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Original Article

Construction of predictive model for prognosis of patients after radical resection of colon cancer based on nomogram

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Abstract: Objective: To construct a predictive model for 3-year survival of patients after curative resection of colon cancer by nomogram. Method: A retrospective analysis was conducted to analyze the clinicopathologic data of 102 patients who underwent radical resection of colon cancer in Baoji Central Hospital from April 2015 to April 2017. The optimal cutoff values of preoperative CEA, CA125, and NLR for predicting overall survival were analyzed by receiver operating characteristic (ROC) curves. To observe the relationship between NLR, CEA and CA125 and clinicopathologic data, we performed multivariate Cox regression to analyze the independent factors affecting the prognosis of patients, and Kaplan-Meier test to identify the relationship between NLR, CEA and CA125 and patient survival. A nomogram prediction model was drawn for patients' 1-, 2-, and 3-year survival after radical resection of colon cancer, and the efficacy of the prediction model was evaluated. Results: The area under the curve (AUC) of NLR, CEA and CA125 in predicting patient death was 0.784, 0.790 and 0.771, respectively. NLR was correlated with clinical stage, tumor diameter and differentiation (all $P < 0.05$); CEA was associated with clinical stage, tumor diameter, differentiation and lymph node metastasis (all $P < 0.05$); CA125 was only associated with tumor diameter in patients ($P < 0.05$). Differentiation, NLR, CEA and CA125 were independent risk factors affecting the prognosis of patients (all $P < 0.05$). The nomogram predicted a model C-index of 0.918 (95% CI 0.885-0.952), and the risk model score was found to have a high clinical value in the 3-year survival of preexisting patients. Conclusion: Preoperative NLR, CEA, CA125 and clinical stage are correlated with the prognosis of patients with colon cancer. The nomogram model constructed based on NLR, CEA, CA125 and clinical stage has good accuracy.

Keywords: CEA, CA125, NLR, colon cancer, nomogram prediction model

Introduction

In the past two decades, the incidence of colon cancer has increased substantially in China, of which the patients mostly concentrated in elderly population [1]. Colon cancer is a common gastrointestinal tumor, with morbidity and mortality ranking in the top five of all malignant tumors, which seriously endangers human life expectancy and vigor [2, 3]. At present, the etiology of colon cancer is still not very clear, but its related risk factors have been gradually clarified with the development of research, such as high-fat and low-cellulose diet, physical inactivity, and genetic factors [4]. The economic development and improved living standard of Chinese citizens are bringing changes in dietary structure that leads to increased incidence and mortality of colon cancer patients [5]. More attention should be paid to this situation, and the prevention and treatment of colon cancer should be strengthened.

With the maturity of surgical approach, laparoscopic surgery has become the main surgical treatment for colon cancer because of advantages of less trauma and rapid postoperative recovery [6]. However, according to incomplete statistics, the prognosis of vast majority of patients treated with radical resection of colon cancer detected in their middle and advanced stages varies individually [7]. Therefore, it is particularly important to develop a comprehensive yet individualized treatment plan to improve

the prognosis, as well as to find effective clinicopathological factors affecting the prognosis of radical resection of colon cancer.

A growing number of studies have found that cancer-related inflammatory responses promote the development of malignant tumors and are associated with the survival of patients [8]. Neutrophil/lymphocyte ratio (NLR) is a balance index of antitumor inflammatory response and proinflammation inflammatory response, which can comprehensively reflect the inflammatory and immune status of cancer patients [9]. Carcinoembryonic antigen (CEA) belongs to the surface structural antigen of tumor cells and can enter the surrounding body fluids through the cell membrane after formation in the cytoplasm, which is common in the digestive tract and fetal serum and is a non-specific tumor marker that can be detected in a variety of body fluids [10]. In addition, carbohydrate antigen 125 (CA125) is a macromolecular carbohydrate antigen derived from the coelomic epithelium during embryonic development and is common in the serum of patients diagnosed with ovarian epithelial tumors with high sensitivity but poor specificity [11]. Its positivity in digestive system tumors is also proven to be of detective significance in recent studies [12].

This study was conducted to analyze the relationship between NLR, CEA and CA125 and postoperative survival of patients with colon cancer, and to construct a nomogram prediction model for survival rate after radical resection of colon cancer in order to provide a more convenient prognostic prediction method for clinical practice.

Methods and materials

Ethics statement

This study was approved by the Medical Ethics Committee of Baoji Central Hospital.

Clinical data

The clinicopathologic data of 102 patients with colon cancer who underwent radical resection of colon cancer in Baoji Central Hospital from April 2015 to April 2017 were retrospectively analyzed.

Inclusion and exclusion criteria

Inclusion criteria: Patients who were diagnosed with colon cancer according to the 8th edition of the American Joint Committee on Cancer (AJCC) diagnostic criteria in 2016 [13]; Patients confirmed with colon cancer by pathological examination; Patients with complete clinical laboratory tests and pathological data; Patients without neoadjuvant chemoradiotherapy before surgery; Patients who had R0 resection of the tumor; Patients who had postoperative combined therapy of Oxaliplatin and chemotherapy. All participants were adenocarcinoma patients.

Exclusion criteria: Patients with a survival time < 30 days due to severe postoperative complications; Patients with repeated or concurrent rectal cancer; Patients with prior history of other malignancy; Patients with evidence or history of infection with inflammatory disease affecting routine blood results; Patients with severe respiratory, hepatic, renal, or cardiovascular disease; Pregnant women.

Data collection

The clinical and pathological data of the patients were collected by electronic medical records and outpatient review records. Patients' gender, age, depth of tumor invasion, lymph node metastasis, tumor location, differentiation, clinical stage, tumor diameter, NLR, CEA and CA125 levels were collected and analyzed.

Patient follow-up data collection

Patients were followed up by telephone every 3 months for the first year after treatment and every 6 months after 2 years. All follow-up data of cancer patients were stored in and can be queried from the electronic archives.

Statistical analysis

Statistical analysis was performed using SPSS 26.0 software. Data were visualized using GraphPad Prism 8.00 software. Measurement data were expressed as mean ± standard deviation, and t-test was used for inter-group comparison. Enumeration data were expressed as case (%), and chi-square test or Fisher χ^2 s exact test was used for comparison between the two groups. Kaplan-Meier method and log-rank test were applied to analyze the difference of survival between the two groups, time-dependent receiver operating curve (ROC) was used to analyze the clinical value of risk score

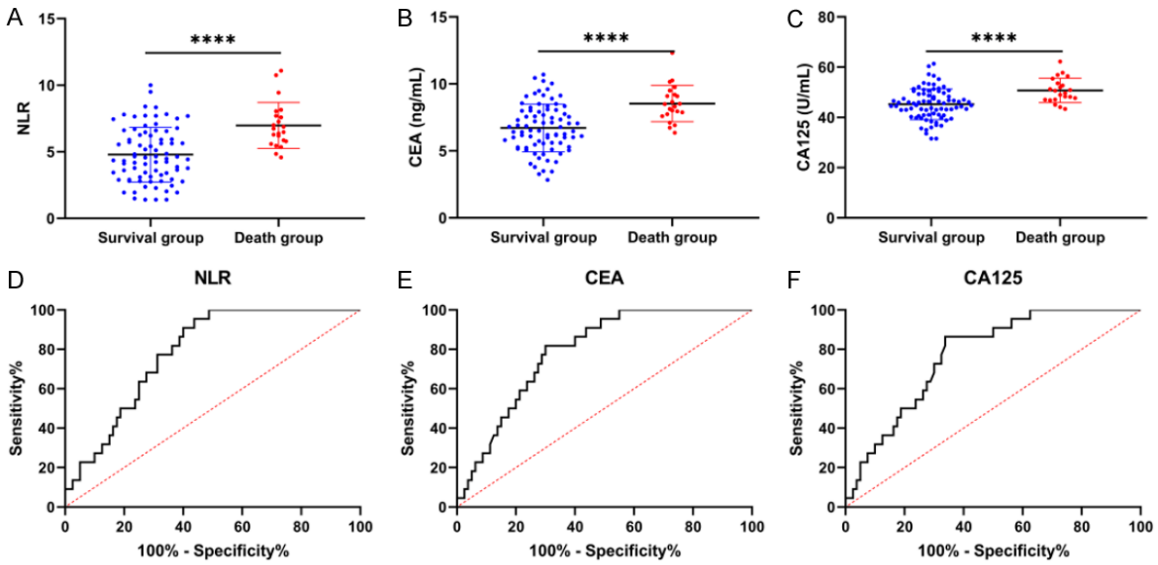

Figure 1. Expression of NLR, CEA and CA125 in dead and surviving patients. A. NLR expression levels in dead versus surviving patients. B. CEA expression levels in dead versus surviving patients. C. CA125 expression levels in dead versus surviving patients. D. ROC curve of NLR for predicting survival in colon cancer patients. E. ROC curve of CEA for predicting survival in colon cancer patients. F. ROC curve for CA125 in predicting survival in colon cancer patients. Note: **** indicates P < 0.0001, carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA125) and neutrophil/lymphocyte ratio (NLR).

in predicting the 1-, 2-, and 3-year survival of patients, and Cox proportional hazards regression model was utilized to analyze the factors affecting patient prognosis after radical resection of colon cancer.

Results

Expression of NLR, CEA and CA125 in survival patients

To determine the optimal cutoff value, we divided patients into survival and death groups. Comparison of NLR, CEA and CA125 levels between patients in the survival and death groups revealed that above indexes were comparatively lower in the survival group (all P < 0.0001, **Figure 1A-C**). Subsequently, ROC curves were plotted based on the results, which showed that the areas under the curves (AUCs) for NLR, CEA, and CA125 in predicting patient death were 0.784, 0.790, and 0.771, respectively (**Figure 1D-F**), and their cut-off values were 4.83, 7.58 (ng/mL), and 46.79 (U/mL), respectively.

Relationship between NLR, CEA and CA125 and clinical data of patients

According to the cut-off of NLR, CEA and CA125, patients were divided into high expression group and low expression group. The relationship between NLR, CEA, CA125 and clinical data of patients was further compared, and it was found that NLR was correlated with clinical stage, tumor diameter and differentiation of patients (all P < 0.05, **Table 1**). In addition, we also found that CEA was associated with clinical stage, tumor diameter, differentiation and lymph node metastasis (all P < 0.05, **Table 2**). However, CA125 was only correlated with tumor diameter in patients (P < 0.05, **Table 3**).

Prognostic factors of colon cancer patients after operation

According to the 3-year survival of patients, we analyzed the prognostic factors by Cox regression, and found that lymph node metastasis, differentiation, clinical stage, tumor diameter, NLR, CEA and CA125 were prognostic factors affecting the 3-year survival of colon cancer patients (**Table 4**, all P < 0.05). To further identify independent prognostic factors affecting postoperative outcome in colon cancer patients, multivariate Cox regression analysis was performed, and the results showed that differentiation, NLR, CEA and CA125 were independent risk factors affecting the prognosis of patients (**Table 4**; **Figure 2**, all P < 0.05).

Table 1. Relationship between NLR and clinical data of patients

Variable	NLR		χ^2 value	*P* value
	≥ 4.83 (n=56)	< 4.83 (n=46)		
Gender			0.060	0.806
Male (n=59)	33	26		
Female (n=43)	23	20		
Age			1.414	0.234
≥ 60 years (n=60)	30	30		
< 60 years (n=42)	26	16		
Tumor invasion depth				0.687*
T1-T2 (n=6)	4	2		
T3-T4 (n=96)	52	44		
Metastases to lymph nodes			0.380	0.537
N0 (n=52)	27	25		
N1-N2 (n=50)	29	21		
Tumor site			0.431	0.511
Left colon (n=48)	28	20		
Right colon (n=54)	28	26		
Degree of differentiation			5.120	0.023
Poorly differentiated (n=24)	18	6		
Moderately + well differentiated (n=78)	38	40		
CLINICAL PHASE			5.899	0.015
I-II (n=53)	23	30		
III-IV (n=49)	33	16		
Tumor diameter			5.526	0.018
≥ 5 cm (n=53)	35	18		
< 5 cm (n=49)	21	28		

Note: *indicates neutrophil/lymphocyte ratio (NLR) using Fisher χ^2 s exact test.

Construction of nomograms for colon cancer patients at 1st, 2nd and 3rd year after operation

Factors affecting 3-year survival (degree of differentiation, NLR, CEA, and CA125) were included in multivariate Cox regression analysis using R4.1.1 software to build functional models and draw nomograms. And the scores of each number or category of these factors were summed on a number scale, corresponding to the total score scale. A line was then drawn downward, and the intersection point with the coordinate axis of 1-, 2-, and 3-year overall survival rates indicated the probability of survival. The results showed that the C-index of the nomogram prediction model was 0.918 (95% CI 0.885-0.952), indicating that the model had good discrimination capability (**Figure 3A**). In addition, the time-dependent ROC curve for predicting 3-year survival of patients was further plotted according to the risk model score, and the results showed that the risk model score had a high clinical value in predicting 3-year survival of preexisting patients (**Figure 3B**).

Discussion

The process of tumor occurrence and development is accompanied by inflammatory response, which accelerates the occurrence and progression of tumors. The immune process between the two is very complex and is affected by a variety of factors [14]. Related studies have shown that tumor-associated inflammation can induce the expression of various molecules such as tumor necrosis factor-α, interleukin-6, and interleukin-17 in the tumor itself or surrounding cells, thus forming a micro-environment that may promote tumor progression [15, 16].

Studies have reported that multiple inflammation-related markers are associated with the

Table 2. Relationship between CEA and clinical data of patients

Variable	CEA (ng/mL)		χ^2 value	*P* value
	≥ 7.58 (n=43)	< 7.58 (n=59)		
Gender			2.472	0.115
Male (n=59)	21	38		
Female (n=43)	22	21		
Age			0.014	0.904
≥ 60 years (n=60)	25	35		
< 60 years (n=42)	18	24		
Tumor invasion depth				0.692*
T1-T2 (n=6)	3	3		
T3-T4 (n=96)	40	57		
Metastases to lymph nodes			7.070	0.005
N0 (n=52)	15	37		
N1-N2 (n=50)	28	22		
Tumor site			0.246	0.619
Left colon (n=48)	19	29		
Right colon (n=54)	24	30		
Degree of differentiation			10.548	0.001
Poorly differentiated (n=24)	17	7		
Moderately + well differentiated (n=78)	26	52		
CLINICAL PHASE			14.060	< 0.001
I-II (n=53)	13	40		
III-IV (n=49)	30	19		
Tumor diameter			5.154	0.023
≥ 5 cm (n=53)	28	25		
< 5 cm (n=49)	15	34		

Note: *indicates carcinoembryonic antigen (CEA) using Fisher χ^2 exact test.

prognosis of colorectal cancer patients, and the combination of multiple inflammatory factors can further improve the predictive efficacy for the prognosis of colorectal cancer patients [17, 18].

In this study, the expression of preoperative CEA, CA125 and NLR of surviving patients were observed and were found to be evidently lower in survival group than that in the death group. Previously, Baqar et al. [19] revealed that preoperative CEA levels were associated with age, BMI, ASA, and tumor stage, and CEA could be used as a reliable predictor of recurrence and survival in colon cancer patients. However, in the study by Björkman et al. [20], it was shown that CA125, an important and independent prognostic factor for colorectal cancer patients, is superior to CEA. Nevertheless, CA125 was not found to be more potent than CEA in our study. Moreover, Chen et al. [21] found that patients with lower NLR, PLR, and SII had better overall survival and disease-free survival in their study, which mainly because high NLR and low LMR suggest lymphopenia, and that may lead to a decrease in the immune response to tumors. Neutrophils can promote the formation of the tumor microenvironment by secreting cytokines and chemokines, thereby promoting the proliferation and metastasis of tumor cells, while tumor-associated macrophages from peripheral monocytes can inhibit the acquired immune response and promote tumor cell growth and tumor trophoblast angiogenesis, which in turn causes tumor invasion and metastasis [22]. Cho et al. [23] found that M1 stage was significantly increased in breast cancer patients with NLR > 1.34 and AJCC high stage patients. In addition, in Mazaki's study [24], it was found that the proportion of stage III patients with colon cancer was significantly higher than that of stage II patients when NLR was > 3. In our study, NLR was found to be associated with clinical stage, tumor diameter,

Table 3. Relationship between CA125 and clinical data of patients

Variable	CA125 (U/mL)		χ^2 value	*P* value
	≥ 46.79 (n=46)	< 46.79 (n=56)		
Gender			0.929	0.335
Male (n=59)	29	30		
Female (n=43)	17	26		
Age			0.183	0.668
≥ 60 years (n=60)	26	34		
< 60 years (n=42)	20	22		
Tumor invasion depth				> 0.999
T1-T2 (n=6)	3	3		
T3-T4 (n=96)	43	53		
Metastases to lymph nodes			0.333	0.563
N0 (n=52)	22	30		
N1-N2 (n=50)	24	26		
Tumor site			0.431	0.511
Left colon (n=48)	20	28		
Right colon (n=54)	26	28		
Degree of differentiation			2.220	0.136
Poorly differentiated (n=24)	14	10		
Moderately + well differentiated (n=78)	32	46		
CLINICAL PHASE			0.129	0.719
I-II (n=53)	23	30		
III-IV (n=49)	23	26		
Tumor diameter			5.898	0.015
≥ 5 cm (n=53)	30	23		
< 5 cm (n=49)	16	33		

Note: *indicates carbohydrate antigen 125 (CA125) using Fisher χ^2 exact test.

Table 4. Cox regression analysis

Variable	Univariate analysis			Multivariate analysis		
	P value	HR value	95% CI	*P* value	HR value	95% CI
Gender	0.178	0.562	0.243-1.300			
Age	0.680	1.200	0.503-2.861			
Tumor invasion depth	0.529	1.595	0.373-6.824			
Metastases to lymph nodes	0.043	2.531	1.032-6.210	0.641	1.279	0.455-3.592
Tumor site	0.743	1.150	0.498-2.652			
Degree of differentiation	< 0.001	13.541	5.255-34.893	< 0.001	10.615	3.943-28.576
Clinical phase	0.014	3.258	1.274-8.331	0.671	1.245	0.453-3.420
Tumor diameter	0.373	1.472	0.629-3.444			
NLR	< 0.001	1.544	1.266-1.883	< 0.001	1.656	1.296-2.115
CEA	< 0.001	1.608	1.272-2.033	0.007	1.366	1.091-1.712
CA125	< 0.001	1.125	1.055-1.201	0.009	1.110	1.026-1.201

Note: carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA125), and neutrophil/lymphocyte ratio (NLR).

and differentiation in patients. This is consistent with previous findings suggesting that tumors in patients with high NLR are more aggressive.

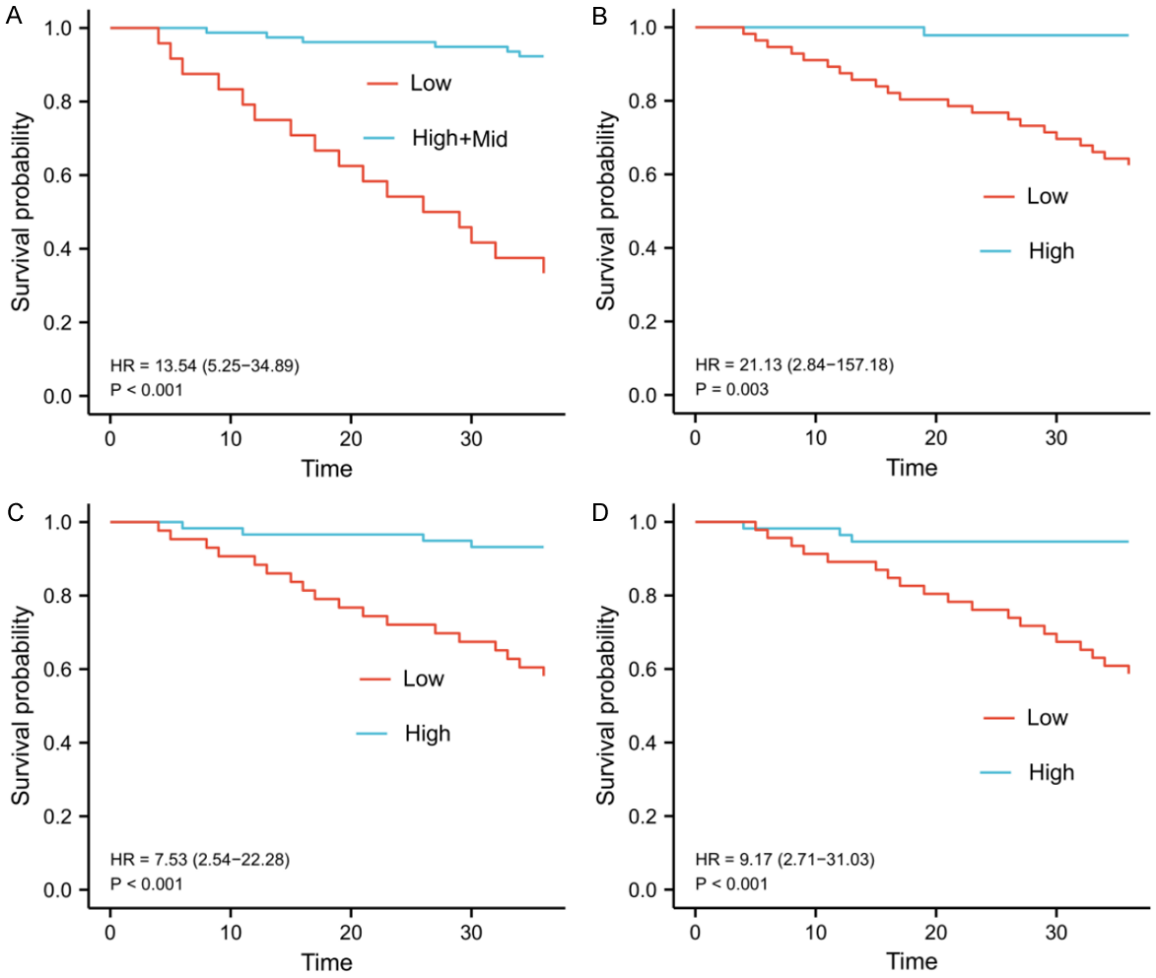

Figure 2. Relationship between prognostic factors and patient survival. A. 3-year overall survival in patients with different degrees of differentiation. B. Overall survival at 3 years in patients with high and low NLR expression. C. Overall survival at 3 years in patients with high and low CEA expression. D. Overall survival at 3 years in patients with high and low CA125 expression. Note: carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA125), and neutrophil/lymphocyte ratio (NLR).

At the end of the study, we constructed nomograms that quantify and predict the probability of a clinical event, thereby guiding clinical decision-making and risk stratification. In our study, we included the factors affecting 3-year survival, including differentiation, NLR, CEA and CA125, in multivariate Cox regression analysis to establish functional models and nomograms, and performed consistency analysis and discrimination evaluation, and the results showed a good predictive effect of this nomogram model. Guo et al. [25] found that nomograms constructed by NLR, platelet-lymphocyte ratio (PLR), CEA, CA199, lactate dehydrogenase (LDH) and C-reactive protein (CRP) successfully predicted the 1-, 3- and 5-year survival of patients with advanced colon cancer. In contrast to their study, we plotted time-dependent ROC for the scores obtained by the risk model and found that the risk score had a high predictive value (> 0.9) of 1-, 3- and 5-year survival time after surgery in colon cancer patients. This shows that we successfully constructed an ideal prognostic model.

We determined that the nomogram model constructed by NLR, CEA, and CA125 has a high predictive value for the survival of colon cancer patients after surgery. However, this study has certain limitations. First of all, as a retrospective study, the sample size was limited, and we failed to stage the impact of the constructed column line model on the long-term survival of patients due to time issues. Second, bias may

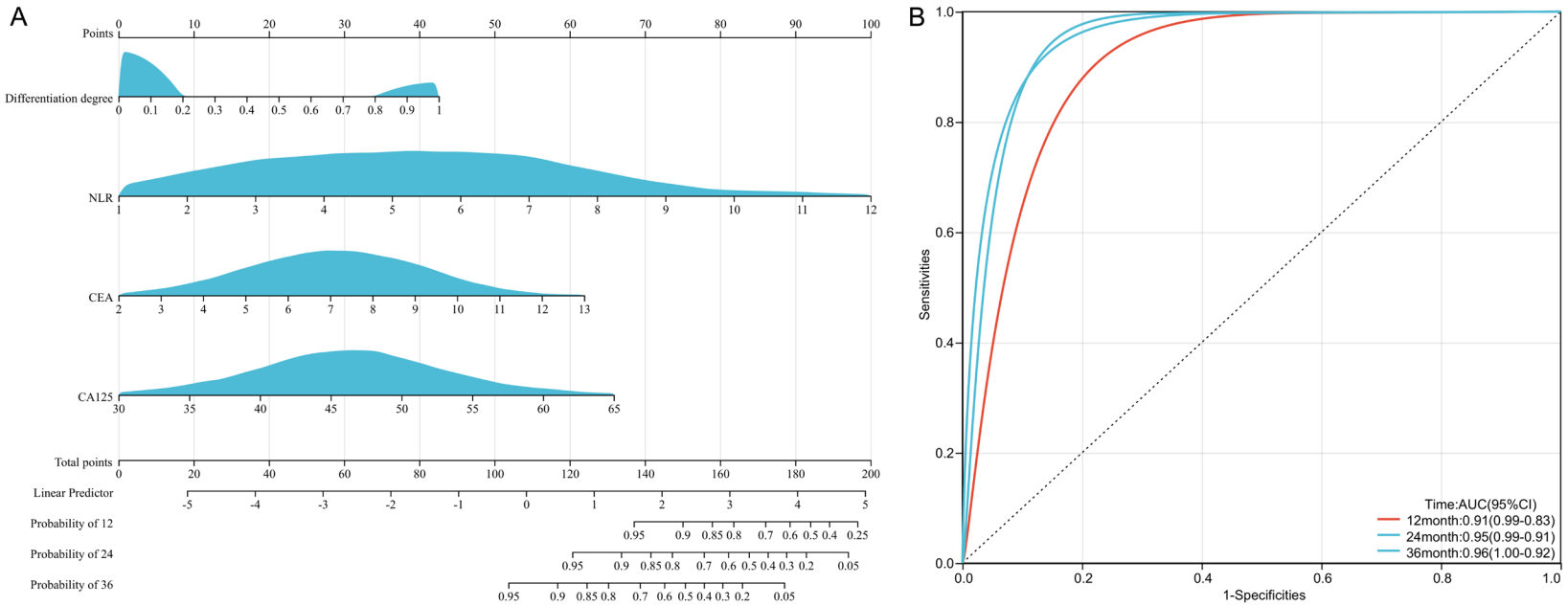

Figure 3. Nomogram construction and survival prediction. A. Nomograms predicting 1-, 2-, and 3-year overall survival in patients after radical resection of colon cancer. B. ROC curve for predicting overall survival at 1, 2, and 3 years in patients.

have occurred in results because this is a retrospective study. Finally, we hope to carry out long-term prospective studies in the future to refine our study conclusions through long-term follow-up of patients.

In summary, preoperative NLR, CEA and CA125 and clinical stage are associated with the prognosis of colon cancer patients, and the nomogram model constructed based on NLR, CEA and CA125 and clinical stage has good accuracy.

Disclosure of conflict of interest

None.

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