ORIGINAL RESEARCH

Nomogram Predicting Overall Survival of Resected Locally Advanced Rectal Cancer Patients with Neoadjuvant Chemoradiotherapy

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Purpose: The overall survival (OS) of resected locally advanced rectal cancer patients who underwent neoadjuvant chemoradiotherapy (nCRT) was significantly different, even among patients with the same tumor stage. The nomogram was designed to predict OS of rectal cancer with nCRT and divide the patients into different risk groups.

Materials and Methods: Based on materials from 911 rectal cancer patients with nCRT, the multivariable Cox regression model was carried out to select the significant prognostic factors for overall survival. And then, the nomogram was formulated using these independent prognostic factors. The discrimination of the nomogram was assessed by concordance index (C-index), calibration curves and time-dependent area under curve (AUC). The patients respective risk scores were calculated through the nomogram. The best cut-off risk score was calculated to stratify the patients. The survival curves of the two different risk cohorts were performed, which assessed the predictive ability of the nomogram.

Results: Age, cT stage, pretreatment CEA, pretreatment CA19-9, surgery, posttreatment CEA, posttreatment CA19-9, pT stage, pN stage and adjuvant chemotherapy were selected for the construction of the nomogram. And then the nomogram was constructed with independent prognostic factors. The C-index of the nomogram was 0.724, which showed the nomogram provided good discernment. The acceptable agreement between the predictions of nomogram and actual observations was illustrated by calibration plots for 3-, 5- and 10-year OS in the cohort. Time-dependent AUC with 6-fold cross-validation also showed consistent results of the nomogram. Risk group stratification confirmed that the nomogram had great capacity for distinguishing the prognosis.

Conclusion: The nomogram was developed and validated to predict overall survival of resected locally advanced rectal cancer patients with nCRT. The proposed nomogram might help clinicians to develop individualized treatment strategies. However, further studies are warranted to optimize the nomogram by finding out other unknown prognostic factors, and more external validation is still required.

Keywords: rectal cancer, nomogram, overall survival, neoadjuvant chemoradiotherapy

Introduction

Colorectal cancer is one of the most prevalent malignancies through the world.[1] Among the locally advanced rectal cancer, neoadjuvant chemoradiotherapy (nCRT) followed by radical surgery has become the standard treatment.[2–5] Various prognostic factors affect the survival outcomes of rectal cancer patients. The American Joint Committee (AJCC) on Cancer TNM staging system is most commonly used in clinical practice. However, survival heterogeneity is frequently present among

patients with the same AJCC stage,[6] which indicates that TNM staging system is not that perfect for predicting prognosis and clinical management of rectal cancer.[6] A nomogram with a variety of factors is a graphic calculating scale designed to assist in diagnosis or predict the incidence and progression of the disease. A number of nomograms concerning colorectal cancer have been reported, due to the friendly user interface and nice statistical capabilities in predicting individualized outcome.[2,7] Among the nomograms related to rectal cancer with nCRT, few are related to prognosis. In the present study, the nomogram was formulated to provide more individualized prognosis of locally advanced rectal cancer (LARC) with nCRT, which might contribute to process informed management and intelligent decisions for clinicians and patients.

Materials and Methods
Ethics Statement
In this study, all information was retrospectively extracted in the context of compliance with the ethical standards of the institutional and/or national research committees. Patients' medical records were analyzed retrospectively. No individual identifiable information was used. Thus, the Fujian Medical University Union Hospital Ethic Review Board approved this study.

Patient Selection
In this study, all information was obtained from the database of our institution between September 2006 and October 2017. The inclusion criteria were as follows: (a) clinical stage Ⅱ or Ⅲ; (b) age at diagnosis ≥18 years; (c) histologically proven rectal adenocarcinoma; (d) patients who underwent nCRT and surgical resection. The exclusion criteria were as follows: (a) histologically proven signet-ring cell carcinoma or other carcinoma; (b) age at diagnosis < 18 years; (c) previous or concurrent other malignancies; (d) patients with inadequate clinicopathological information. The clinicopathological characteristics include age, gender, levels of carcinoembryonic antigen (CEA), levels of carbohydrate antigen 19–9 (CA19-9), therapeutic measure, pathological tumor-node-metastasis staging (pTNM), clinical tumor-node-metastasis staging (cTNM), the total number of examined lymph node (TLN) and tumour location. The pretreatment parameters were defined as the levels one week before the nCRT, and the posttreatment parameters were

deemed as the levels one week before surgery. Patients were staged on the basis of the AJCC staging eighth edition. Clinical T and N stages were classified on the basis of endoscopic ultrasonography and magnetic resonance imaging. Cancer location was categorized as low (<5 cm from the anorectal verge), middle (5–10 cm from the anorectal verge) or high (10–15 cm from the anorectal verge).[8] The CEA level was categorized as normal (< 5.0 ng/mL) or elevated (≥5.0 ng/mL). The CA19-9 level was categorized as normal (< 37U/mL) or elevated (≥37U/mL).

Neoadjuvant Chemoradiotherapy
All patients received nCRT, and the specific protocol of radiotherapy has been published previously.[9] The neoadjuvant radiotherapy regimen consists of 3-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiation therapy (IMRT). The radiation dose of PTV of CTV was 45 Gy with 25 fractions. The radiation dose of PTV of GTV was 50.4Gy in 28 fractions with 3DCRT or 50 Gy in 25 fractions with IMRT. The chemotherapeutic regimens included Capecitabine, CapeOX, FOLFOX4 and mFOLFOX6. Capecitabine was taken with the dosage of 825mg/m^2 twice daily. And the other specific protocol of chemotherapy has also been reported previously [10] The capecitabine or 5-FU based neoadjuvant chemotherapy was initiated on the first day of radiotherapy.

Surgery
Surgery was carried out by experienced experts from our centre 6–12 weeks after nCRT. The operation was performed followed the tumor-specific mesorectal excision or total mesorectal excision principle, including abdominoperineal resection (APR) and other resection.

Follow-Up
The frequency of regular follow-up was once every three months within the first two years, once every six months in the next three years, and annually thereafter. Follow-ups were either by inpatient department or outpatient department review or by telephone or mail or letter. The last follow-up was completed in December 2019. Overall survival (OS) was defined as the period from the date of diagnosis to death from any cause or the last follow-up. When patients were alive or died without evidence of rectal cancer at the last follow-up, the patients were censored.

Nomogram and Data Analysis

The least absolute shrinkage and selection operator (LASSO) regression algorithm was applied to identify the OS-related characteristics. The 10 folds LASSO regression analysis was performed with the "cv.glmnet" function of R package "glmnet". Where features are selected, the value log (λ) was set using the minimum criteria. These features were selected for the construction of the nomogram. The discrimination of the nomogram was evaluated by concordance index (C-index) and calibration curves. The C-index was calculated. The calibration curves were constructed with a 10-fold cross-validation procedure by using the "calibrate" function of R package "hdnom". The validation of the nomogram was assessed by 6-fold cross-validation with time-dependent area under curve (AUC) with the "validate" function of R package "hdnom". Each characteristic variable was given a point from points scale. Then, the total score was obtained by adding up each variable point. The probability of 3-, 5- and 10-year OS was obtained by locating the total score onto the total points scale. The total score of each patient was obtained by using the "nomogramEx" function of R package "nomogramEx". The best cut-off risk score was calculated by using the "surv_cutpoint" function of R package "survminer". Patients were assigned to the low-risk group and the high-risk group on the basis of the cut-off score. The Kaplan–Meier method was carried out to produce the survival curves of the two different risk groups. Statistical analysis were performed with R software 4.0.1and the SPSS software 25.0 (SPSS Inc, Chicago, Illinois, USA).

Results

Clinical Characteristics

In total, 911 LARC patients with nCRT were enrolled. Among these patients, 595 (65.3%) were male, and 316 (34.7%) were female. The mean age was 55.3 years, 340 (37.3%) patients were 60 years of age or older. The percentage of clinical positive lymph node was 90.1%. The percentage of pretreatment normal CEA and pretreatment CA199 was 56.3% and 86.3%, respectively. One hundred and seventy-eight (19.5%) patients got pCR. Four hundred and twenty (46.1%) patients did not achieve the examination of at least 12 lymph nodes. Median follow-up time was 51.4 months. The more detailed characteristics are shown in Table 1.

Feature Selection and Nomogram Construction for OS

The clinicopathological characteristics include gender, age, cT stage, cN stage, pretreatment CEA, pretreatment CA19-9, cancer location, chemotherapy classification, radiotherapy classification, surgery classification, posttreatment CEA, posttreatment CA19-9, pT stage, pN stage, TLN, adjuvant chemotherapy. These 16 features were considered as potential predictors. LASSO regression algorithm was applied for feature selection. The most appropriate tuning parameter λ for LASSO regression was 0.010, when the partial likelihood binomial deviance reached its minimum value (Figure 1A), 10 variables with nonzero coefficients were retained in the LASSO analysis (Figure 1B). As shown in Figure 2, all selected variables were combined to formulate a nomogram which predicts the 3-, 5- and 10-year OS. The nomogram illustrated that pN classification, pT classification and posttreatment CA199 contributed the most to prognosis. Each subtype of these variables was assigned a score on the point scale. The survival probability of the individual patients was predicted though the score addition of all the selected variables.

Validation of the Nomogram

The C-index of the nomogram was 0.724 (95% CI, 0.683–0.765), which showed the nomogram provided good discernment. Additionally, the acceptable agreement between the predictions of nomogram and actual observations was illustrated by calibration plots for 3-, 5- and 10-year OS (Figure 3A–C). Moreover, time-dependent AUC with 6-fold cross-validation also showed consistent results (Figure 3D). These results indicated that the nomogram had proper calibration.

Performance of the Nomogram in Risk Stratification of Patients

The patients respective risk scores were calculated through the nomogram. The optimal cut-off total score was 194.9513. Then, all patients were assigned to the low-risk group and the high-risk group on the basis of the cut-off score. As shown in Figure 4, overall survival of the low-risk group and the high-risk group is different (P-value <0.0001).

Discussion

At present, neoadjuvant chemoradiotherapy is the standard treatment for LARC patients. However, individualized

Table 1 Baseline Characteristics of Rectal Cancer Patients

All Patients (n)	911
Gender (n (%))	
Female	316 (34.7)
Male	595 (65.3)
Age (years) (mean (SD))	55.30 (11.33)
Age (n (%))	
<60 years	571 (62.7)
≥60 years	340 (37.3)
cT classification (n (%))	
cT2	48 (5.3)
cT3	338 (37.1)
cT4	525 (57.6)
cN classification (n (%))	
Negative	90 (9.9)
Positive	821 (90.1)
Pretreatment CEA (n (%))	
Normal	513 (56.3)
Elevated	398 (43.7)
Pretreatment CA199 (n (%))	
Normal	786 (86.3)
Elevated	125 (13.7)
Location (n (%))	
Low	376 (41.3)
Middle	464 (50.9)
High	71 (7.8)
Chemotherapy (n (%))	
CapeOx	232 (25.5)
Capecitabine	524 (57.5)
5-Fu based	155 (17.0)
Radiotherapy (n (%))	
3DRT	292 (32.1)
IMRT	619 (67.9)
Surgery (n (%))	
NO APR	813 (89.2)
APR	98 (10.8)
TLN (n (%))	
<12	420(46.1)
≥12	491(53.9)
Posttreatment CEA (n (%))	
Normal	781 (85.7)
Elevated	130 (14.3)
Posttreatment CA199 (n (%))	
Normal	860 (94.4)
Elevated	51 (5.6)

(*Continued*)

Table 1 (Continued).

| All Patients (n)	911
pT classification (n (%))	
pT0	187 (20.5)
pT1	55 (6.0)
pT2	235 (25.8)
pT3	377 (41.4)
pT4	57 (6.3)
pN classification (n (%))	
pN0	665 (73.0)
pN1	184 (20.2)
pN2	62 (6.8)
pCR (n (%))	
NO	733(80.5)
YES	178(19.5)
Adjuvant chemotherapy (n (%))	
NO	198 (21.7)
YES	713 (78.3)
Status (n (%))	
Censored	736 (80.8)
Death	175 (19.2)
Follow-up time (months, median(IQR))	51.4(37.7, 71.5)

Abbreviations: 3DRT, 3-dimensional conformal radiotherapy; IMRT, intensity-modulated radiation therapy; APR, abdominoperineal resection; TLN, the total number of examined lymph node; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19–9; IQR, interquartile range.

treatment may offer improved OS in high-risk rectal cancer patients. Thus, it is crucial to determine the proper prognostic factors. Currently, the TNM staging system is usually used to predict the individual survival of rectal cancer.[11] However, there are still limitations in the accuracy of the TNM staging system. This study attempts to construct and validate a model to predict the prognosis of LARC patients who underwent nCRT.

Several studies identified CEA as a significant factor for predicting tumor response following nCRT and outcomes of rectal cancer.[12–16] In this study, pretreatment CEA and posttreatment CEA were proved to be both of those prognostic factors. Pretreatment CEA also was a predictor for pCR (Figure S1). Multiple scholars reported that CA19-9 was good predictor of response to nCRT and survival after curative surgery of rectal cancer.[10,17–19] This study also showed pretreatment CA19-9 and posttreatment CA199 were prognostic factors for overall survival of LARC patients with nCRT.
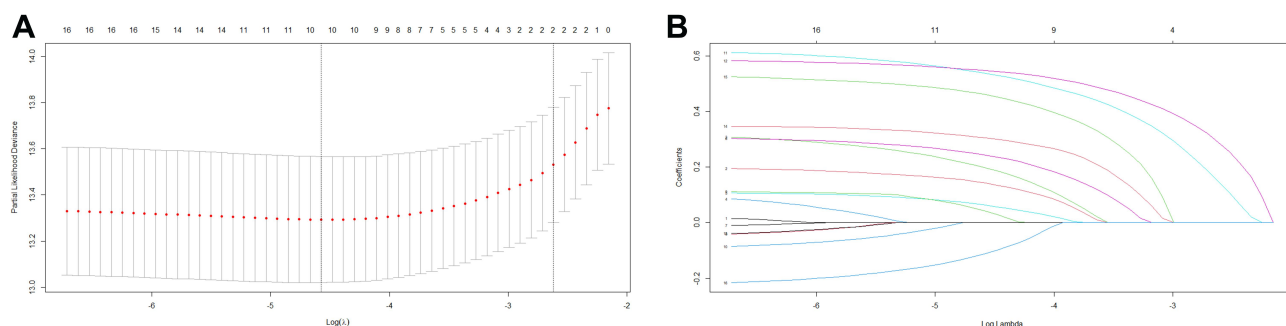
Figure 1 Feature selection. Selection of tuning parameter (λ) in the LASSO regression (**A**), LASSO coefficient profiles for clinical features (**B**).
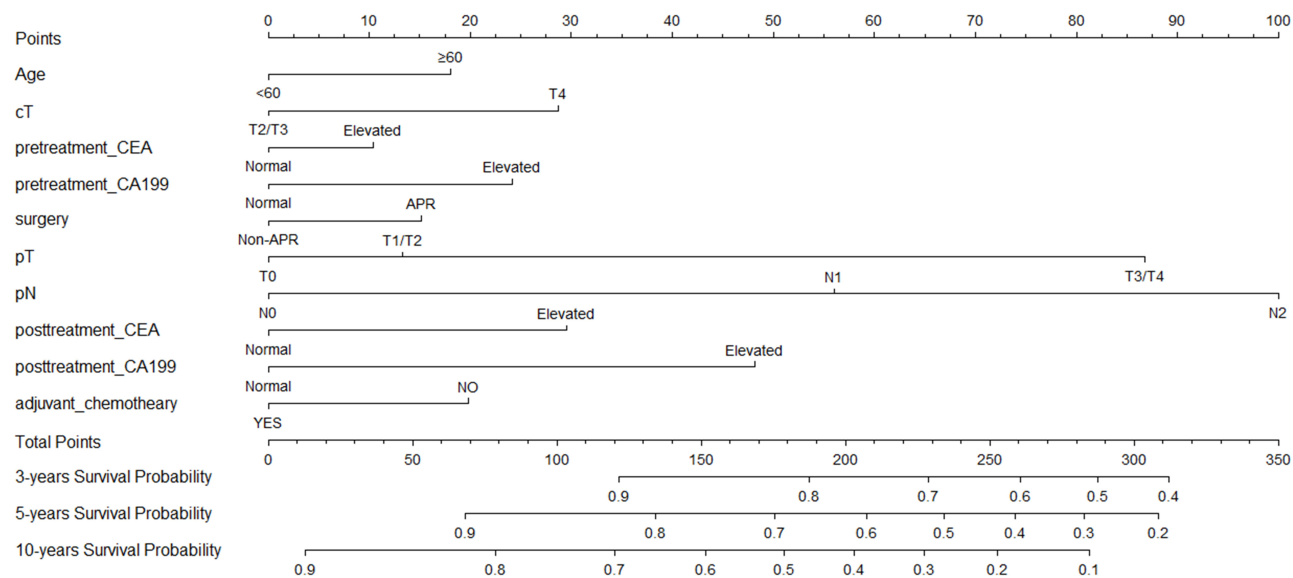

Figure 2 Nomogram for predicting 3-, 5-, and 10-year OS probabilities of rectal cancer patients. Draw a vertical straight line from the variable value to the axis labeled "Points". Then calculate all variables' points. The total points on the bottom scales that correspond to the 3-, 5-, and 10-year OS were showed apparently.

Some studies demonstrated that neoadjuvant chemoradiotherapy have decreased lymph node yield.[20–22] Miller, E. D. et al showed that the decrease ranged from 7% to 53% in patients with nCRT.[20] In Mechera, R. study, compared with patients without neoadjuvant treatment, patients who underwent nCRT yield 3.9 less lymph nodes.[21] Ha, Y. H. et al showed that nCRT decreased retrieved lymph nodes count by approximately 33%.[22] The minimum 12 lymph nodes examination was recommended by the College of American pathologists (CAP) and AJCC for accurate stages of rectal cancer.[23–25] However, patients who received neoadjuvant treatment did not always achieve the examination of at least 12 lymph nodes.[26–28] Xu, Z. et al showed that 36.8% of patients who underwent neoadjuvant treatment did not achieve 12 lymph nodes examined.[26] Damin, D. C. et al showed that 29.6% of patients with nCRT achieved fewer than 12 lymph nodes.[27] Baxter,

N. N. et al showed only 20% of patients treated with neoadjuvant therapy had at least 12 nodes sampling.[28] In the study, 46.1% of patients did not achieve 12 lymph nodes examined. There were controversies about the impact of retrieved node counts on outcome of rectal cancer patients with nCRT. Ceelen, W.et al showed that per node examined got 2.7% decrease of hazard of death of in patients with surgery alone, no effect in patients with nCRT.[29] Bhangu, A.et al showed that total lymph node yield was associated with overall survival in stage Ⅰ and Ⅱ rectal cancer, did not correlate with survival of stage Ⅲ patients.[30] Sun, Y.et al showed that negative lymph nodes count was associated with disease-free survival in ypN+ patients with nCRT.[31] Hall, M. D. et al showed that examination of 8 or more LNs had better OS.[32] Kim, H. J. et al showed that reduced lymph node yield after nCRT does not indicate inadequate oncologic surgery.[33] Among patients with a good tumor
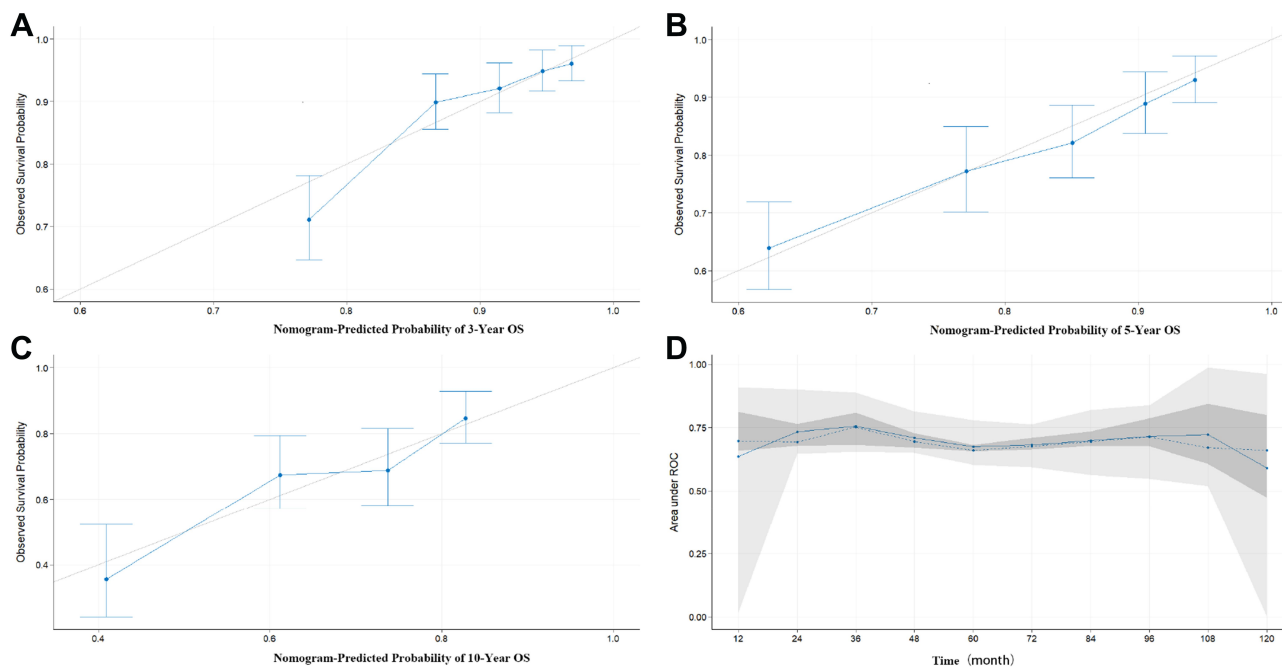
Figure 3 Calibration curves and time-dependent AUC. Calibration curves for predicting 3-, 5-, and 10-year OS (**A, B, C**). Time-dependent AUC with 6-fold cross-validation (**D**).
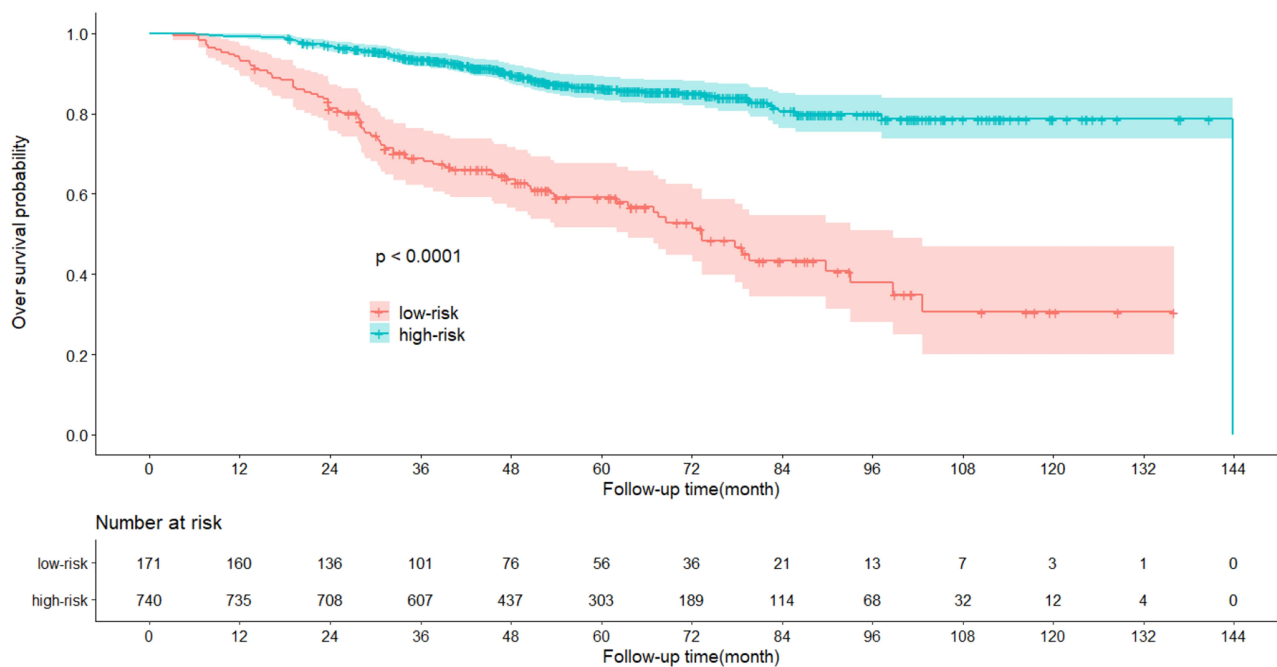
Figure 4 Kaplan–Meier curves of OS for patients in high-risk and low-risk groups.

response, patients with fewer than 12 lymph nodes got better 3-year disease-free survival.[33] On the basis of CAP and AJCC, the cut-off of TLN still was 12 in the study. However, the present study showed TLN was not significant with the survival.

Nomograms with a graphical presentation of statistical prediction models are widely used as prognostic facilities in oncology and medicine.[34] In the present study, ten characteristics were selected by LASSO regression analysis. The clinical prognostic indicators including CEA and

CA199 were incorporated to set up the novel nomogram with better OS prediction for LARC patients. Clinical factors were applied for the nomogram, because of their widely and easily accessible. The nomogram was successfully set up to predict 3-, 5- and 10-year OS of LARC patients with nCRT. The nomogram illustrated that pT classification and pN classification contributes most to prognosis. The C-index was 0.724, revealing the nomogram provided good discernment. Validation is a basic procedure in nomogram studies, which might avoid poor goodness-of-fit and assess the generalizability of the nomogram.[35] In our study, the calibration curves of the 3-, 5- and 10-year survival fraction were executed. The calibration curves reveal favorable agreement between the predicted and actual observed probabilities. The calibration curve ensured the repeatability as well as the reliability of the constructed nomogram. The individual survival probability was conveniently calculated by clinicians and patients via this point-based nomogram. According to the total scores and the defined cut-off value, LARC patients with nCRT were stratified into high-risk and low-risk groups. The survival of these two groups was significantly different, which confirmed that the nomogram had a decent discriminatory capacity of the prognosis of patients and satisfactory predictive performance.

The nomogram was successfully constructed. And the nomogram was also validated to calculate the individual prognosis probability for LARC patients with nCRT. However, the study did have several limitations. Firstly, the study has selection bias because of retrospective nature of the analysis, in which some factors associated with survival were unavailable, such as smoking status, genetic alterations, lymphovascular invasion and so on. Secondly, due to the data are relatively small and from a single institution, these are some restriction on the applicable scope and generalizability of the nomogram. Thirdly, the nomogram is based on the experience of our single institution. It is necessary for more other institution external validations.

Conclusion

The nomogram is developed and validated to predict overall survival of resected LARC patients with nCRT. The proposed nomogram may help clinicians to perform individual treatment. Due to the limitations of the study, it is absolutely essential to further seek the unknown prognostic factors to optimize the model, and it is necessary for more other institution external validations.

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Disclosure

The authors have no conflicts of interest to declare.

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