and AUC values of the nomogram for the predicted 24-, 36-, and 60-month OS rates for the training cohort (A, B, C) and the validation cohort (D, E, F). AUC, area under the curve; ROC, receiver operating characteristic; OS, overall survival.

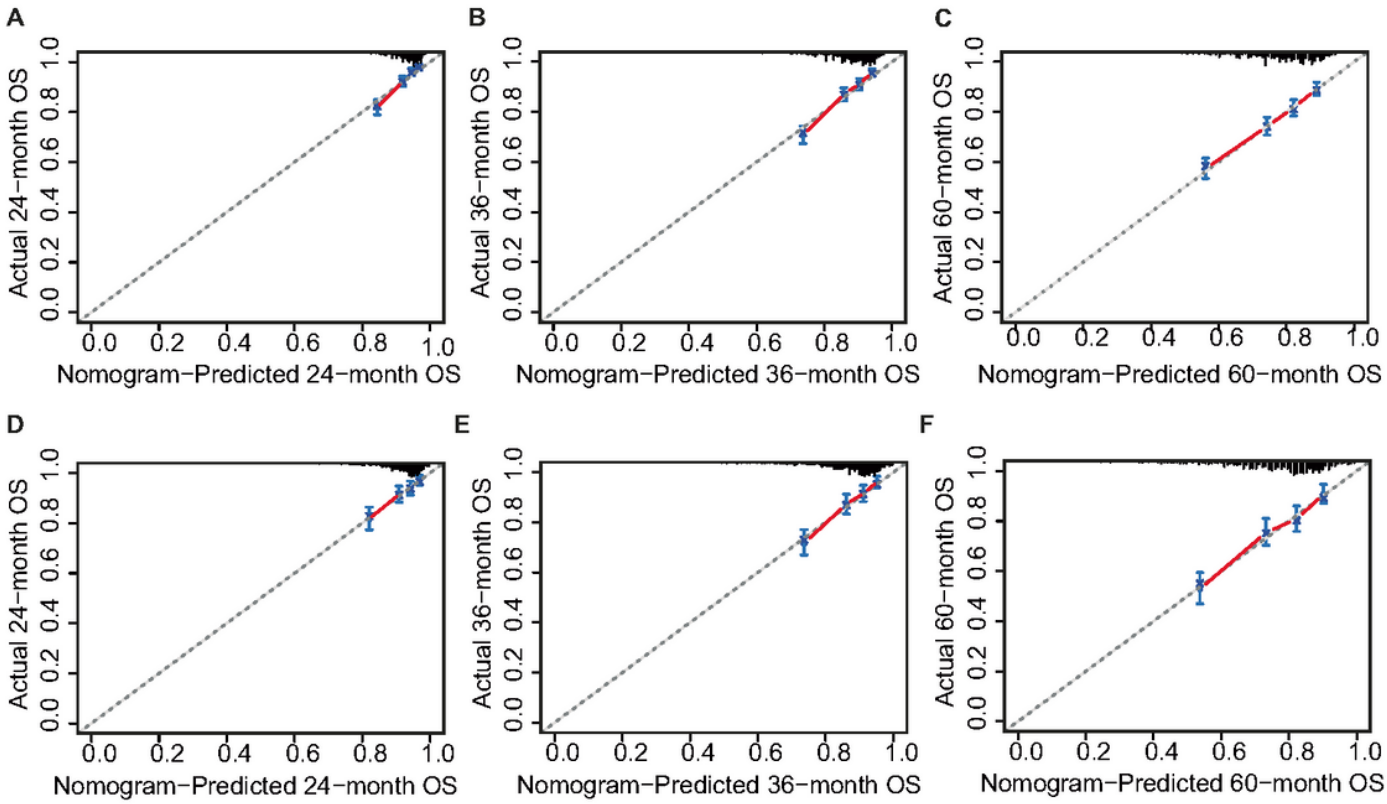

Figure 4

The calibration curves predicting 24-, 36-, 60-month OS in the training cohort (A-C) and the validation cohort (D-F). The dashed line represents a perfect match between the nomogram predicted probability (x-axis) and the actual probability calculated. OS, overall survival.

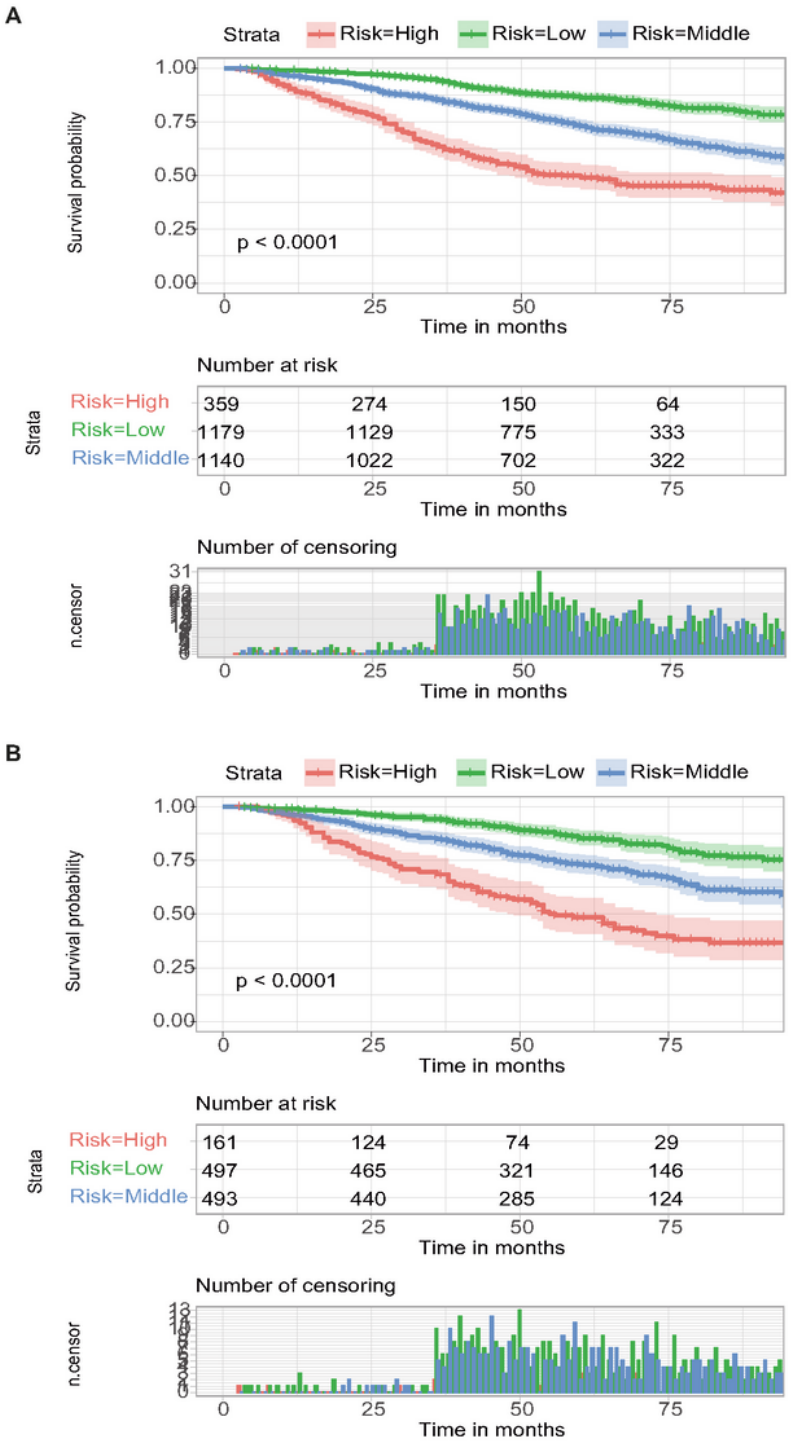

Figure 5

Kaplan–Meier overall survival curves of patients at three risk groups in the training cohort (A) and validation cohort (B) according to the nomogram.