To Explore the Effect of NLR and PLR on Prognosis of Rectal Cancer on the basis of T3 substage, and to draw the related nomogram

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Abstract

Background: Approximately 50% of patients with rectal cancer are classified into T3 stage, and they are positioned as substage by various criteria. These patients with different neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) develop disparate outcomes. We sought to develop and validate nomograms to predict survival in patients with rectal cancer on the basis of T3 substage.

Methods: We conducted a retrospective cohort study by collecting 170 cases from China. Individuals with rectal cancer after 2 or more years of follow up after surgery were eligible for inclusion. Candidate predictors consisted of NLR, PLR, T3 substage and clinical characteristics available at the time of rectal cancer diagnosis. The optimal cut-off values for NLR and PLR were determined using X-Tile (Version 3.6.1) software and were determined before statistical analyses. Variables with P values below 0.1 in the univariable analyses were further evaluated using Cox multivariate analysis. Model discrimination was assessed using receiver operating characteristic (ROC) curve and concordance index (C-index) analysis. Results were internally validated using related software.

Results: We analyzed data from 170 patients with T3 rectal cancer. The optimal cut-off value of NLR in relation to overall and disease-free survival were 3.1 and 2.9, and that of PLR were 181.9 and 202.7. Among them, postoperative adjuvant chemotherapy, T3 substage, N stage, CA199 and NLR were independent risk factors affecting overall survival（OS）and disease-free survival (DFS). There was no significant difference in survival rate between T3a and T3b, or between T3c and T3d. The final nomograms of 2-year OS (area under the curve,0.886; The c-index,0.870) and 2-year DFS (area under the curve,0.895; The c-index,0.867) were developed according to independent risk factors analyzed by SPSS 26 (SPSS Inc., Chicago, IL, USA) software. The calibration curves showed negligible optimism.

Conclusion: We developed nomograms based on postoperative adjuvant chemotherapy, T3 substage, N stage, CA199 and NLR to help identify patients with poor prognosis and to guide individualized therapy.

Introduction

Statistically, there were estimated 1.9 million new cases of colorectal cancer and 935,000 deaths from the disease in 2020. The mortality rate was about 10%, ranking the second in the world[1]. At present, TNM stage was the world recognized clinical data related to prognosis. The widely accepted TNM stage system was established by UICC and AJCC which provided no further explanation for the T3 stage[2]. However, if we didn't take into account liver and lung metastasis, the prognosis of patients with the same N stage and T stage was very different. Under this background, European Society for Medical Oncology (ESMO) further subdivided T3 stage based on preoperative high-quality rectal MRI assessment of the Depth of invasion beyond the muscularis propria[3]. Such subdivision did help to refine the treatment of tumors, but it was still not exhaustive. In recent years, studies had shown that inflammation was related to the prognosis of rectal cancer. We hoped to explore the effect of NLR, PLR and other clinical

characteristics on prognosis of rectal cancer on the basis of T3 substage and N stage in order to more accurately identify high-risk patients.

NLR and PLR were one of the typical representatives of inflammation, and many studies had shown that they were closely related to tumor progression, metastasis and prognosis[4-8]. The association of elevated NLR and PLR with breast, prostate, biliary, gastric, and pancreatic cancers had been reported in recent years[9-14]. PD-1 inhibitors were one of the representative agents of inflammation-related immunotherapy and were widely used in the treatment of cancer, The complement and expansion of immunotherapy was also ongoing Exploring the relationship between NLR and PLR and prognosis of rectal cancer was not only a supplement to TNM staging, but also a further exploration of immunotherapy for rectal cancer.

In this study, we investigated the relationship between inflammatory markers and other clinical data and the survival of patients with stage T3 rectal cancer, screened out independent risk factors, and established nomograms to predict the prognosis of patients, in order to guide the individualized treatment of patients with T3 rectal cancer.

Materials And Methods

Patients

The study was conducted under the guidance of the Changchun Medical Institution Review Committee, which determined that informed consent was not required. We retrospectively studied 226 patients with stage T3 rectal cancer who underwent surgery at the Second Hospital of Jilin University from January 2017 to December 2019 with complete clinical data. Eventually, 170 cases were included. Tumors were all 5cm-10cm away from the anus, which was confirmed as adenocarcinoma by postoperative pathology. The operation followed the principle of total mesorectal resection (TME). All patients did not receive preoperative radiotherapy, and no postoperative complications such as hemorrhage, obstruction and perforation occurred. There was no distant metastasis in all patients (Fig. 1).

Hematological indicators after exclusion of infection were collected one week before operation, including neutrophils, lymphocytes, platelets, albumin, CEA and CA199. The general information of the patients included age, sex, BMI, smoking, hypertension, diabetes, maximum tumor diameter, extramural vascular invasion, tumor differentiation, and mucinous adenocarcinoma. The ACJJ 8th edition colorectal cancer staging system was used to classify N stage[2]. T3 substage was performed according to European Society for Medical Oncology (ESMO) criterion. Overall survival (OS) was defined as the time from surgery to death. Disease-free survival (DFS) was defined as the date from surgery to the first recurrence or last follow-up.

Postoperative Adjuvant Chemotherapy

The postoperative adjuvant chemotherapy regimen was mainly XELOX. The first chemotherapy should be given within one month after surgery. First of all, oxaliplatin was intravenously injected with a dose of 130mg/㎡. During treatment, capecitabine was taken orally at a single dose of 1250mg/㎡ twice daily for 14 days, followed by 7 days of rest. 21 days as a course of treatment.

Definition Of T3 Substage

We used the 2017 European Society for Medical Oncology (ESMO) guidelines to define the substage of T3[3]. The maximum depth of invasion at the outer boundary of the muscular layer was measured by preoperative high-quality rectal MRI. T3a, T3b, T3c and T3d are classified as < 1mm, 1 ~ 5mm, 6 ~ 15mm and > 15mm respectively. When the muscularis propria was well defined, the length of the deepest tumor invasion could be measured directly. If the muscular boundary was not clear, look for the clear boundary at both ends of the tumor to estimate the location of the muscular outer boundary. Specific T3 substages were shown in Fig. 2.

Statistical Analysis

Enumerative data were compared by chi-square test or Fisher's exact test. To determine the optimal cut-off value of relevant hematological indicators affecting prognosis, we performed X-tile plot analysis with X-tile software (Version 3.6.1). Univariate Cox regression, multivariate Cox regression analysis and Kaplan-Meier analysis were conducted by SPSS 26 (SPSS Inc., Chicago, IL, USA). The R software was used to plot the nomograms, receiver operating characteristic (ROC) and calibration curves. The receiver operating characteristic (ROC) curves,concordance index (C-index) and calibration curves analyses were used to evaluate the accuracy of nomograms.

Results

Clinical data of patients

The enrolled patients and their basic characteristics were shown in Table 1. Of the 170 patients included in the study, there were 122 males (71.8%) and 48 females (28.2%). The mean age was 62 years, ranging from 32 to 86 years; The media values of NLR and PLR were 2.41 (range 0.85–6.89) and 154.3 (range 45.2-319.89).

Table 1
Demographic and Clinical data of patients

Variable	NO.	Percentage(%)
Age		
mean ± SD	62 ± 10	
Gender		
Male	122	71.8
Female	48	28.2
Smoking		
No	148	87.1
Yes	22	12.9
Albumin		
<35	13	7.6
≥ 35	157	92.4
Hypertension		
NO	140	82.4
YES	30	17.6
Diabetes		
NO	154	90.6
YES	16	9.4
Differentiation		
High	6	3.5
Middle	154	90.6
Low	10	5.9
EMVI		
NO	112	65.9
YES	58	34.1
Tumor size(cm)		

EMVI: extramural vascular invasion; BMI: Body Mass Index; NLR: neutrophil to lymphocyte ratio; PRL: platelet to lymphocyte ratio

Variable	NO.	Percentage(%)
< 5	101	59.4
≥ 5	69	40.6
N stage		
N0	73	43
N1	57	33.5
N2	40	23.5
CEA		
Positive	65	38.2
Negative	105	61.8
CA199		
Positive	27	15.9
Negative	143	84.1
Adjuvant chemotherapy		
NO	89	52.3
YES	81	47.7
mucinous		
NO	150	88.2
YES	20	11.8
BMI		
< 18.5	8	4.7
18.5 ~ 23.9	85	50
> 23.9	77	45.3
NLR		
high	47	27.6
low	123	72.4
PRL		

EMVI: extramural vascular invasion; BMI: Body Mass Index; NLR: neutrophil to lymphocyte ratio; PRL: platelet to lymphocyte ratio

Variable	NO.	Percentage(%)
High	43	25.3
Low	127	74.7
T3 substage		
T3a	42	24.7
T3b	59	34.7
T3c	61	35.9
T3d	8	4.7
EMVI: extramural vascular invasion; BMI: Body Mass Index; NLR: neutrophil to lymphocyte ratio; PRL: platelet to lymphocyte ratio		

Relationship between different levels of NLR, PLR and T3 substages and clinical data

Cox univariate analysis showed that NLR, PLR and T3 substages all affected the prognosis, the best cut-off values of NLR and PLR were obtained using X-tile (Version 3.6.1), It can be found that for OS, the optimal cut-off value of NLR was 3.1, and that of PLR was 181.9 (Figure 3). The optimal cut-off value of NLR was 2.9, and that of PLR was 202.7 (Figure 4) based on DFS.

Table 2

Comparing the clinical information of different groups according to the optimal cut-off, we found the young patients in the high-PLR group were significantly more than those in the low-PLR group. In the T3c + d group, there were fewer patients with high BMI and hypertension.

Table 2
Associations between NLR, PLR and T3substage level and clinical characteristics in all patients

Variable	LOW NLR	HIGH NLR	P	LOW PLR	HIGH PLR	P	T3a + b	T3c + d	P
Age			0.764			0.007			0.518
<65	72	19		58	33		52	39	
≥ 65	61	18		65	14		49	30	
Gender			0.854			0.072			0.857
Female	38	10		30	18		28	20	
Male	95	27		93	29		73	49	
Smoking			0.502			0.966			0.153
NO	117	31		107	41		91	57	
YES	16	6		16	6		10	12	
Albumin			0.905			0.121			0.311
<35	10	3		7	6		6	7	
≥ 35	123	34		116	41		95	62	
Hypertension			0.091			0.895			0.034
NO	113	27		101	39		78	62	
YES	20	10		22	8		23	7	
Diabetes			0.345			0.403			0.424
NO	119	35		110	44		90	64	
YES	14	2		13	3		11	5	
Differentiation			0.889			0.103			0.198
High + Middle	125	35		118	42		97	63	
Low	8	2		5	5		4	6	
EMVI			0.524			0.708			0.142
NO	86	26		80	32		71	41	
YES	47	11		43	15		30	28	

EMVI: extramural vascular invasion; BMI: Body Mass Index; NLR: neutrophil to lymphocyte ratio; PRL: platelet to lymphocyte ratio

Variable	LOW NLR	HIGH NLR	P	LOW PLR	HIGH PLR	P	T3a + b	T3c + d	P
Tumor size(cm)			0.453			0.307			0.057
< 5cm	81	20		76	25		66	35	
≥ 5cm	52	17		47	22		35	34	
N stage			0.624			0.615			0.566
N0	56	17		53	20		44	29	
N1	47	10		39	18		31	26	
N2	30	10		31	9		26	14	
CEA			0.744			0.716			0.245
negative	83	22		77	28		66	39	
positive	50	15		46	19		35	30	
CA199			0.340			0.802			0.682
negative	110	33		104	39		84	59	
positive	23	4		19	8		17	10	
Adjuvant chemotherapy			0.085			0.216			0.784
NO	65	24		68	21		52	37	
YES	68	13		55	26		49	32	
mucinous			0.435			0.416			0.955
NO	116	34		107	43		89	61	
YES	17	3		16	4		12	8	
BMI			0.373			0.163			0.001
< 18.5	6	2		6	2		1	7	
18.5 ~ 23.9	63	22		56	29		44	41	
> 23.9	64	13		61	16		56	21	

EMVI: extramural vascular invasion; BMI: Body Mass Index; NLR: neutrophil to lymphocyte ratio; PRL: platelet to lymphocyte ratio

Univariate And Multivariate Analysis

Patients with EMVI(P = 0.046), advanced T3 stage (P = 0.007) and N stage (P < 0.001), without chemotherapy (P = 0.01), and with high NLR (P < 0.001),PLR (P = 0.003), CEA(P = 0.02),and CA199(P < 0.001) had a trend toward worse OS,On univariate analysis for DFS. Advanced T3 stage (P = 0.001) and N stage (P = 0.001), without chemotherapy (P = 0.042), and with high NLR (P = 0.005),PLR (P = 0.009), CEA（P = 0.002）,and CA199(P < 0.001) as poorer prognostic indicators of outcome. Variables with P values below 0.1 in the univariable analyses were further evaluated using Cox multivariate analysis, which showed that postoperative adjuvant chemotherapy (P = 0.022, P = 0.042), T3 substage (P = 0.019, P = 0.002), N stage (P = 0.003, P = 0.002), CA199(P = 0.001, P = 0.001) and NLR (P = 0.001, P = 0.033) were identified as being independently prognostic for OS and DFS. (Table 3 and Table 4)

Table 3
Univariate and multivariate analyses related to OS

Variable	Univariate			multivariate		
	HR	95% CI	P	HR	95% CI	P
Age	0.7	0.318–1.543	0.376			
Gender	1.318	0.529–3.281	0.553			
Smoking	0.889	0.267–2.961	0.848			
Albumin	0.890	0.210–3.767	0.874			
Hypertension	1.487	0.596–3.710	0.395			
BMI			0.404			
< 18.5	1					
18.5 ~ 23.9	0.895	0.115–6.995				
> 23.9	1.540	0.203–11.663				
mucinous	1.445	0.498–4.197	0.498			
Diabetes	0.375	0.051–2.768	0.336			
Differentiation	0.429	0.129–1.430	0.168			
EMVI	2.118	1.013–4.729	0.046	1.188	0.442–3.193	0.733
Tumor size(cm)	1.559	0.722–3.364	0.258			
Adjuvant chemotherapy	0.304	0.122–0.756	0.01	0.322	0.122–0.850	0.022
T3 substage	3.040	1.355–6.822	0.007	2.850	1.185–6.543	0.019
N stage			< 0.001			0.003
N0	1			1		
N1	4.185	1.132–15.479		4.821	1.155–20.125	
N2	11.290	3.213–39.668		13.053	2.921–58.337	
CEA	1.021	1.003–1.038	0.02	1.003	0.983–1.023	0.786
CA199	1.021	1.011–1.031	< 0.001	1.021	1.009–1.034	0.001
NLR	1.668	1.275–2.182	< 0.001	1.989	1.323–2.990	0.001
PLR	1.009	1.003–1.015	0.003	1.008	1.000-1.016	0.061

EMVI: extramural vascular invasion; BMI: Body Mass Index; NLR: neutrophil to lymphocyte ratio; PRL: platelet to lymphocyte ratio

Table 4
Univariate and multivariate analyses related to DFS

Variable	Univariate			multivariate		
	HR	95% CI	P	HR	95% CI	P
Age	0.853	0.424–1.716	0.656			
Gender	1.208	0.543–2.690	0.643			
Smoking	0.692	0.211–2.273	0.544			
Albumin	0.542	0.190–1.547	0.253			
Hypertension	1.598	0.718–3.557	0.251			
BMI			0.585			
< 18.5	1					
18.5 ~ 23.9	1.265	0.166–9.620				
> 23.9	1.781	0.237–13.388				
mucinous	1.134	0.398–3.233	0.814			
Diabetes	0.291	0.040–2.135	0.225			
Differentiation	0.381	0.133–1.086	0.071	0.403	0.131–1.239	0.113
EMVI	1.899	0.948–3.804	0.07	0.848	0.368–1.954	0.699
Tumor size(cm)	1.541	0.77–3.081	0.222			
Adjuvant chemotherapy	0.46	0.218–0.971	0.042	0.426	0.187–0.969	0.042
T3 substage	3.656	1.730–7.724	0.001	3.618	1.616–8.098	0.002
N stage			0.001			0.002
N0	1			1		
N1	4.44	1.447–13.619		4.259	1.268–14.301	
N2	8.479	2.812–25.569		9.494	2.667–33.788	
CEA	1.024	1.008–1.039	0.002	1.008	0.990–1.026	0.398
CA199	1.02	1.011–1.030	< 0.001	1.019	1.007–1.031	0.001
NLR	1.458	1.120–1.898	0.005	1.532	1.035–2.269	0.033
PLR	1.008	1.002–1.013	0.009	1.006	0.999–1.014	0.094

EMVI: extramural vascular invasion; BMI: Body Mass Index; NLR: neutrophil to lymphocyte ratio; PRL: platelet to lymphocyte ratio

T3 Substage In Relation To Os And Dfs

For OS, the survival rate was 93% in T3a, 90% in T3b, 78.7% in T3c, and 63% in T3d,There was no statistically significant difference between T3a and T3b, or between T3c and T3d, However, when recategorized as T3a + b and T3c + d, the survival rate of T3a + b(91%) patients was higher than that of T3c + d□75%□ (Fig. 5). The disease-free survival rate was 93% in T3a, 88% in T3b, 70% in T3c, and 50% in T3d. The difference was not statistically significant between T3a and T3b, or between T3c and T3d. Similarly, the survival rate of patients with T3a + b□90%□was higher than that of patients with T3c + d□68%□, with statistical difference (Fig. 6).

Draw and verify the validity of the nomogram related to 2-year OS

The nomogram based on the cox multivariate analysis related to OS was presented in Fig. 7,This model included adjuvant chemotherapy, T3 substage, CA199, NLR and N stage. The top of each variable in the figure corresponds to its own value, and all the values finally obtained were added up. The percentage corresponding to the total score at the bottom of the nomogram was the probability of the event occurring. The area under the curve of the ROC curve and c-index were 0.886 and 0.870. the calibration curves of the nomogram showed the validity of the model.

Draw and verify the validity of the nomogram related to 2-year DFS

We used independent risk factors derived from Cox regression model to plot a nomogram to predict 2-year DFS (Fig. 8). The top of each variable in the figure corresponds to its own value, and all the values finally obtained were added up. The percentage corresponding to the total score at the bottom of the nomogram was the probability of the event occurring. The C-index and the area under the ROC curve of the 2-year DFS-related model were 0.867 and 0.895. There was no deviation from the baseline shown in the calibration curves of the nomogram.

Discussion

Identifying high-risk patients in the treatment of rectal cancer was critical to individualizing patients care. In this study, we found that in addition to T3 substage and N stage, NLR, CA199 and postoperative adjuvant chemotherapy were also closely related to prognosis. Therefore, it made sense for us to combine these factors to identify high-risk patients and explore treatment options for these patients to improve their outcomes.

The exploration of T3 substage was also a process of constant correction and improvement. Picon took the distance of tumor invasion beyond the muscularis propria as a cut-off value of 3 mm, and he found no statistically significant difference[15] But Yoshida thought it was wrong[16]. However, a single study had significant limitations. Zinicola conducted statistical analysis, induction and summary of all the studies, and concluded that the best cut-off value was 5mm[17] In 2017, the European Society for Medical Oncology (ESMO) divided T3 into four stages (T3a < 1mm, T3b: 1 ~ 5mm, T3c: 6 ~ 15mm, and T3d > 15mm) [3]. According to the standard of Radiological Society of North America(RSNA), T3a, T3b and T3c were classified as < 5mm, 6 ~ 15mm and > 15mm respectively[18]. We did our research according to the ESMO, and found that T3a and T3b, T3c and T3d had no statistical difference in the influence of prognosis, while the survival rate of patients with T3a + b was higher than that of patients with T3c + d, with statistical difference. We believed that the classification criteria of RSNA may be more suitable for Chinese patients. Since only 8 patients with T3d were included in this group, the difference between T3c and T3d also needed to be further verified.

NLR reflected the balance between antitumor and pro-tumor activities of the host's immune system, and the shin study showed that NLR could be used as one of the indicators of poor prognosis[19]. Neutrophils promote tumor development. Because it produces vascular endothelial growth factor, which promotes angiogenesis and thus stimulates tumor growth[20]. Lymphocytes inhibit tumor progression by inducing tumor cells apoptosis[21]. In this study, NLR was significantly associated with prognosis and was one of the independent risk factors.

Elevated PRL is also an adverse factor for the prognosis. Platelet and tumor are a mutually promoting result. On the one hand, ADP produced by tumor cells can cause platelet aggregation[22]. Tumor cells can also activate platelets by producing thrombin and microvesicles [23]. On the other hand VEGF and PDGF secreted by platelets can promote tumor angiogenesis[24]. Another function of platelets is to allow tumor cells to escape immune surveillance [25]. In this study, patients with elevated PLR had poor prognosis, but it was not an independent risk factor.

We developed and internally validated nomograms for the prediction of 2-year OS and 2-year DFS among patients with T3 rectal cancer. The model was based on Blood, Pathological and Imaging variables. The C-index of this nomogram for predicting 2-year OS and 2-year DFS were 0.870 and 0.867, and the area under the ROC curves were 0.886 and 0.895. The final nomograms were shown to have excellent discrimination with negligible optimism.

Conclusion

In patients with stage T3 rectal cancer, elevated NLR, PLR and T3c + d predicted poor prognosis, and elevated NLR and T3c + d were one of the independent risk factors. T3a and T3b or T3c and T3d had no statistically significant effect on OS and DFS. We developed nomograms on easily available clinical parameters to help find patients with poor prognosis and to direct individualized therapy.

Abbreviations

EMVI
extramural vascular invasion;
BMI
Body Mass Index;
NLR
neutrophil to lymphocyte ratio;
PRL
platelet to lymphocyte ratio;
ESMO
European Society for Medical Oncology;
RSNA
Radiological Society of North America;
ROC
receiver operating characteristic
C-index
concordance index;
OS
overall survival;
DFS
Disease- Free survival;
TME
total mesorectal resection;

Declarations

Availability of data and materials

The datasets generated and analyzed during the current study available from the corresponding author on reasonable request.

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Contributions:

LD and MW conceived the study design. SW, YY, and AS acquired the data for the study. ZZ, DL, and YG analyzed and interpreted the data. AS drafted the manuscript. SW and YY revised the manuscript critically. The authors read and approved the final manuscript.

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Ethics declarations

Ethics approval and consent to participate

The study protocol was approved by the institutional review board of The Second Hospital of Jilin University. Due to the retrospective design of the study, the local ethic committee confirmed that informed consent was not necessary from participants. The demand of patient informed consent was deserted because of the retrospective nature of this study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

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Figures

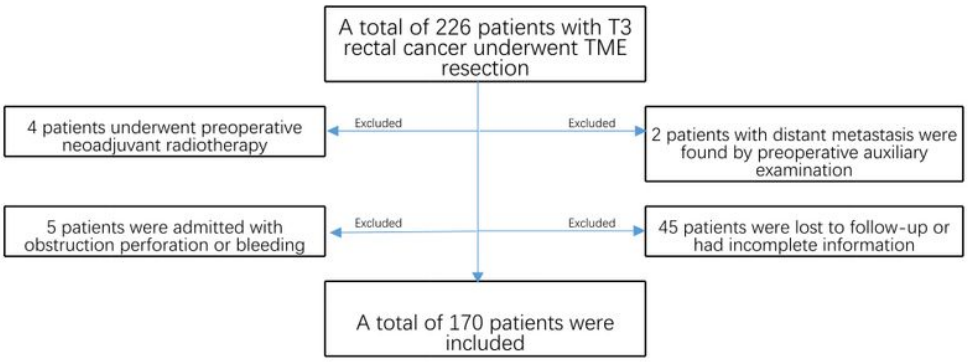

Figure 1

Data inclusion and exclusion

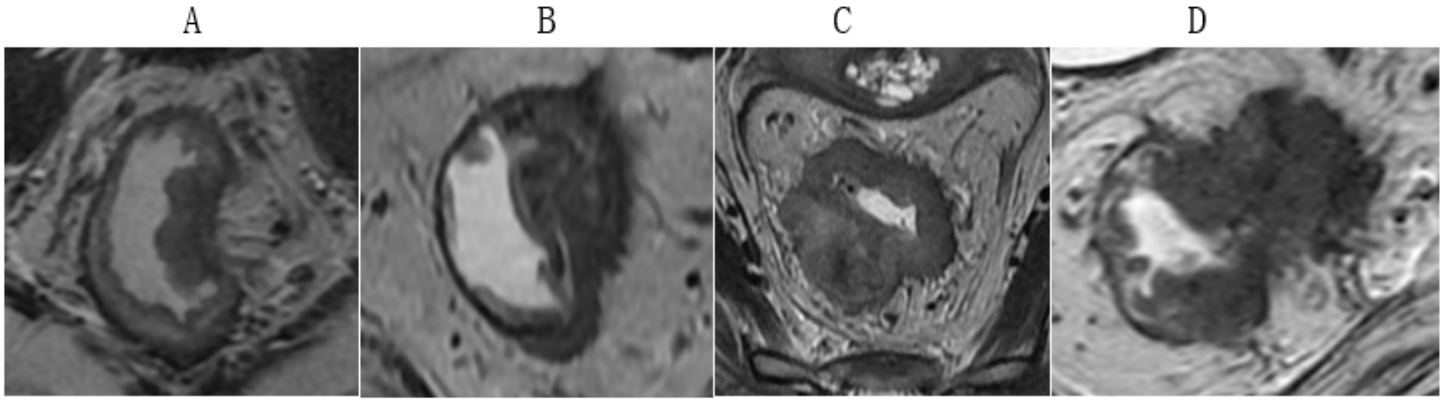

Figure 2

A, B, C, and D were T3a, T3b, T3c, and T3d respectively

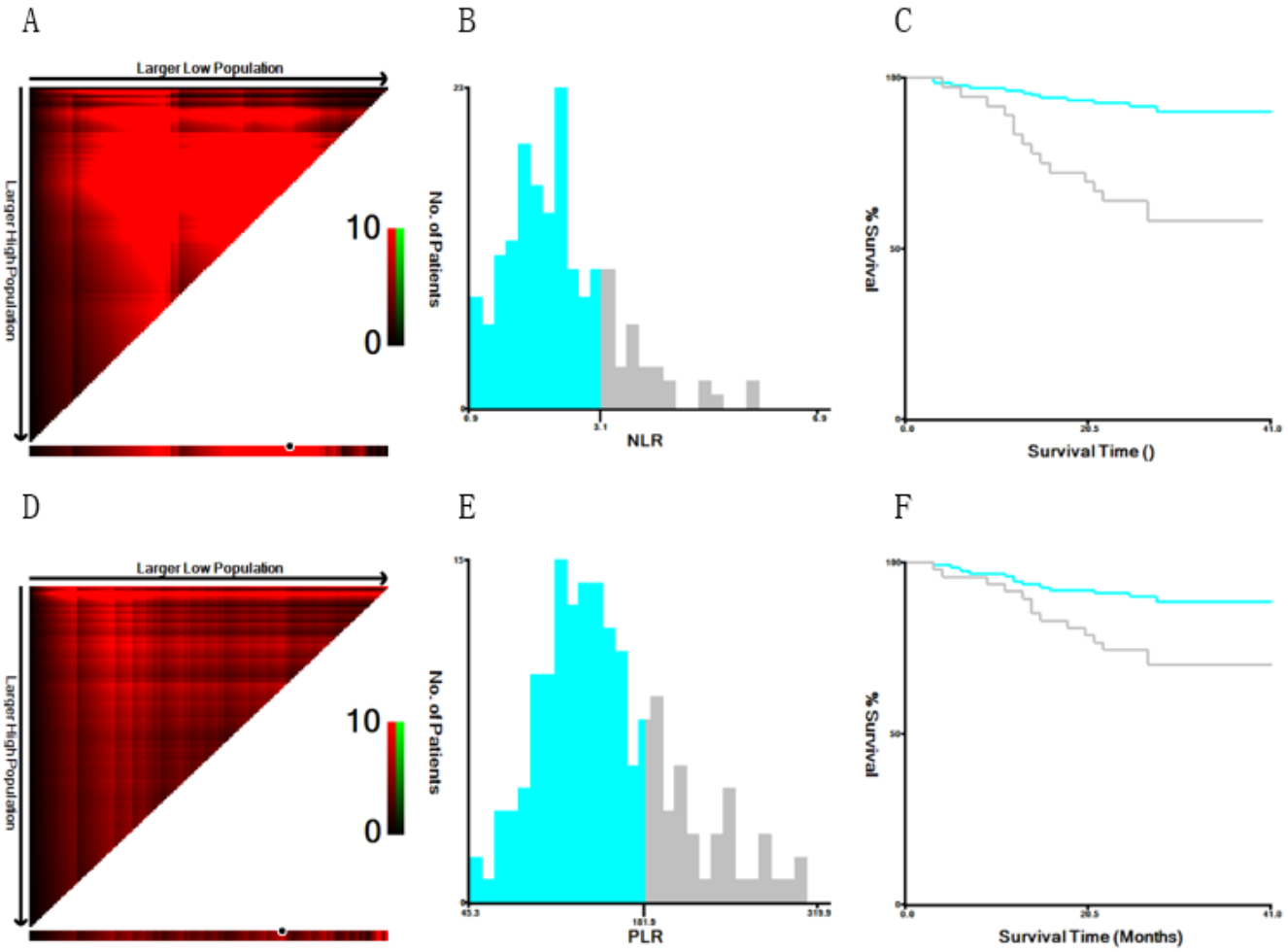

Figure 3

The optimal cut-off values for NLR and PLR were analyzed by X-tile. The location of the black dot in the left panels represented the optimal cut-off values, which were also shown in histograms (middle panels). Kaplan-Meier plots appeared in right panels, and according to OS, the best cut-off values of NLR and PLR were 3.1 and 181.9, respectively.

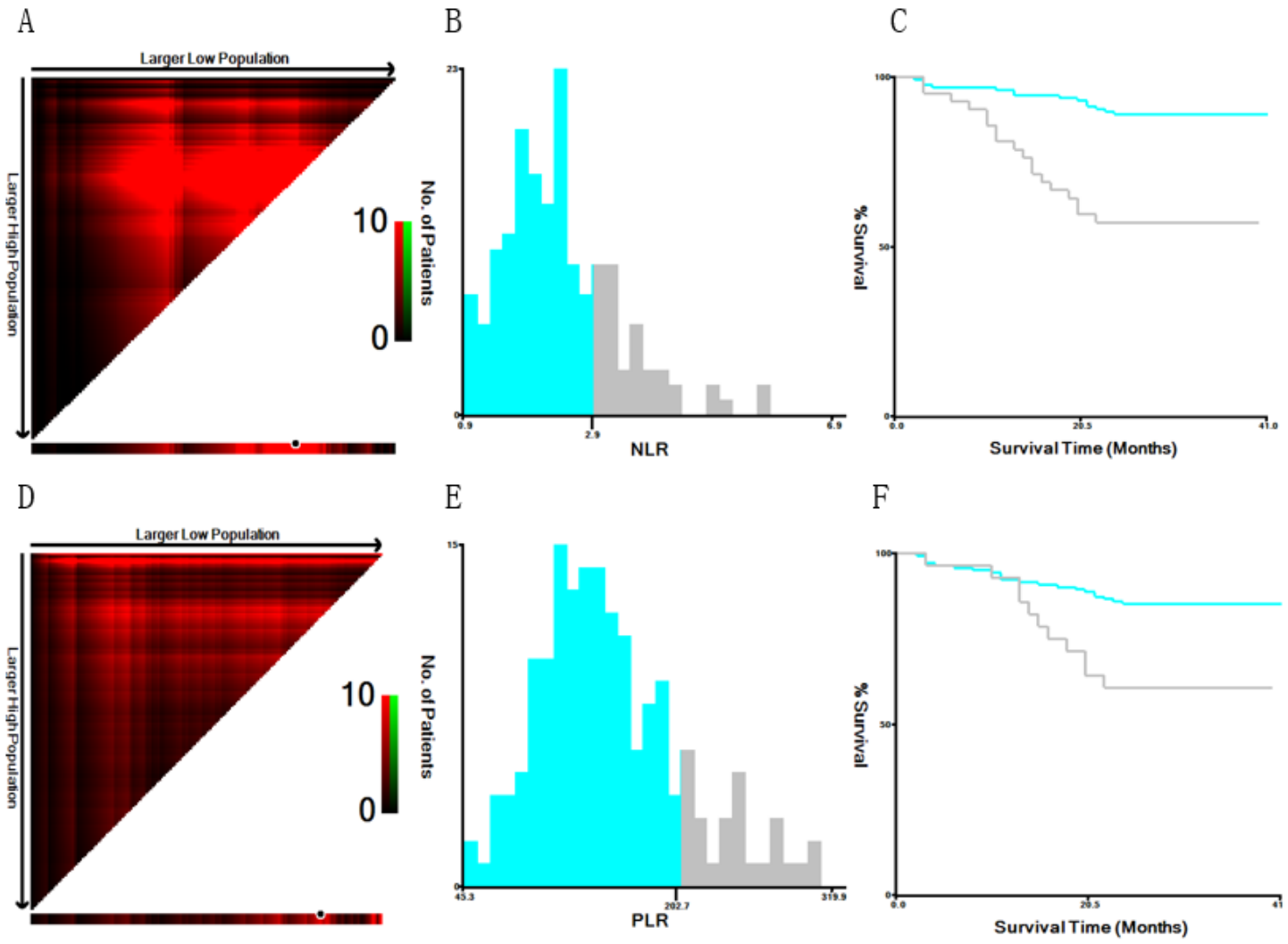

Figure 4

The optimal cut-off values for NLR and PLR were analyzed by X-tile. The location of the black dot in the left panels represented the optimal cut-off values, which were also shown in histograms (middle panels). Kaplan-Meier plots appeared in right panels, and according to DFS, the best cut-off values of NLR and PLR were 2.9 and 202.7, respectively.

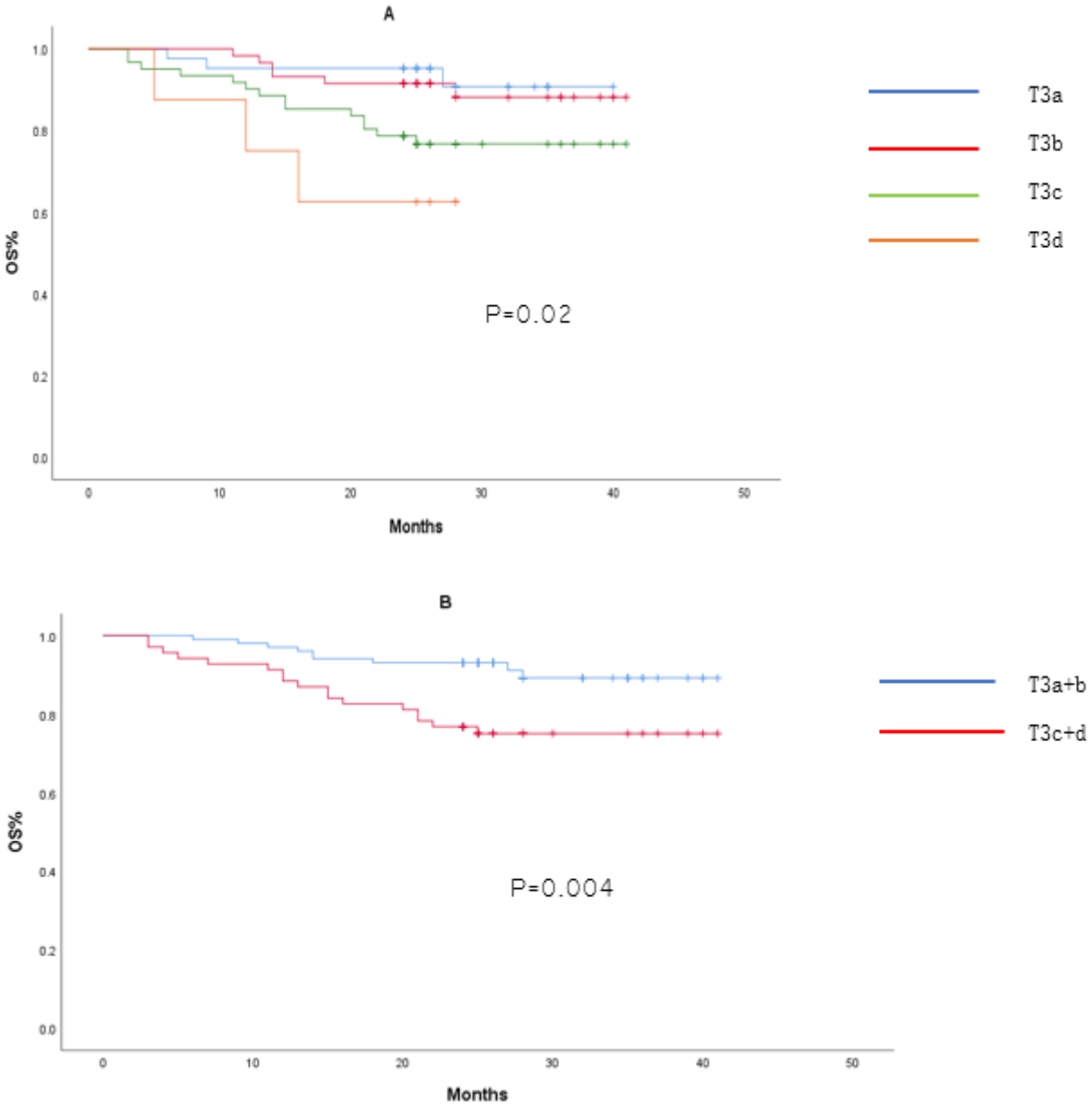

Figure 5

T3 substage survival curve A: There was no significant difference in overall survival rate between T3a /T3b (P=0.613) and T3c/T3d (P=0.335). B: The difference of overall survival rate between T3a + b and T3c + d was statistically significant.

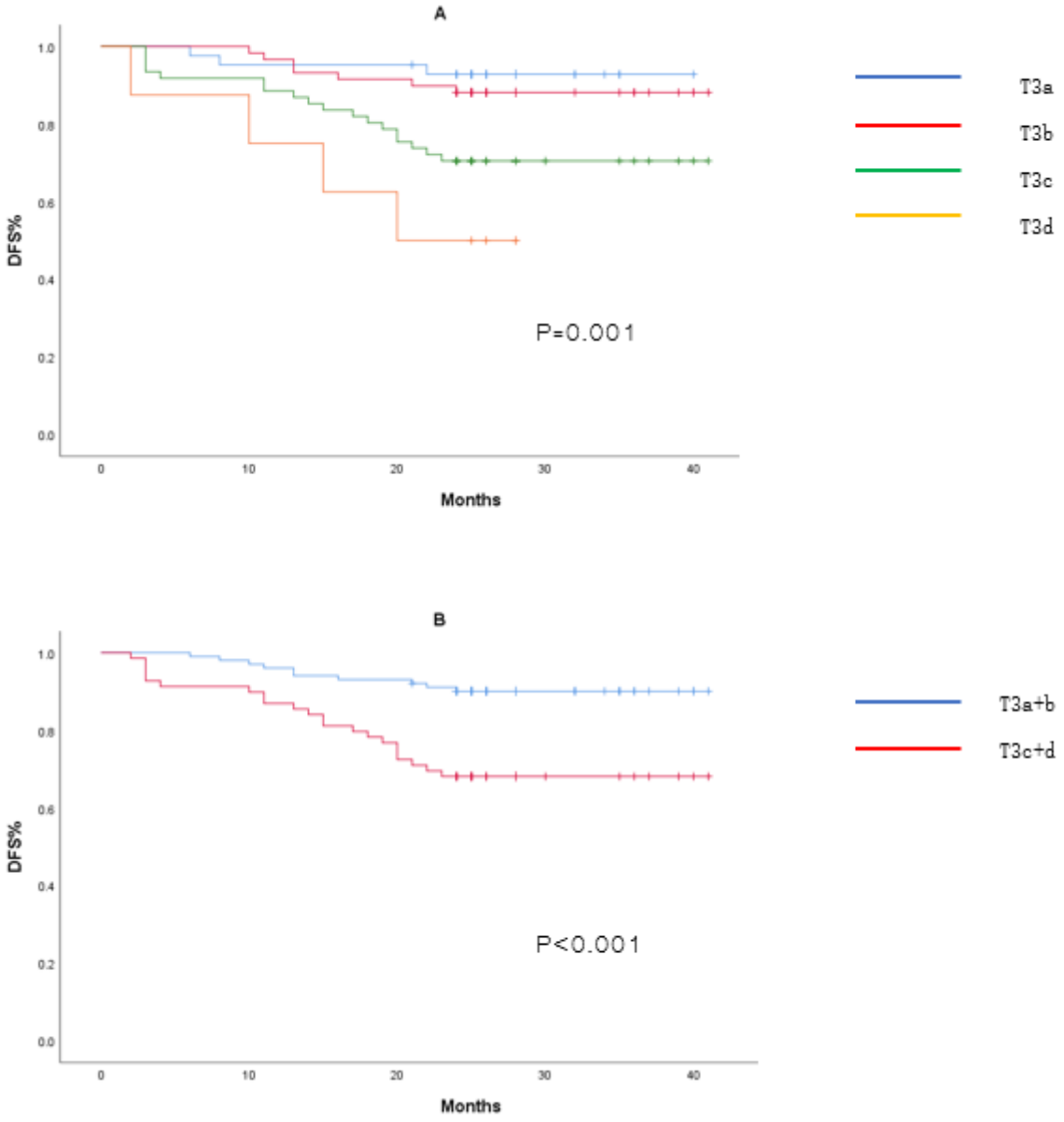

Figure 6

T3 substage survival curve A: There was no significant difference in disease-free survival rate between T3a/T3b (P=0.460), and T3c/T3d (P=0.181). B: The difference of disease-free survival rate between T3a + b and T3c + d was statistically significant.

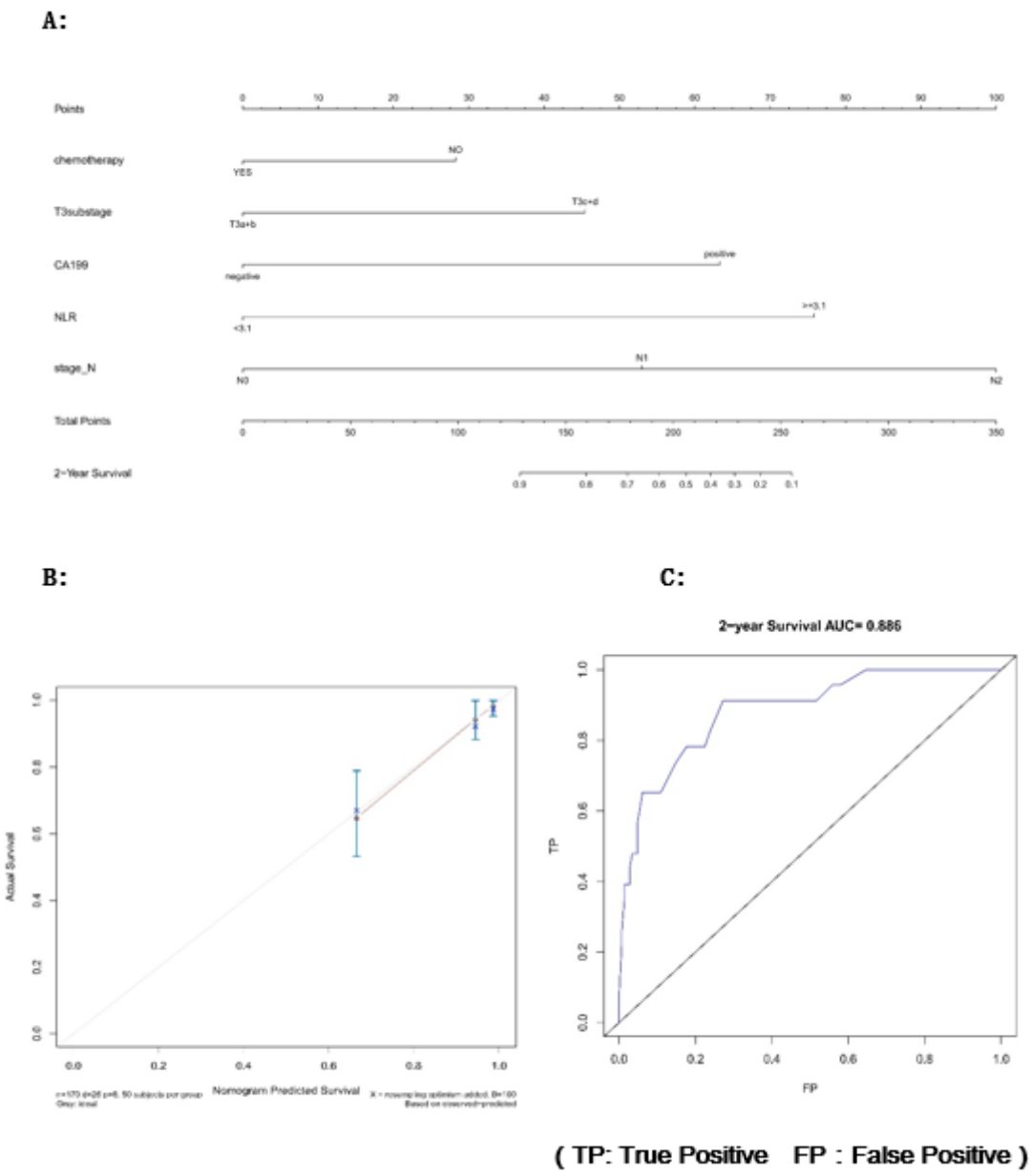

Figure 7

A: Nomogram for predicting 2-year OS. B: The calibration curve for predicting 2-year OS. Predicted probability of overall survival was plotted on the x-axis; actual overall survival was plotted on the y-axis C: ROC curve related to true positive and false positive were constructed based on the model, and the area under the curve was 0.886.

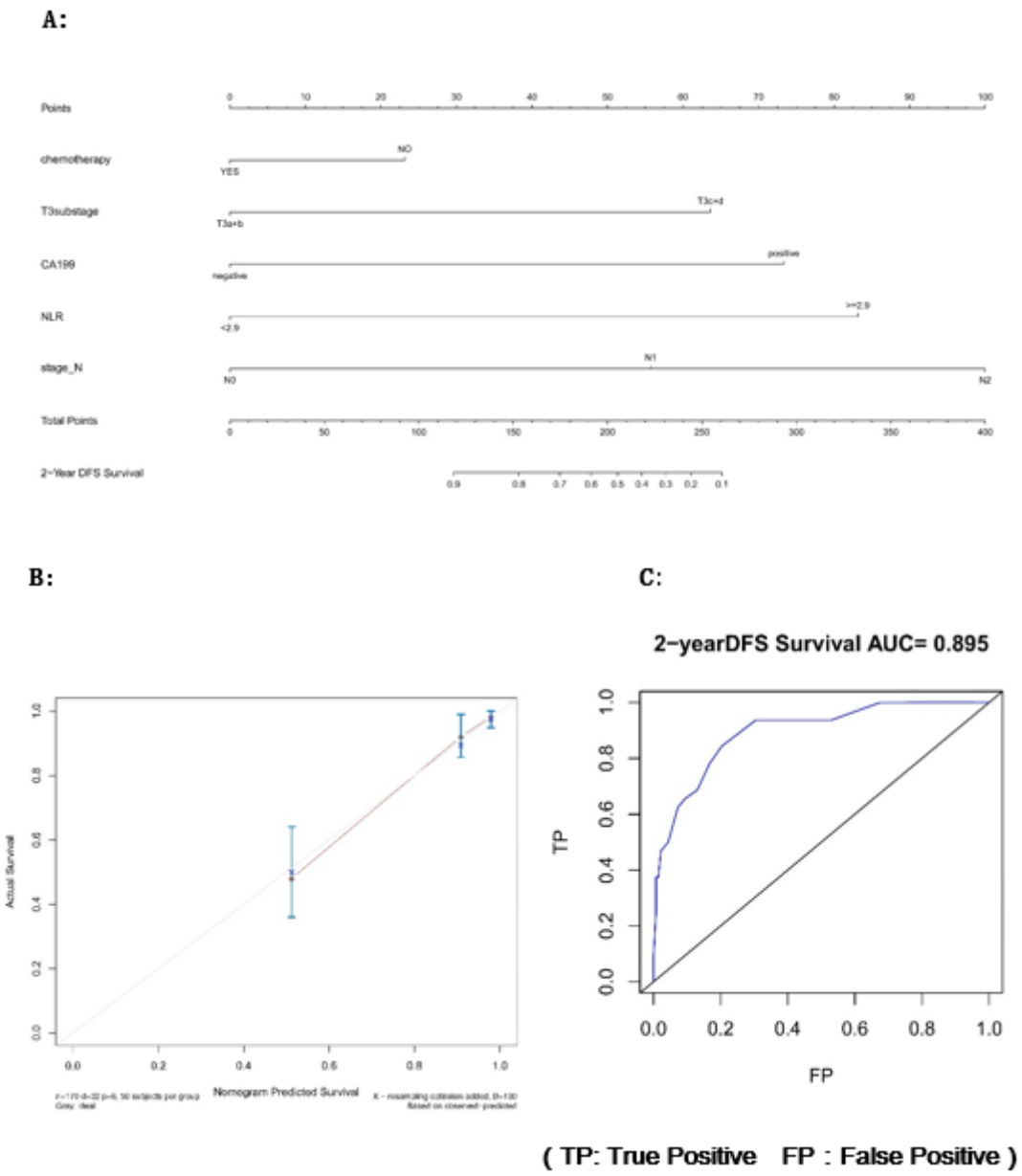

Figure 8

A: Nomogram for predicting 2-year DFS. B: The calibration curve for predicting 2-year DFS. Predicted probability of overall survival is plotted on the x-axis; actual overall survival was plotted on the y-axis C: ROC curve related to true positive and false positive were constructed based on the model, and the area under the curve was 0.895.