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Original Article

A nomogram based on the log odds of positive lymph nodes for predicting the prognosis of T1 stage rectal cancer

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Abstract: Early detection and timely treatment is the key to improving the prognosis of rectal cancer. Lymph node metastasis is one of the reasons for the poor prognosis of rectal cancer, especially early-stage rectal cancer. In this study, we developed a nomogram based on log odds of positive lymph nodes (LODDS) to predict cancer-specific survival (CSS) in patients with T1 rectal cancer. We included 1934 patients from the Surveillance, Epidemiology, and End Results (SEER) database and divided them into a training cohort and an in-validation cohort. 140 patients from our hospital formed the ex-validation cohort. Multivariate Cox regression analysis indicated that age, sex, grade, and M stage were independent prognostic factors for CSS. LODDS showed better predictive ability than the N stage and PLNs (positive lymph nodes) and was further selected as an independent prognostic factor for the construction of the nomogram. The C-index of the nomogram was 0.743, 0.756, and 0.876 in the training, in-validation, and ex-validation cohorts, respectively. The AUC values of the three cohorts were 0.750, 0.703, and 0.958 at 3 years and 0.731, 0.678, and 0.783 at 5 years. The calibration curves and DCA demonstrated the nomogram's excellent performance. In conclusion, we developed and validated a new nomogram based on LODDS that can effectively predict CSS at 3 and 5 years for patients with T1 rectal cancer.

Keywords: Rectal cancer, nomogram, prognosis, cancer-specific survival, LODDS

Introduction

With an estimated 1.9 million new cases and 935,000 deaths worldwide in 2020, colorectal cancer ranks the third most frequent cancer and the second leading cause of cancer death, representing about one in 10 cancer cases and deaths [1]. In recent years, colorectal cancer incidence has stabilized and declined slightly in high-income countries due to increased endoscopic screening and population-level changes toward healthier lifestyle choices. However, in developing countries, the incidence continues to increase and may reach 2.5 million by 2035 [2].

Rectal cancer accounts for about 40% of colorectal cancer and is associated with worse clinical outcome [3, 4]. The incidence of early-stage rectal cancers has increased due to the extensive population screening and advances in rectal cancer diagnosis [5]. The evaluation of lymph nodes in rectal cancer is critical, as it determines staging, prognosis, and treatment strategy, especially for early rectal cancer [5, 6]. Currently, the N staging system from the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) classification is the most broadly used lymph node staging system, which is based on the number of PLNs [7, 8]. However, for accurate nodal staging, the number of lymph nodes examined is clinically important, and inadequate lymph node assessment may result in understaging [9]. The lymph node ratio (LNR) is defined as the ratio of the number of PLNs to the total number of examined lymph nodes, which has been regarded as a sensitive prognostic factor in rectal cancer

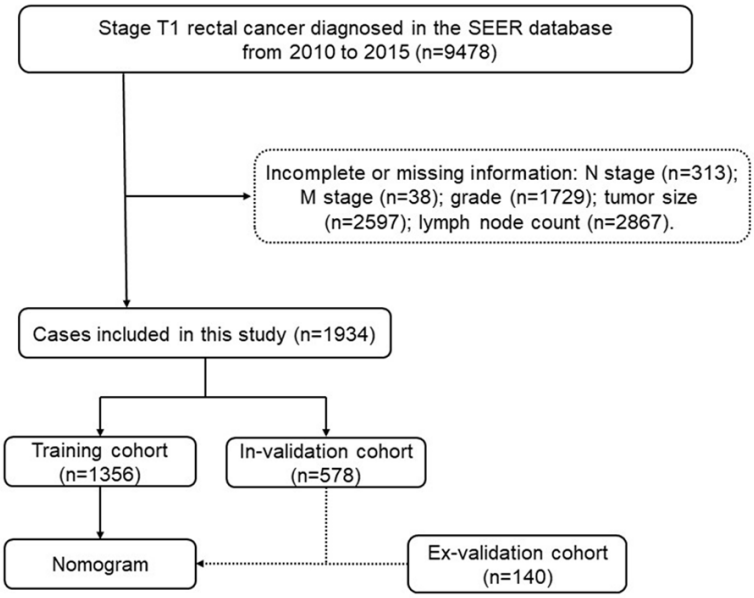

Figure 1. Flowchart for selection of T1 stage rectal cancer.

[10, 11]. But when LNR is close to 0 or 1, it cannot precisely predict the prognosis of cancer patients [12].

LODDS, the logarithm of the ratio between the number of PLNs and the negative lymph nodes, has been recently introduced as a valuable tool for predicting the prognosis of cancer patients. LODDS combines the number of PLNs and negative lymph nodes, which may make it a more precise predictor of cancer patients. Recently, several studies have demonstrated that LODDS is preferable to the LNR for predicting the prognosis of rectal cancer [12, 13]. Nevertheless, the prognostic value of LODDS in early rectal cancer remains elusive. Therefore, we focused on the correlation between LODDS and prognosis in T1 rectal cancer, aiming to construct a nomogram including LODDS to help clinicians identify high-risk patients early.

Materials and methods

Patient cohorts

All the patients diagnosed with rectal cancer from 2010 to 2015 were extracted from SEER*Stat software (version 8.4.0). Clinical variables were also downloaded, including age, gender, tumor size, tumor grade, the number of PLNs and the biopsied lymph nodes, TNM stage (AJCC 7th edition), and treatment methods. The data extraction process was free from medical ethics review and did not require informed consent. The following inclusion criteria were applied: (1) rectal cancer is the only malignant tumor; (2) diagnosed as T1 stage rectal cancer. The exclusion criteria were as follows: incomplete demographic information and pathological information including N stage (n=313), M stage (n=38), tumor grade (n=1729), tumor size (n=2597), and the number of lymph nodes (n=2867). The complete data screening process was shown in **Figure 1**.

Using the same inclusion and exclusion criteria as the training cohort, we enrolled 140 patients with T1 rectal cancer between 2010 and 2019 from the First Affiliated Hospital of Nanchang University as the ex-validation cohort. The study was approved by the ethics committee of the hospital, and all patients signed informed consent.

The LODDS system

$$LODDS = \log\frac{\text{the number of PLNs} + 0.05}{\text{the number of negative lymph nodes} + 0.05},$$

0.05 was added to both the denominator and numerator to avoid the singularity. The number of negative lymph nodes was the total number of lymph nodes examined minus the number of positive lymph nodes. The definition of LODDS was based on the previous research [14], which took into account both the number of PLNs and the number of lymph nodes examined.

Prognostic factors and nomogram

Firstly, we analyzed all included variables using univariate Cox regression analysis, and the variables with $P<0.05$ were regarded as prognostic factors associated with CSS. Then, three multivariate Cox models, model1 (LODDS), model2 (N stage), and model3 (PLNs), were constructed by incorporating lymph node-related indicators separately. The C-index and AUC values were utilized to assess the predictive performance of the models. Next, the model

Table 1. Demographic and clinicopathological characteristics of the training, in-validation, and ex-validation cohorts

Variable	Total cohort (n=2074)	Training cohort (n=1356)	In-validation cohort (n=578)	Ex-validation cohort (n=140)
	N (%)	N (%)	N (%)	N (%)
Age				
<60	921 (44.4%)	615 (45.4%)	241 (41.7%)	65 (46.4%)
60-73	815 (39.3%)	534 (39.4%)	222 (38.4%)	59 (42.1%)
>73	338 (16.3%)	207 (15.3%)	115 (19.9%)	16 (11.4%)
Sex				
Female	877 (42.3%)	578 (42.6%)	239 (41.3%)	60 (42.9%)
Male	1197 (57.7%)	778 (57.4%)	339 (58.7%)	80 (57.1%)
Tumor size				
<25	1307 (63.0%)	869 (64.1%)	378 (65.4%)	60 (42.9%)
25-48	551 (26.6%)	347 (25.6%)	141 (24.4%)	63 (45.0%)
>48	216 (10.4%)	140 (10.3%)	59 (10.2%)	17 (12.1%)
Grade				
I	255 (12.3%)	162 (11.9%)	85 (14.7%)	8 (5.71%)
II	1635 (78.8%)	1079 (79.6%)	439 (76.0%)	117 (83.6%)
III	154 (7.43%)	97 (7.15%)	46 (7.96%)	11 (7.86%)
IV	30 (1.45%)	18 (1.33%)	8 (1.38%)	4 (2.86%)
PLN				
<1	1747 (84.2%)	1137 (83.8%)	493 (85.3%)	117 (83.6%)
≥1	327 (15.8%)	219 (16.2%)	85 (14.7%)	23 (16.4%)
LODDS				
<-1.0	1373 (66.2%)	881 (65.0%)	371 (64.2%)	121 (86.4%)
-1.0~0.02	530 (25.6%)	357 (26.3%)	155 (26.8%)	18 (12.9%)
>0.02	171 (8.24%)	118 (8.70%)	52 (9.00%)	1 (0.71%)
N Stage				
N0	1699 (81.9%)	1102 (81.3%)	479 (82.9%)	118 (84.3%)
N1	324 (15.6%)	222 (16.4%)	86 (14.9%)	16 (11.4%)
N2	51 (2.46%)	32 (2.36%)	13 (2.25%)	6 (4.29%)
M Stage				
M0	2034 (98.1%)	1324 (97.6%)	571 (98.8%)	139 (99.3%)
M1	40 (1.93%)	32 (2.36%)	7 (1.21%)	1 (0.71%)
Chemotherapy				
No/unknown	1528 (73.7%)	966 (71.2%)	432 (74.7%)	130 (92.9%)
Yes	546 (26.3%)	390 (28.8%)	146 (25.3%)	10 (7.14%)
Radiotherapy				
No/unknown	1626 (78.4%)	1035 (76.3%)	454 (78.5%)	137 (97.9%)
Yes	448 (21.6%)	321 (23.7%)	124 (21.5%)	3 (2.14%)

with the best predictive performance was used to construct the nomogram. In this study, the training cohort was used for nomogram construction, and the in-validation cohort and the ex-validation cohort were used for nomogram validation.

Statistical analysis

R software (version 4.2.0), X-tile software (Yale University, New Haven, USA, version 3.6.1), and SPSS (version 26.0) were used for statistical analysis. Baseline characteristics of the includ-

Table 2. Univariate Cox proportional hazards regression analysis of T1 rectal cancer prognosis in the training cohort

Variable	Univariate analysis		
	HR	95% CI	*P*-value
Age			
<60	Ref		
60-73	1.727	1.135-2.629	<0.011*
>73	3.675	2.320-5.821	<0.001*
Sex			
Female	Ref		
Male	1.541	1.066-2.227	0.022*
Tumor size			
<25	Ref		
25-48	0.999	0.650-1.536	0.996
>48	2.1074	1.329-3.343	0.002*
Grade			
I	Ref		
II	1.6994	1.045-2.764	0.444
III	1.869	0.460-7.599	0.382
IV	2.1641	1.287-3.640	0.004*
PLNs			
<1	Ref		
≥1	2.593	1.786-3.765	<0.001*
LODDS			
<-1.0	Ref		
-1.0~0.02	0.980	0.628-1.529	0.928
>0.02	3.388	2.206-5.202	<0.001*
N Stage			
N0	Ref		
N1	2.510	1.704-3.696	<0.001*
N2	3.989	2.001-7.951	<0.001*
M Stage			
M0	Ref		
M1	9.24	5.594-15.26	<0.001*
Chemotherapy			
No/unknown	Ref		
Yes	2.148	1.514-3.048	<0.001*
Radiotherapy			
No/unknown	Ref		
Yes	1.475	1.016-2.142	0.041*

*: statistical difference.

ed population were depicted as numbers and percentages (n, %). Nomogram, as a widely used visualization tool, can be used to predict individual survival by incorporating variables. In this study, the nomogram was constructed using the "rms" R package, C-index and AUC values of ROC curves were performed to evaluate the accuracy of the nomogram. The calibration curves, with the Hosmer-Lemeshow test, were used to assess the agreement between the predicted survival and the actual survival. DCA was conducted to determine the clinical usefulness of the nomogram by quantifying the net benefits at different threshold probabilities. The Kaplan-Meier method and the log-rank test were used to construct and compare the survival curves, respectively. *P*-values of <0.05 were considered significant in this study.

Results

Demographic and clinical characteristics

According to the inclusion and exclusion criteria, 1934 patients diagnosed with T1 rectal cancer in the SEER database were included and randomly divided into a training cohort and an in-validation cohort in a ratio of 7:3. Another 140 patients from our hospital were included as the ex-validation cohort. Demographic and clinicopathological characteristics of the training and validation cohorts were shown in **Table 1**. For subsequent analysis, the X-tile software was performed to calculate the optimal cut-off values for continuous variables such as age, tumor size, PLNs, and LODDS, which were 60 and 73 years, 25 mm and 48 mm, 1, and 0.02 and -1.0, respectively.

In the total cohort, the vast majority of T1 rectal cancer patients were younger than 73 years old (83.7%), and more than half of the patients were male (57.7%). In addition, the patients with tumor size less than 25 mm (63.0%), grade II (78.8%), N0 stage (81.9%), and M0 stage (98.1%) accounted for a higher proportion. In terms of treatment, 26.3% of patients received chemotherapy and 21.6% received radiotherapy.

Identifying independent prognostic factors

According to the result of univariate Cox regression analysis, variables, including age, sex, tumor size, grade, PLNs, LODDS, N stage, M stage, chemotherapy, and radiotherapy were significantly correlated with CSS in patients with T1 rectal cancer (P<0.05) (**Table 2**). Based on the PLNs, LODDS, and N stage, we performed three multivariate Cox regression analysis, respectively (**Table 3**). The comparison of

Table 3. Multivariate Cox regression analysis for CSS in the training cohort (N=1356)

Variable	Model1 (LODDS)		Model2 (N stage)		Model3 (PLNs)	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age						
<60	Ref		Ref		Ref	
60-73	1.922 (1.249-2.956)	<0.001*	1.908 (1.243-2.929)	0.003*	1.925 (1.253-2.959)	0.002*
>73	4.480 (2.794-7.182)	<0.001*	4.539 (2.838-7.258)	<0.001*	4.659 (2.907-7.465)	<0.001*
Sex						
Female	Ref		Ref		Ref	
Male	1.606 (1.106-2.332)	0.013*	1.732 (1.189-2.523)	0.004*	1.704 (1.173-2.475)	0.005*
Tumor size						
<25	Ref		Ref		Ref	
25-48	0.942 (0.610-1.455)	0.789	0.959 (0.621-1.481)	0.850	0.963 (0.624-1.488)	0.867
>48	1.466 (0.874-2.461)	0.148	1.342 (0.794-2.269)	0.272	1.466 (0.871-2.466)	0.149
Grade						
I	Ref		Ref		Ref	
II	1.646 (1.004-2.701)	0.048*	1.570 (0.972-2.623)	0.064	1.651 (1.006-2.711)	0.047*
III	1.727 (0.450-6.939)	0.052	1.758 (1.028-3.004)	0.039*	1.738 (1.017-2.973)	0.043*
IV	1.741 (1.020-2.974)	0.042*	1.768 (0.430-7.268)	0.430	1.782 (0.435-7.308)	0.422
M Stage						
M0	Ref		Ref		Ref	
M1	5.573 (3.032-10.242)	<0.001*	5.230 (2.858-9.828)	<0.001*	5.900 (3.194-10.899)	<0.001*
Chemotherapy						
No/unknown	Ref		Ref		Ref	
Yes	1.514 (0.819-2.798)	0.186	1.329 (0.699-2.527)	0.385	1.258 (0.660-2.396)	0.486
Radiotherapy						
No/unknown	Ref		Ref		Ref	
Yes	0.814 (0.459-1.443)	0.481	0.865 (0.499-1.501)	0.607	0.966 (0.549-1.700)	0.905
LODDS						
<-1.0	Ref					
-1.0~0.02	0.980 (0.617-1.558)	0.933				
>0.02	2.263 (1.364-3.754)	0.002*				
N Stage						
N0			Ref			
N1			1.891 (1.140-3.135)	0.013*		
N2			2.412 (1.093-5.321)	0.029*		
PLNs						
<1					Ref	
≥1					2.035 (1.268-3.267)	0.003*

*: statistical difference.

the multivariate Cox regression analysis showed that model1 (LODDS) had the best predictive performance (C-index: 0.743, 3-year AUC: 0.750, 5-year AUC: 0.731) (**Table 4**). Therefore, the LODDS combined with age, sex, grade, and M stage were selected as the independent prognostic factors.

Development and validation of nomogram

Independent prognostic factors from multivariate Cox regression analysis were selected for the construction of a simple-to-use nomogram (**Figure 2**). After the nomogram was successfully constructed, we predicted the 3- and 5-year survival probabilities of patients with T1 rectal cancer by calculating the total score of each variable (Supplementary Table 1). From the nomogram, M stage and age showed a greater contribution to the prognosis.

The C-index was 0.743 in the training cohort, 0.756 and 0.876 in the in-validation cohort and ex-validation cohort, respectively. Next, the

Table 4. Predictive performance of different Cox models in the training cohort

Model	C-index (95% CI)	AUC	
		3-year CSS	5-year CSS
Model1 (LODDS)	0.743 (0.700-0.786)	0.750	0.731
Model2 (N stage)	0.741 (0.699-0.784)	0.749	0.727
Model3 (PLNs)	0.738 (0.696-0.782)	0.743	0.724

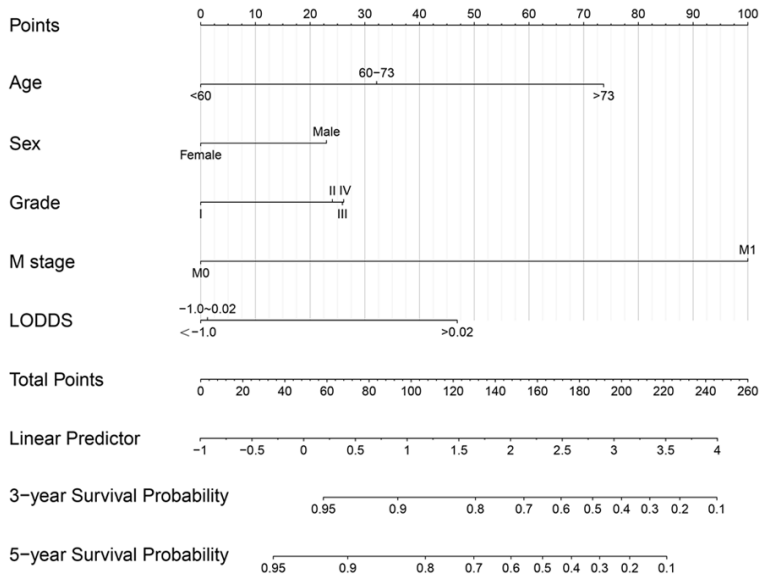

Figure 2. Nomogram for predicting the 3- and 5-year CSS of T1 stage rectal cancer.

ROC curves were performed to identify the accurate predictability for 3-year and 5-year CSS. And the AUC values were 0.750 and 0.731 for the training cohort (**Figure 3A**, **3B**), 0.703 and 0.678 for the in-validation cohort (**Figure 3C**, **3D**), and 0.958 and 0.783 for the ex-validation cohort (**Figure 3E**, **3F**), respectively. Furthermore, calibration curves for 3-year and 5-year CSS probabilities showed good agreement between the predicted and actual probabilities in both training and validation cohorts (Supplementary Figure 1), demonstrating the nomogram's reliability.

Next, to further verify the predictive performance and clinical applicability of the nomogram, we compared the nomogram with AJCC_stage using ROC and DCA, respectively. The ROC results demonstrated that the nomogram had superior CSS predictive ability over AJCC_stage in both the training cohort and validation cohort (**Figure 3**). Moreover, DCA results showed a higher net benefit for nomogram at most risk thresholds, suggesting that nomogram had excellent clinical applicability (Supplementary Figure 2).

Survival analysis

To further explore the relationship between the nomogram prognostic model and patient survival, we calculated the scores for each patient and divided them into a high-risk group and a low-risk group according to the median score of 56, and the K-M survival curves showed that high-risk patients have lower survival probability than low-risk patients. Moreover, the same median score was applied in the validation cohort, and the results of K-M survival curves were the same as the training cohort (**Figure 4**, $P<0.05$). In addition, we also stratified the variables and detected the difference in survival probability between different subgroups of the same variable included in the nomogram, and we found that age, sex, grade, M stage, and LODDS all showed significant statistical differences in the K-M analysis (Supplementary Figure 3, $P<0.05$), moreover, patients with older age, male, poorer differentiation, metastasis, and higher LODDS scores had lower survival probability.

Discussion

With the popularization of colonoscopy screening, the incidence of early-stage rectal cancer (T1/T2) has increased. Results from population screening in the UK demonstrate an increase of stage I rectal cancers from approximately 25% to 50% for screen-detected carcinomas [15]. For rectal cancer patients, the presence of lymph node metastasis is related to poor prognosis and determines the need for adjuvant therapy [5, 16]. Clinically, lymph node metastasis is not uncommon in early colorectal cancer,

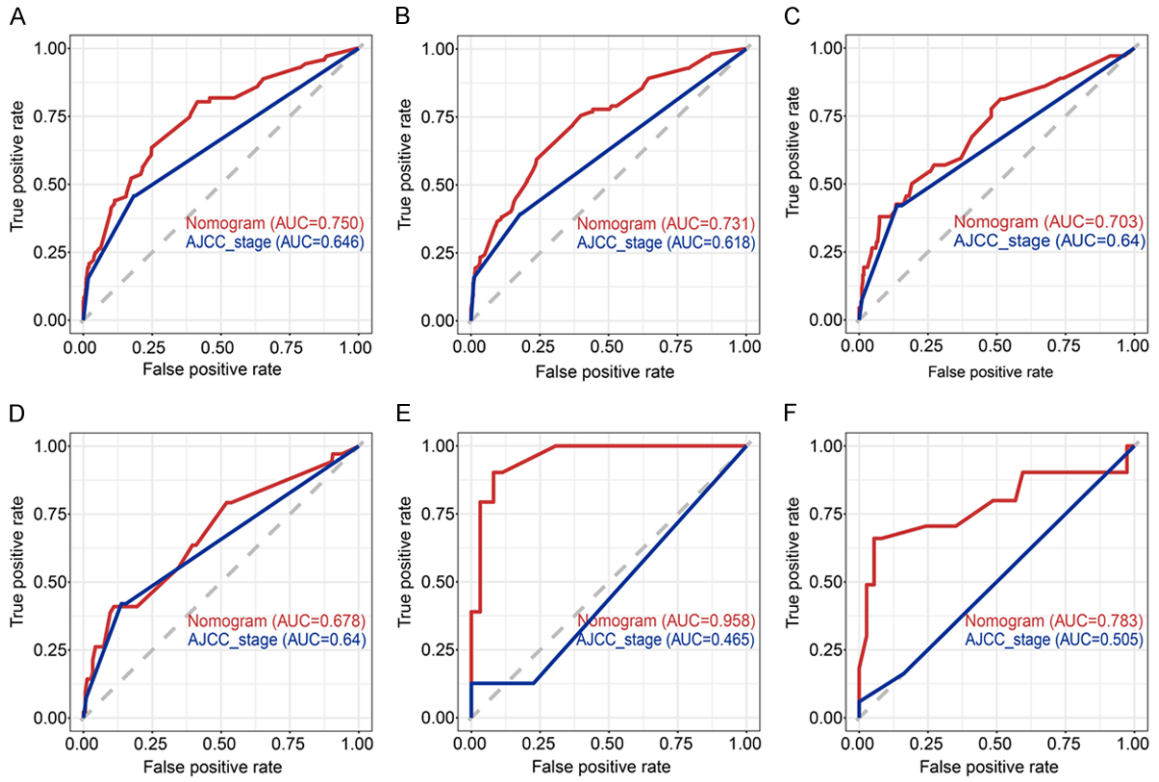

Figure 3. Comparison of the AUC values of the nomogram with the AJCC_stage. In the training cohort and validation cohort, the 3- and 5-year AUC values of nomogram are higher than those of AJCC_stage.

with 10-20% of T1 tumors and up to 23% of T2 tumors having LNRs [5].

At present, the N staging proposed by AJCC-TNM classification is widely applied to assess the status of the lymph node. As we all know, the N staging is influenced by the number of total examined lymph nodes, and previous studies had demonstrated that LNR is superior to N staging for predicting the prognosis of rectal cancer patients. However, the prognosis of patients with four positive lymph nodes out of four lymph nodes harvested is markedly different from patients with 20 positive lymph nodes out of 20 lymph nodes harvested. Many clinicians suggested that LNR could not accurately evaluate the prognosis of rectal cancer when LNR=1. In contrast, LODDS, a novel lymph node metastasis-related indicator for predicting cancer prognosis, is better than LNR in the prognosis of node-positive rectal cancer [17].

Currently, the main treatment options for early-stage rectal cancer include radical surgery and local excision. Compared to local excision, radical surgery, which is currently standard of care, has a relatively low recurrence rate, but it is also associated with significant negative effects on functional outcomes and quality of life, such as sexual dysfunction and urinary disturbances [18]. Local excision is sufficient for low-risk early-stage rectal cancer; however, the treatment of high-risk early-stage rectal cancer is still controversial. High-risk rectal cancer may be defined as high histological grade, Sm3 and possibly Sm2 depth of invasion, the presence of lymphatic or vascular invasion [19]. As we all know, chemoradiotherapy is an adjuvant treatment modality for cancer therapy, but previous studies had shown that preoperative treatment of T1 rectal cancer patients has no significant correlation with prognosis [20]. Additionally, in a large population-based study in the Netherlands, patients with early-stage rectal cancer without lymph node involvement did not benefit from short-course radiotherapy, whereas surgery alone had gradually become the standard treatment [21, 22]. In our study, we also found that chemoradiotherapy was not

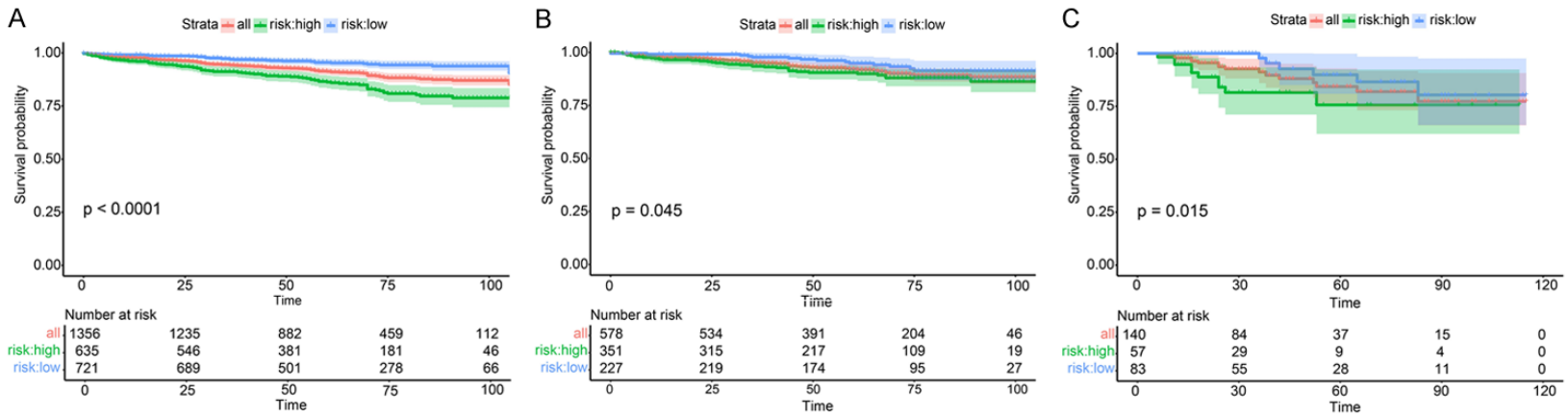

Figure 4. Kaplan-Meier curves of CSS for risk stratification in the training cohort (A), the in-validation cohort (B), and the ex-validation cohort (C).

an independent prognostic factor for patients with T1 rectal cancer. However, there was increasing evidence that some patients with early-stage rectal cancer may benefit from adjuvant chemoradiotherapy combined with local resection. Al-Sawat et al. showed that compared to radical surgery, local excision supplemented with adjuvant therapy significantly reduced the risk of complications and anastomosis formation in patients with high-risk T1 rectal cancer, although there was no significant difference in OS and disease-free survival between the two surgical methods [18, 23]. Therefore, the treatment of patients with early-stage rectal cancer should be considered comprehensively and an individualized treatment plan should be developed.

In a study of middle-aged and elderly patients with rectal cancer, age, race, grade, tumor size, and CEA were prognostic indicators, and the results were similar to those of this study [24]. Here, we constructed a nomogram including age, grade, sex, LODDS, and M stage to predict the survival probability of patients with T1 rectal cancer. Among these variables, age over 60 years, poor differentiation grade, male, higher LODDS scores, and distant metastasis could significantly reduce the survival probability of patients with T1 rectal cancer. Moreover, the higher LODDS scores mean poorer prognosis, which was consistent with previous studies on colorectal cancer [25, 26]. Furthermore, the 3-year and 5-year calibration curves basically coincided with the 45° dashed line in both the training and validation cohorts, indicating that the nomogram had good predictive accuracy and stability. Finally, The comparison of nomogram model with AJCC_stage also showed that nomogram had the excellent predictive ability and clinical applicability.

There are inevitably some limitations in our retrospective study. For example, in previous studies, tumor markers such as CEA and CA199 can well predict the risk of cancer and metastasis, but the SEER database did not contain such information. In the treatment mode, we only know whether the patient has received chemoradiotherapy or not, but can not obtain the specific chemotherapy drugs and radiotherapy dosage. Meanwhile, the patient's specific surgical procedure is not known, so we cannot compare the differences in patient prognosis between the various surgical procedures. Additionally, we excluded some patients with missing lymph nodes, which may cause selective deviation to some extent. Although we used clinical data from our research center for external validation of the model, a large number of prospective clinical trials are needed to further validate its clinical applicability.

Conclusions

Based on the new prognostic factor, LODDS, we constructed a simple nomogram to predict the CSS of T1 rectal cancer patients. Validation of the nomogram showed excellent predictive performance. We expect the nomogram will be helpful for clinicians to accurately predict the prognosis of patients and provide individualized treatment recommendations.

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Disclosure of conflict of interest

None.

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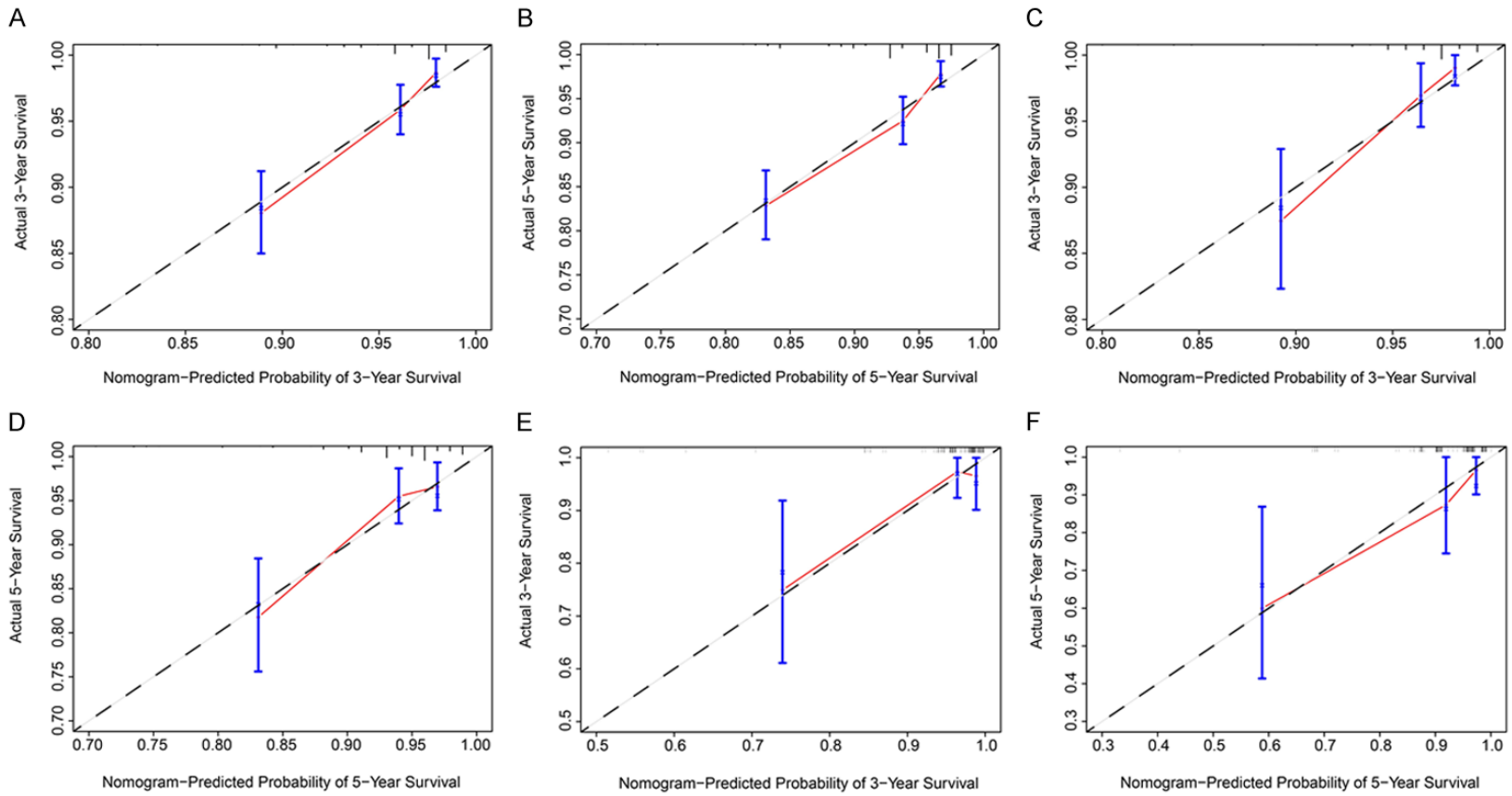
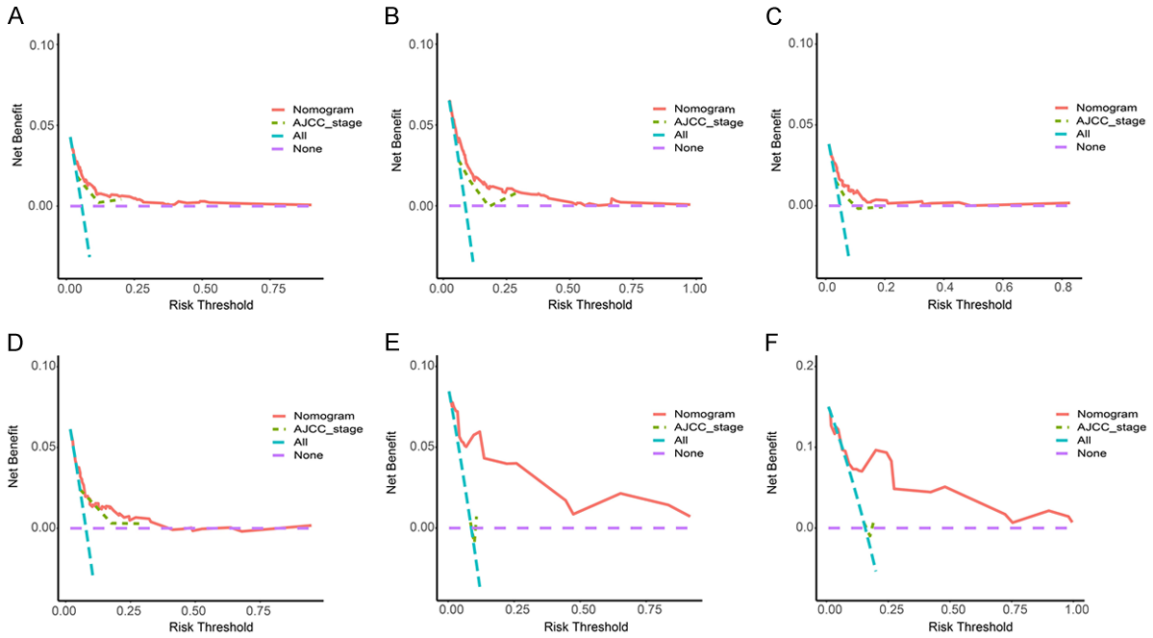
Supplementary Table 1. Nomogram scoring system

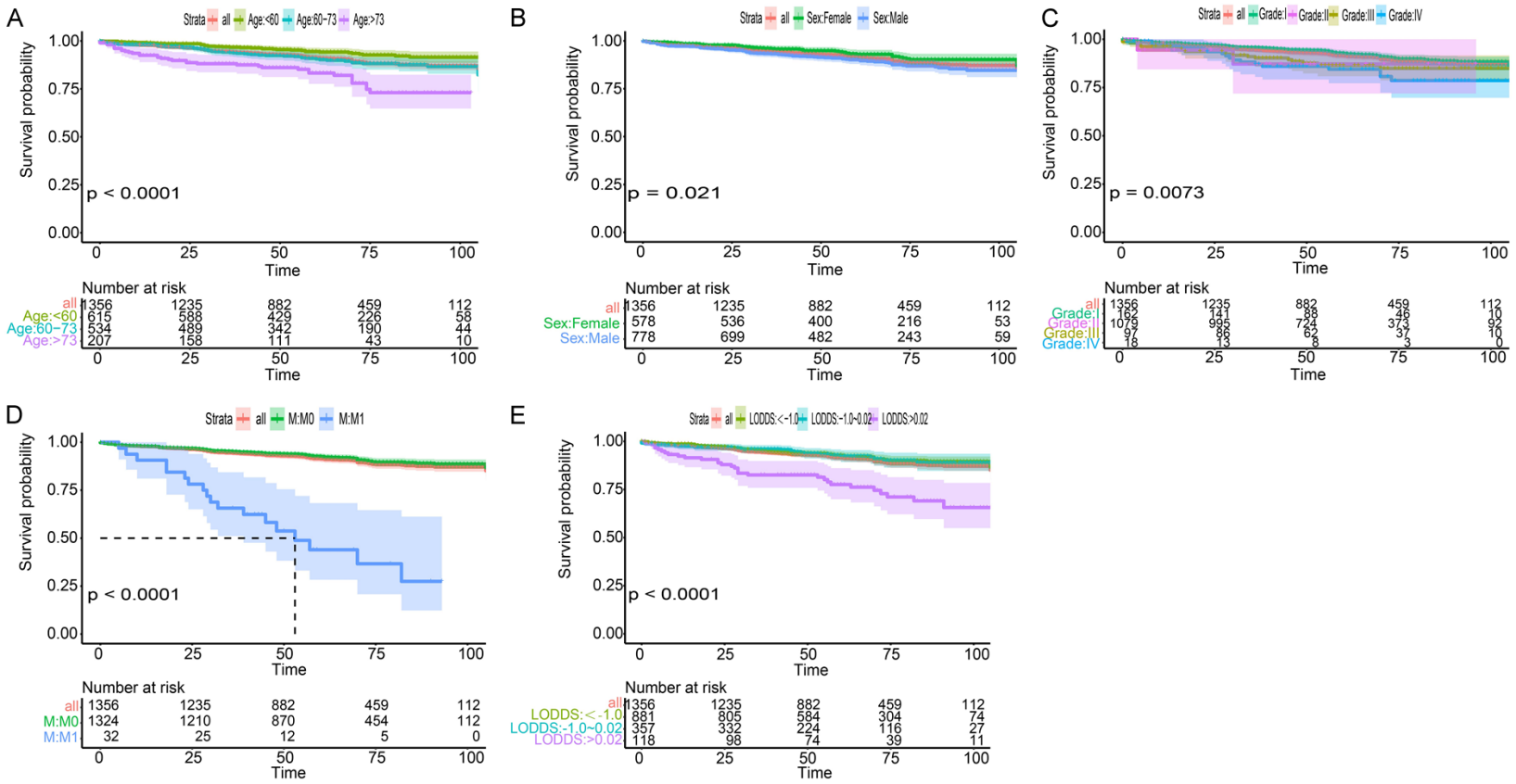
Variables	Points	Variables	Points	Variables	Points
Age		LODDS		Sex	
<60	0	<-1.0	0	Female	0
60-73	32	-1.0~0.02	1	Male	23
>73	74	>0.02	47		
Grade		Grade		M Stage	
I	0	III	26	M0	0
II	24	IV	26	M1	100
3-year Survival Probability		5-year Survival Probability			
0.95	58	0.95	34		
0.9	94	0.90	70		
0.8	131	0.80	107		
0.7	154	0.70	130		
0.6	171	0.60	147		
0.5	186	0.50	162		
0.4	200	0.40	176		
0.3	213	0.30	190		
0.2	228	0.20	204		
0.1	245	0.10	221		



Supplementary Figure 1. The calibration curves of nomogram at 3- and 5-year in the training cohort (A, B) in-validation cohort (C, D), ex-validation cohort (E, F).



Supplementary Figure 2. Comparing the 3- and 5-year clinical applicability of the nomogram model with AJCC_stage by DCA in the training cohort (A, B), the in-validation cohort (C, D), and the ex-validation cohort (E, F).



Supplementary Figure 3. Predicted probability of CSS by age (A), sex (B), grade (C), M stage (D), LODDS (E) shown using Kaplan-Meier curves.