A prediction model for risk factors of stage II to III colon cancer based on postoperative serum carcinoembryonic antigen and tumor deposition: a retrospective multicenter cohort study

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Abstract

Purpose: This study aimed to establish a recurrence risk prediction model composed of postoperative CEA combined with pathological features for postoperative recurrence risk stratification in stage II to III colon cancer.

Methods: A retrospective analysis of 1,321 patients who underwent radical surgery for stage II/III colon cancer from April 2008 to January 2019. Cox proportional hazards regression model was used to analyze the independent recurrence prognostic factors of patients with recurrence-free survival (RFS). The recurrence risk score was established based on independent recurrence prognostic factors, and the Kaplan-Meier method was used to draw the patient's recurrence-free survival curve and overall survival (OS) curve.

Results: The median follow-up period of all patients was 49.73 months. Multivariate analysis of COX proportional hazards model showed that postoperative CEA increased (HR, 2.0; 95% CI, 1.1-3.5), higher stage N (HR, 2.0; 95 % CI, 1.1-3.5), tumor deposition (HR, 2.0; 95% CI, 1.1-3.5) is independently associated with shorter RFS. The recurrence risk score is an independent stratified prognostic factor of RFS and OS.

Conclusion: Based on postoperative CEA, N stage and tumor deposition positive are powerful predictors of recurrence survival and prognosis for patients with stage II to III colon cancer.

Introduction

The global incidence and mortality of colorectal cancer are increasing year by year, which seriously threatens global life and health. Therefore, the diagnosis and treatment of colorectal cancer are becoming more and more important (1). Current guidelines recommend that the most important treatment for patients with stage II/III colon cancer is radical surgical resection, but some patients with surgical resection are still prone to recurrence. The American Joint Commission on Cancer (AJCC) TNM classification system is used to stratify the prognosis of colorectal cancer according to the pathological characteristics of the tumor tissue after the operation, to choose different treatment methods. However, recent studies have found that there are obvious limitations, especially whether to use adjuvant therapy after surgery for stage II/III colon cancer. Subject to more and more challenges and doubts (2). Therefore, it is very important to find simpler and limited prognostic indicators to predict the risk of recurrence of colon cancer after surgery.

Carcinoembryonic antigen is an important indicator of the prognosis of colon cancer. It is the most widely used prognostic indicator ever. CEA levels greater than 5 ng/mL or elevated detection levels are associated with colorectal cancer recurrence (3). So far, preoperative CEA has been used as a prognostic indicator of colon cancer (4). In our latest study, 2,160 patients with colorectal cancer from three Chinese hospitals were included. Analyze the relative importance of each risk parameter to relapse-free survival. The results obtained are: T stage: 11.24%; N stage: 49.51%; preoperative CEA: 1.59%. Preoperative CEA is not as important as other risk factors in predicting the prognosis of colon cancer (5).

Preoperative CEA has played an important role in previous studies. However, with the deepening of research, it was discovered that there are great limitations in using preoperative CEA. It cannot be used solely as a prognostic indicator for recurrence of colon cancer after surgery. More and more studies are turning to focus on postoperative CEA. Because some patients with elevated preoperative CEA levels have their CEA returned to normal after radical surgery. The prognosis of this part of patients needs to be combined with higher postoperative CEA levels to predict a poor prognosis. Preoperative CEA for colon cancer patients cannot be used as a good prognostic indicator (6). The National Comprehensive Cancer Network (NCCN) guidelines also recommend CEA postoperative monitoring for patients with resected stage II and stage III colorectal cancer every 5 to 6 months. However, with such limitations in TNM staging, postoperative CEA combined with TNM staging can be used to predict the recurrence of colon cancer. To provide a new basis for the prognostic stratification of colon cancer (2). Therefore, postoperative CEA is more important than preoperative CEA.

Generally speaking, most of the previous prognostic models were established based on preoperative CEA as a risk factor. This study aims to incorporate postoperative CEA into the establishment of a risk score for recurrence of stage II/III colon cancer. Provide a simpler and more accurate stratification basis for the implementation of precision medicine for patients with stage II/III colon cancer after surgery.

Methods

Ethics approval and consent to participate

The local ethics committee of the Yunnan Cancer Hospital, Xishan Region, Kunming, People's Republic of China, approved this retrospective study (No. KY201824), which complied with the Declaration of Helsinki and good clinical practice guidelines. The requirement for informed consent was waived by the committee owing to the study's retrospective nature. All the patient data in the survey were anonymized.

Study Design and Patient Cohort

We conducted a multicenter retrospective study on 1799 patients with stage II/III colon cancer. Initially, colon cancer patients who underwent radical surgical resection and pathologically confirmed colon cancer at Yunnan Cancer Hospital between April 2008 and January 2019 were included in the single-center testing group (n = 1321). Establish a recurrence risk score based on postoperative CEA. Then randomly selected patients with colon cancer (n = 458) in the Sixth Hospital of Sun Yat-sen University between April 2008 and December 2017) Verified the hypothesis. This study has been approved by the institutional review board, and because the study is retrospective, informed consent is not required.

Extract the CEA value closest to the operation time from the electronic medical record. The preoperative CEA was defined as the CEA value closest to the operation time, and the postoperative CEA was defined as the final CEA value within 12 weeks after the operation and before starting adjuvant chemotherapy. At the same time, collect demographic, clinical, and pathological data of patients (6). All CEA measurements in Yunnan Cancer Hospital were performed with COBAS 800 e602 immunoassay analyzer (Roche

Diagnostics, Tokyo, Japan) with chemiluminescence immunoassay analyzer. Sun Yat-sen University uses the Alinity I immunoassay analyzer (Abbott Diagnostics, Chicago, USA), following the World Health Organization standard method (code 73/601) (7). The reference range of serum CEA is between 0.0 and 5.0 ng/mL. A value higher than 5.0 ng/mL is considered an increase in CEA, and a value lower than 5.0 ng/mL is considered normal (2,6).

Adjuvant Chemotherapy Protocol

According to NCCN clinical practice guidelines in colon cancer, some patients with stage II-III colon cancer received postoperative adjuvant chemotherapy (2). Adjuvant chemotherapy regimens include FOLFOX, CapeOX, single-agent capecitabine or 5-FU/leucovorin (5).

Surveillance protocol

The patient's clinical evaluation includes serum CEA test level, physical examination, imaging examination (CT/MRI), and colonoscopy biopsy. The CEA level is measured every 3 to 6 months for 3 years. Perform imaging examinations at least every 12 months and at least 3 years, including plain scans of the patient’s chest, abdomen, and pelvis and contrast enhancement. Colonoscopy is performed once a year after the operation, at intervals of every three years. Colonoscopy, histopathological examination, or imaging examination confirmed all cases of recurrence and metastasis.

Outcomes

This study combines postoperative CEA levels to predict and evaluate the likelihood and value of recurrence in colon cancer patients undergoing radical surgery. It is worth noting that the recurrence-free survival time refers to the duration between surgery and recurrence, metastasis and death of the patient. If the patient cannot be followed up, the recurrence-free survival time will be calculated based on the last follow-up date. Each enrolled patient underwent a 3-year full follow-up, and patients less than 3 years were not included in this study. A total of 1321 patients had been followed up for more than 3 years and met the enrollment requirements. Among them, 313 had recurrence and metastasis, with a recurrence rate of 23.69%. The median follow-up time was 49.73 months.

Establish recurrence risk score

The Kaplan-Meier method was used to estimate the RFS, and the log-rank test was used to compare the groups. Tested the Cox proportional hazards hypothesis. Use the Cox proportional hazards regression model for univariate and multivariate modeling, and examine the prognostic significance of the variables identified in the model. Then, variables with $P < 0.10$ in the univariate analysis were included in the multivariate analysis. Use backward stepwise selection to obtain the final multivariate model, and keep the variables with $P<0.05$ in the final model. Each independent risk factor is defined as 1 point, and finally, a risk score that can stratify the prognosis of colon cancer patients is formed.

Statistical analysis

Use χ2 or Fisher's exact test (discrete variables) and unpaired t-test, Wilcoxon signed-rank test, or continuous variable analysis of variance to compare patient characteristics. Kaplan-Meier method and log-rank test were used for survival analysis. All P values below 0.05 are statistically significant. Cox proportional hazards regression model was used to evaluate factors independently related to RFS. According to the clinical relevance and statistical significance in the univariate analysis, the variables included in the final multivariate model were selected (cutoff value, P = 0.10). Factors related to disease control are tested through logistic regression in single factor and multivariate analysis. The alpha level is 5%. The internal validation of the final multivariate model of RFS was carried out on the population with an overall recurrence risk score through the bootstrap sample program (n = 1000 samples). Use SPSS23.0 software and GraphPad-prism 8 drawing software for statistical analysis (8).

Results

Test Set

In the Test Set cohort, there were 1321 patients with II/III CRC. Follow-up found that there were 197 deaths and 313 recurrences. Clinicopathological characteristics are presented in Table 1. We conducted the shortest 36 months and longest 134 months follow-up on 1321 test sets and 458 validation set cohorts. Median OS was 48.03 months (95% CI, 46.73-48.77 months) and median RFS was 44.33 months (95% CI,42.73-46.10 months).

Multivariate analyses of all variables

Table 2 shows the univariate and multivariate analysis of factors related to RFS. In univariate analysis, the degree of tumor differentiation is poor, the pathological type contains mucus components, there are vascular infiltrating lymphatic vessels, the N stage is higher, tumor deposition and postoperative CEA increase are related to the shortening of RFS（log-rank P＜0.05）. Multivariate analysis showed that postoperative CEA elevation (HR, 2.0, 95% CI, 1.1-3.5)，higher N stage(HR, 2.0, 95% CI, 1.1-3.5), and tumor deposition(HR, 2.0, 95% CI, 1.1-3.5) was independently associated with shorter RFS. But higher T stage (HR, 2.0, 95% CI, 1.1-3.5) was not independently associated with shorter RFS.

Kaplan-Meier analysis of different risk score (0-3) groups

The recurrence risk score was developed based on whether the CEA was elevated after the operation, the pathological N stage, and the presence or absence of tumor deposition. According to the risk factors (the highest pathological N stage can have two risk factors), it can be divided into 4 groups: good, 0 factors, medium, 1 factor, poor, 2 factors, very poor, 3 factors. We first estimated the OS and RFS for each risk score group using the Kaplan-Meier method.

The 3-year RFS rate in the risk score of the 0 groups was 87.5% (95% confidence interval [CI]: 83.1%-90.9%), which was significantly higher than that of the other three groups, as demonstrated in Figure 1B. ，The risk score of 1 group, HR 1.51, 95%CI 1.13-2.04, the risk score of 2 groups, HR 3.56, 95%CI

2.68-4.73, the risk score of 3 groups, HR 5.67, 95%CI 3.74-8.61, P <.001). A similar difference of the OS rate among four groups was observed, as shown in Figure 1A.The risk score of 1 group, HR 1.42,95%CI 0.96-2.09, the risk score of 2 groups, HR 3.64,95%CI 2.53-5.24, the risk score of 3 groups, HR 8.33,95%CI 5.22-13.3, P <.001).

In patients with stage II (Figure 2A and 2B) disease, due to the uniqueness of stage II colon cancer, there is only one stage of N0. Therefore, stage II colon cancer is the only risk factor for postoperative CEA elevation. The 3-year RFS rate for the 61 patients with elevated preoperative CEA was 80.1% (95% CI, 73.1%-87.9%) compared with 88.7% (95% CI, 85.2%-93.8%) for the 548 patients with normal preoperative CEA (HR,2.26,95%CI,1.18-4.34, P = .012). Similar associations between Risk score and OS were observed (HR,2.44,95%CI,1.48-4.01, P <.001).

In patients with stage III (Figure 2C and 2D) diseaseThe RFS rate in the risk score of 0 group was 88.2% (95% CI, 82.7%-95.3%), which was significantly higher than that of the other three groups, as demonstrated in Figure 1A (the risk score of 2 groups, HR 3.64,95%CI 2.53-5.24, the risk score of 3 groups, HR 8.33,95%CI 5.22-13.3, P <.001).

Validation Set

The RFS rate in the risk score of the 0 groups was 89.4% (95% CI, 81.6%-92.3%), which was significantly higher than that of the other three groups, as demonstrated in Figure 1D. The risk score of 1 group, HR 1.58, 95%CI 0.65-3.84, the risk score of 2 groups, HR 2.95, 95%CI 1.16-7.54, the risk score of 3 groups, HR 12.58, 95%CI 3.77-42.03, P <.001). A similar difference of the OS rate among four groups was observed, as shown in Figure 1C.The risk score of 1 group, HR 1.40,95%CI 0.82-2.40, the risk score of 2 groups, HR 2.48,95%CI 1.38-4.46, the risk score of 3 groups, HR 4.29,95%CI 1.49-12.39, P =.002).

Discussion

In this study, the risk factors that may affect the recurrence of colon cancer were included in the Cox proportional hazard model, and finally, three independent risk factors were derived. They are pathological N staging, tumor deposition, and postoperative CEA. It is worth mentioning that the preoperative increase in CEA is not an independent risk factor for the three-year recurrence-free survival of patients with stage II/III colon cancer, which may be somewhat different from previous studies. The prognostic stratification of colon cancer using only the tumor-node-metastasis (TNM) stage has some limitations. We sought to increase the accuracy of stratifying patients with stage III colon cancer by constructing a prognostic model combining carcinoembryonic antigen (CEA) with TNM. But this is only used for patients with stage III colon. It is temporarily unclear whether it applies to patients with stage II colon cancer (9). The study revealed that T4 invasion, vascular invasion, postoperative CEA level, and the number of examined lymph nodes may significantly affect the prognosis of stage II CRC patients after radical resection. The risks of postoperative early relapse and worse clinical outcomes increase in proportion to the values of these four parameters (10). In this study, the risk score established by pathological N staging combined with postoperative CEA and tumor deposition was applied to patients with stage II/III colon cancer.

Lymph node dissection is very important in colon cancer surgery. If the lymph nodes are not completely cleaned or the number is insufficient, the patient will relapse and metastasize after surgery. There is no minimum number of lymph nodes that can ensure an accurate determination of the status of the lymph nodes. Rather than focusing on the recommended minimum number of nodules, it is better to turn to develop methods to ensure that colon cancer specimens are dissected in a standardized manner to optimize lymph node collection. (11). The inter-group trial INT-0089 is a mature trial of adjuvant chemotherapy for high-risk patients with stage II and stage III colon cancer. Even if lymph nodes were not involved, OS and CSS improved by analyzing more lymph nodes (P = .0005 and P = .007, respectively). The impact of this variable makes it an important variable to consider when evaluating future trials (12). The current recommendations for the retrieval and examination of at least 12 lymph nodes apply to the correct treatment and prognosis of patients undergoing CRC surgical resection (13). These results indicate that when the same number of lymph nodes is metastasized, the prognosis of the micrometastatic disease may be similar to that of large metastatic disease (14). Internationally recognized serum CEA is an important prognostic indicator of colorectal cancer (15,16). Postoperative CEA is an independent risk factor for 3-year recurrence-free survival in patients with stage II/III colon cancer. Positive postoperative CEA and CEA increment are independent prognostic factors for stage II and III CRC. Patients with elevated postoperative CEA levels and positive CEA increment have the worst PFS and OS compared to other groups (17). Our results may be helpful to the adjuvant treatment of stage II and III CRC after radical surgery. Prognostic factors are not only related to the pathological stage (T4 and/or N2) but also related to the high preoperative CEA level. The combination of pT, pN, and high preoperative CEA levels may be predictive factors for anti-CapeOX adjuvant chemotherapy (18).

The new histological grade using nerve infiltration, vascular tumor thrombus, and tumor sprouting risk grouping is a powerful predictor of disease-free survival for patients with colorectal cancer. A comprehensive evaluation of these familial histological factors can be used as a new clinically useful prognostic system for individualized prognosis and selection of appropriate adjuvant therapy for patients with colorectal cancer (19). Tumor deposition has been considered as a predictor of lymph node metastasis and poor survival in patients with colorectal cancer and has been increasingly recognized (20,21). Tumor deposition is also called tumor budding, which refers to the phenomenon that cancer cells separate from aggressive tumors and migrate into the tumor stroma (22). Although the impact of tumor sprouting on the prognosis of colorectal cancer should be fully clarified, according to some recent publications, tumor sprouting is an independent prognostic factor of colorectal cancer and is related to poor differentiation, nerve infiltration, and vascular tumor thrombi (23). In addition, the number of tumor deposits is an independent prognostic factor for the survival of colon cancer patients (24).

This exploratory study has limitations. First of all, because of the retrospective study design, there are differences in the time of postoperative CEA measurement, but the time we selected is the value closest to the operation time. Patients who have received postoperative adjuvant treatment for more than 12 weeks or at the time of the test have been excluded. Secondly, tumor deposition is defined as the N1c stage in the guidelines, and it is still divided into the NI stage at the time of analysis. This part of the

patients is not separately grouped due to the small number of patients. It is not clear whether the result will be biased. This study will continue to include more cases Wait for the follow-up results to be released.

Conclusions

Risk score developed based on postoperative CEA appears to be an important prognostic biomarker. It can distinguish the recurrence risk and long-term prognosis of stage II/III colon cancer after radical surgery. Provide an important basis for individualized treatment of colon cancer patients.

Declarations

Author contributions All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication. WRH and ZDF contributed to the study design. PXL and MJG contributed to data collection. CYX was responsible for check the data. PHJ contributed to statistical analysis and preparing manuscript.

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Data availability All data and material relevant to the study are available from the authors upon request.

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Tables

Table 1. Patient and tumor characteristics

Characteristic	All (N=1321)	Not Recurred (n=1008)	Recurred (n=313)	P-value[Ý]
Age (years)				0.276
Median (IQR)	59.00(50.00-67.00)	59.00(50.00-67.00)	60.00(51.00-67.00)	
Mean (SD)	57.85 (12.49)	57.65 (12.60)	58.53 (12.12)	
Sex, no. (%) of patients				0.469
Male	784 (59.3%)	604 (59.9%)	180 (57.5%)	
Female	537 (40.7%)	404 (40.1%)	133 (42.5%)	
BMI（Kg/m2）				
Median (IQR)	22.31(20.45-24.91)	22.86(20.58-24.74)	22.24(20.26-25.08)	
Mean (SD)	22.63(3.32)	23.03(3.437)	22.52(3.238)	
Surgical approach				0.067
OR	754 (57.1%)	561 (55.7%)	193 (61.7%)	
LR	567 (42.9%)	447 (44.3%)	120 (38.3%)	
Tumor differentiation, no. (%) of patients				0.001
Well	56 (4.2%)	53 (5.3%)	3 (1.0%)	
Moderate	840 (63.7%)	644 (63.8%)	196 (62.6%)	
Poor-undifferentiated	373 (28.2%)	278 (27.6%)	95 (30.3%)	
Unknown	52 (3.9%)	33 (3.3%)	19 (6.1%)	
Mucinous type				0.001
No	927 (70.2%)	685 (68.0%)	242 (77.3%)	
Yes	394 (29.8%)	323 (32.0%)	71 (22.7%)	
T stage, no. (%) of patients				0.078
T0-1	36 (2.7%)	33 (3.3%)	3 (1.0%)	
T3	1142 (86.4%)	864 (85.7%)	278 (88.8%)	
T4	143 (10.9%)	111 (11.0%)	32 (10.2%)	
N stage, no. (%) of patients				<0.001
N0	646 (48.9%)	542 (53.8%)	104 (33.2%)	

N1	478 (36.2%)	344 (34.1%)	134 (42.8%)	
N2	197 (14.9%)	122 (12.1%)	75 (24.0%)	
AJCC 7th ed. stage				<0.001
II	645 (48.8%)	541 (53.7%)	104 (33.2%)	
III	676 (51.2%)	467 (46.3%)	209 (66.8%)	
LVI				0.013
Yes	131 (9.9%)	88 (8.7%)	43 (13.7%)	
No	1190 (90.1%)	920 (91.3%)	270 (86.3%)	
PNI				0.017
Yes	107 (8.1%)	71 (7.0%)	36 (11.5%)	
No	1214 (91.9%)	937 (93.0%)	277 (88.5%)	
Tumor deposit, no. (%) of patients				<0.001
Yes	82 (6.2%)	36 (3.6%)	46 (14.7%)	
No	1239 (93.8%)	972 (96.4%)	267 (85.3%)	
Adjuvant chemotherapy, no. (%) of patients				0.673
Yes	1086 (82.2%)	826 (81.9%)	260 (83.1%)	
No	235 (17.8%)	182 (18.1%)	53 (16.9%)	
Preoperative CEA, ng/mL				0.029
Median (IQR)	4.00(2.03-10.83)	3.62(2.00-9.91)	5.47(2.49-13.37)	
Mean (SD)	19.45 (145.11)	14.61 (41.98)	35.13 (145.11)	
Postoperative CEA, ng/mL				
Median (IQR)	2.00(1.25-3.28)	1.94(1.18-3.01)	2.38(1.49-4.55)	0.001
Mean (SD)	8.84 (90.48)	3.43 (10.61)	25.5 (181.03)	

Note1 Data are median (IQR) Mean (SD) or n (%).

2Abbreviations: BMI, Body Mass Index; CEA, carcinoembryonic antigen; LR, laparoscopic resection; LVI, lymphovascular invasion; OR, open resection; PNI, perineural invasion.

3 P value, using Wilcoxon Mann-Whitney test, chi-square test or exact Fisher test depending on whether the variable is continuous or categorica.

Table 2. Univariate and multivariate analyses of 3-year recurrence free survival

Variable	Univariate			Multivariate		
	% 3-year RFS	95% CI	P-value	Hazard ratio	95% CI	P-value
Age			0.879			
<65	75.03	72.78-85.07				
≥65	74.27	70.32-81.57				
BMI			0.393			
<28	77.69	67.64-81.73				
≥28	74.07	59.09-79.06				
Sex			0.262			
Male	76.10	72.41-86.17				
Female	77.70	75.15-83.99				
Surgical approach			0.079			
OR	78.70	74.60-82.79				
LR	83.63	79.46-87.80				
Tumor differentiation			0.004			
Well	79.22	74.78-83.66		reference		
Moderate	81.29	77.46-85.11		1.13	0.91-1.42	0.272
Poor-undifferentiated	78.03	72.94-83.13		1.31	0.99-1.73	0.055
Mucinous type			0.007			
No	78.21	74.72-81.70		reference		
Yes	82.76	77.23-88.29		1.40	0.74-2.67	0.305
Lymph node yield			0.153			

≥12	75.78	71.61-83.94				
12	70.79	63.83-87.76				
Pathology T stage			0.094			
T1-2	85.78	78.68-87.88				
T3	74.73	70.49-82.97				
T4	59.95	49.57-61.34				
Pathology N stage			0.001			
N0	82.46	79.26-85.67		reference		
N1	71.38	65.88-76.88		1.96	1.41-2.73	**0.001**
N2	58.75	45.88-76.88		2.99	2.03-4.43	**0.001**
Lymphovascular invasion			0.034			
No	79.93	76.99-82.88		reference		
Yes	71.83	64.28-79.37		1.52	0.94-2.44	0.086
Perineural invasion			0.027			
No	82.23	79.20-85.26		reference		
Yes	67.57	58.99-76.16		1.33	0.53-3.32	0.538
Tumor deposit			0.001			
No	85.28	82.18-88.42		reference		
Yes	50.10	44.20-56.01		1.81	1.25-2.60	**0.002**
Preoperative CEA, ng/mL			0.001			
≤5	86.89	83.02-90.76		reference		

5	70.21	66.11-74.32		1.07	0.80-1.44	0.635
Postoperative CEA, ng/mL			0.001			
≤5	83.31	80.15-86.48		reference		
5	57.19	48.99-65.39		2.41	1.72-3.38	**0.001**
Adjuvant chemotherapy			0.677			
Yes	82.27	79.02-85.53				
No	77.87	71.00-84.75				

NoteP values were calculated using the log-rank test for univariate analysis and the Cox proportional hazards model for multivariate analysis.

Figures

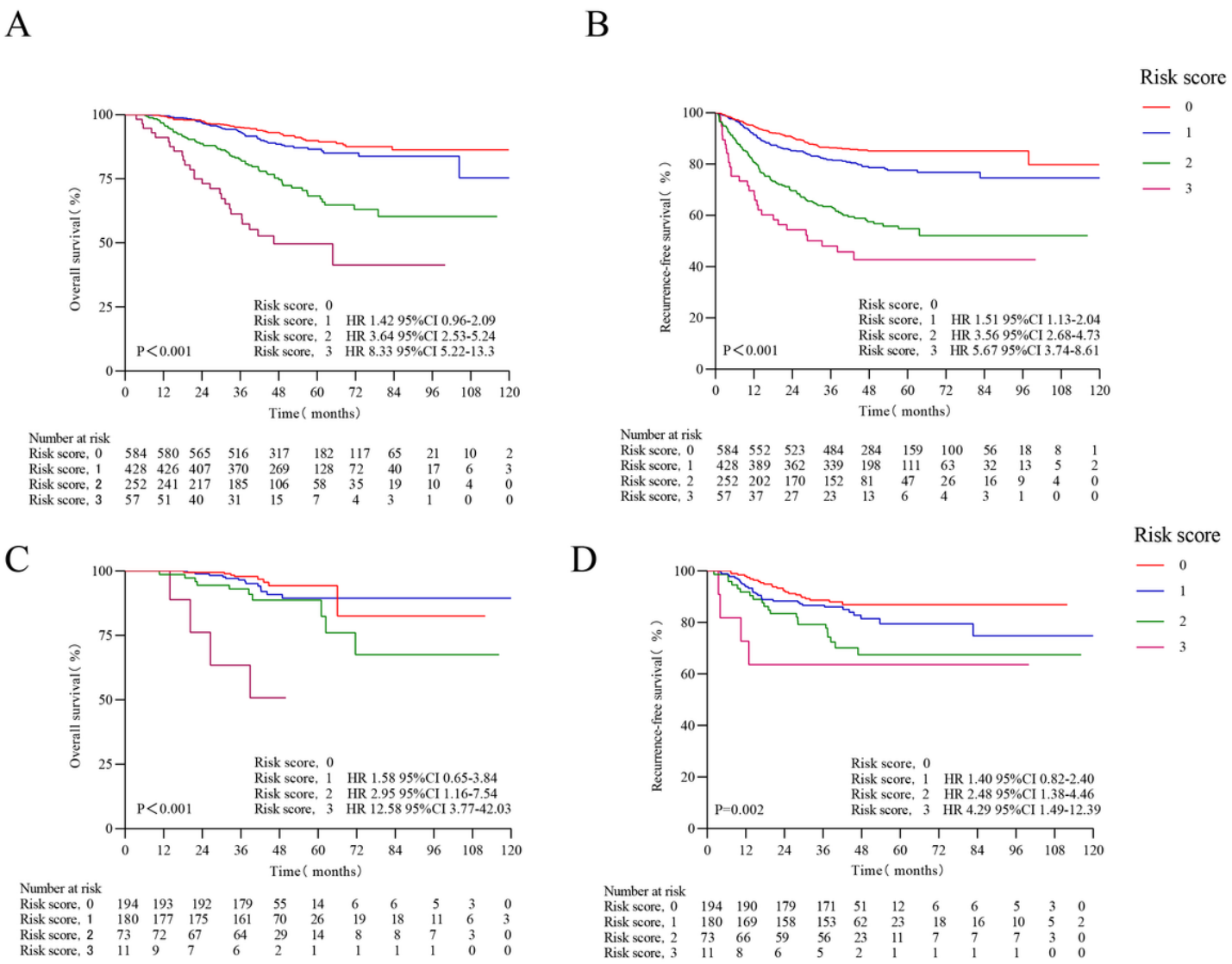

Figure 1

Survival curves of different risk groups based on the recurrence risk score of stage II/III colon cancer established by postoperative CEA.

(A) Overall survival in the training dataset.

(B) Recurrence-free survival in the training dataset.

(C) Overall survival in the validation dataset.

(D) Recurrence-free survival in the validation dataset.

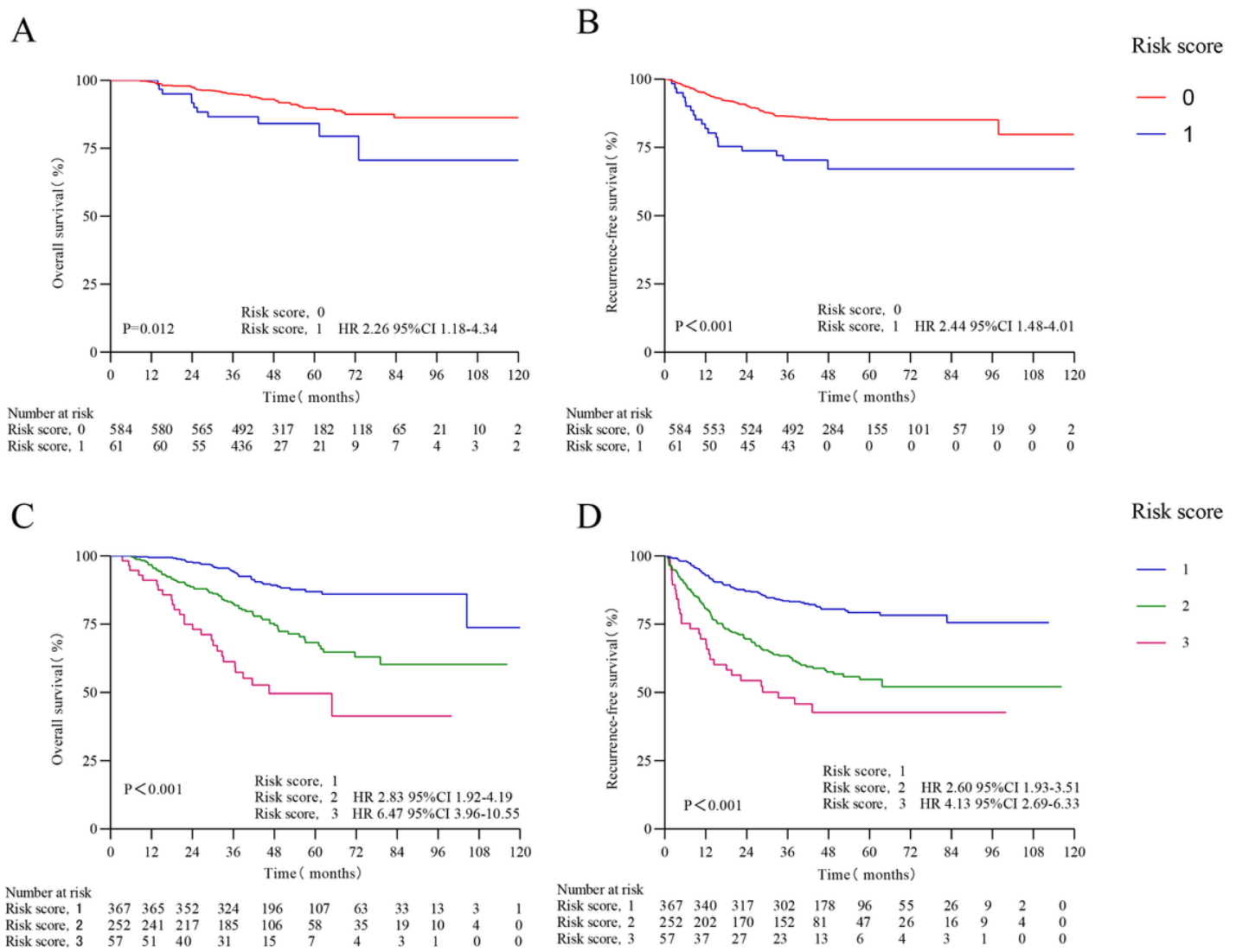

Figure 2

Survival curves of different risk groups in different stages based on the recurrence risk score established by postoperative CEA.

(A) Overall survival in the stage of II patients.

(B) Recurrence-free survival in the stage of II patients.

(C) Overall survival in the stage of III patients.

(D) Recurrence-free survival in the stage of III patients.