

# A Nomogram Model for Predicting Prognosis of Obstructive Colorectal Cancer

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## Research

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# Abstract

**Background:** The prognosis of obstructive colorectal cancer (oCRC) is worse than non-obstructive CRC, but the individualized prediction model for the prognosis of oCRC patients has not been established. The aim of this study was to select prognostic predictors to build a Nomogram model to predict the prognosis of oCRC patients.

**Methods:** A retrospective study was conducted on 181 oCRC patients between February 2012 to December 2017 from three medical hospitals. 129 patients in one of the hospitals were assigned to the training cohort. Univariate and multivariate analysis were used to select independent prognostic indicators in a training cohort and a Nomogram model was constructed. 52 patients from another two hospitals were used as the testing cohort to validate the model.

**Results:** Multivariate analysis illustrated the CEA [ $p=0.037$ , HR=2.872 (1.065-7.740)], N stage [N1 vs. N0,  $p=0.028$ , HR=3.187 (1.137-8.938); N2 vs. N0,  $p=0.010$ , HR=4.098 (1.393-12.051)] and surgical procedure [ $p=0.002$ , HR=0.299 (0.139-0.643)] were independent prognostic factors for OS of oCRC patients. These factors were used to construct the Nomogram model. Both internal and external validation shows its relatively accuracy.

**Conclusions:** CEA, N stage and surgical procedure were independent prognostic factors for OS of oCRC patients, which can be visually exhibited by Nomogram model.

## Introduction

Colorectal cancer (CRC) is one of the leading diagnosed cancers that has contributed to plenty of cancer-related deaths worldwide [1, 2]. Bowel obstruction is one of the severe complications for patients with colorectal cancer, which is also considered to be an emergency associated with high mortality [3]. This is usually the first clinical situation in about 20% CRC patients [4]. Some researchers reported that CRC patients accompanied with obstruction usually have an advanced stage and worse long-term survival compared to non-obstructive CRC patients, whose 5-year survival rate ranges from 31–42% [5, 6]. Although the negative impact of obstruction on the postoperative outcomes has been well documented, however, there is few research on the factors affecting the prognosis of oCRC patients.

The Nomogram model, as a reliable statistical method, can integrate multiple variables into a visual plot to exhibit the predicted probabilities of events [7]. Actually, it is widely used for tumor prognosis evaluation. In the majority of cancer types, Nomogram model have been proved to generate more precise and intuitive prediction when compared with the traditional evaluation methods [8, 9]. However, the individualized prediction model for the prognosis of oCRC patients has not been reported in the literature.

In the present study, we developed a prognostic Nomogram model based on the outcomes and prognostic factors in oCRC patients with the aim of predicting individualized survival in oCRC patients.

## Patients And Methods

# Patients

Total 240 oCRC patients were collected between 2012 and 2017. The inclusion criteria were as follows: histologically confirmed primary CRC with obstruction and complete baseline clinicopathological data. The exclusion criteria included any of the following: (a) recurrent or multiple primary CRC; (b) combined with other malignancy; (c) patients that cannot undergo surgery; (d) have missing data. In total, 181 cases were finally enrolled and analysed in the present study (Fig. 1). 129 of Patients from the Fourth Hospital of Hebei Medical University were considered as the Nomogram training cohort and 52 of Patients from Hebei General Hospital and the First Hospital of Shijiazhuang were considered as the Nomogram validation cohort. As for the treatment time, that is, from January 2013 to April 2017 in the training cohort and from February 2012 to December 2017 in the validation cohort.

## Surgical Procedure

Radical resection for oCRC patients is to perform by removing the cancerous segment of colon or rectum, the mesentery with the primary feeding vessel and the lymphatics, any organ with direct tumor invasion and resectable metastases. A radical resection of a colorectal tumor should achieve at least a 5 cm clearance at the proximal and distal margin. Finally, the margin of both primary and metastatic lesion was negative. Palliative resection for oCRC patients is to perform by local resection of the tumor without resection of the invaded organs and distant metastases. The number of lymph node retrieved in the surgical specimen has paramount impact on prognosis in colorectal cancer, so, radical resection requires the number of removed lymph node  $\geq 12$ [10, 11].

## Data Collection And Variables

Clinicopathological information was obtained from the medical records of the patients including demographics (sex, age), obstructive site, obstructive type, surgical procedures, TNM stage, histologic type at the time of diagnosis, white blood cell count (WBC), neutrophil count percentage(NCP), hemoglobin (Hb), platelet (PLT), albumin, carcinoembryonic antigen (CEA), carbohydrate antigen 19 – 9 (CA19-9), the concentration of sodium (Na), potassium (K), calcium (Ca) and chloride (Cl). Cancer stages were based on the 8th edition of the AJCC/TNM system.

## Follow Up

Patient follow-up was scheduled for every 3 months for the first 2 years, then every 6 months for the next 3 years, and annually thereafter. The last follow-up was obtained on May 2017 in the training cohort and May 2018 in the validation cohort. The OS was calculated from the date of treatment to death for any cause. Patients who were lost to follow-up or did not die at the last follow-up were defined as censored.

## Statistical analysis

Statistical analyses to identify risk factors were performed using SPSS 21.0. Categorical variables were grouped based on clinical reasoning, and decisions on the groups were made before modeling. Categorical variables are expressed as percentages (%). A chi-square test and Wilcoxon rank-sum test were performed to analyze the difference between the training cohort and validation cohort.

Univariate and multivariate Cox proportional hazard models were utilized to identify potential significant prognostic factors for the entire cohort. Survival curves were performed using the Kaplan–Meier method, and a log-rank test was adopted to compare the curves. Variables achieving significant level of  $P < 0.05$  in the univariate analyses were subjected to multivariable Cox regression analysis. Independent prognostic factors were determined if a significant effect was observed in the Cox model ( $P < 0.05$ ). Variables of the final model were backward stepdown selected with the Akaike information criterion.

A Nomogram was formulated based on the final Cox proportional hazard regression model and by using the package of rms in R version 3.4.2 (<http://www.r-project.org/>). The performance of the Nomogram was assessed both internally and externally by discrimination and calibration. Discrimination between survival probability and actual observations was measured using the C-index. The value of the C-index fluctuated between 0.5 and 1.0, with 0.5 representing random chance and 1.0 representing completely corrected discrimination[12]. The calibration curves were used to determine whether the predicted survival and actual survival were in concordance.  $P < 0.05$  was considered statistically significant.

## Results

### Patients' characteristics and survival

The demographic features and clinicopathological characteristics of the training cohort and validation cohort are presented in Table 1. WBC ( $p = 0.009$ ), T stage ( $p = 0.08$ ), M stage ( $p = 0.004$ ) and TNM stage ( $p = 0.002$ ) were significantly different between the training cohort and the validation cohort, possibly due to the selection process. These differences may also indicate that our predictive model can be universally applied across heterogeneous populations of oCRC patients.

Table 1  
Demographics and pathological characteristics of oCRC patients

Variables		Training cohort		Validation cohort		<i>p</i>
		n	%	n	%	
All patients		129	100	52	100	
Sex	Male	69	53.49	31	59.62	0.453
	Female	60	46.51	21	40.38	
Age(years)	< 60	51	39.53	16	30.77	0.27
	≥ 60	78	60.47	36	69.23	
Obstructive type	Acute complete obstruction	9	6.98	8	15.38	0.079
	Chronic incomplete obstruction	120	93.02	44	84.62	
Obstructive site	Right colon	52	40.31	22	42.31	0.929
	Left colon	49	37.98	20	38.46	
	Rectum	28	21.71	10	19.23	
Surgical procedure	Palliative resection	43	33.33	22	42.31	0.255
	Radical resection	86	66.67	30	57.69	
T stage	T2 + 3	9	6.98	7	13.46	0.165
	T4	120	93.02	45	86.54	
N stage	N0	60	46.51	33	63.46	0.161
	N1	46	35.66	8	15.38	
	N2	23	17.83	11	21.15	
M stage	M0	90	69.77	47	90.38	0.004
	M1	39	30.23	5	9.62	
TNM stage	Ⅲ+Ⅳ	47	36.43	30	57.69	0.002
	Ⅱ	43	33.33	17	32.69	
	Ⅰ	39	30.23	5	9.62	
Histopathology	Adenocarcinoma	100	77.52	41	78.85	0.846
	Mucinous or signet ring adenocarcinoma	29	22.48	11	21.15	
WBC (×10 <sup>9</sup> /L)	< 9.5	111	86.05	36	69.23	0.009

Variables		Training cohort		Validation cohort		<i>p</i>
	$\geq 9.5$	18	13.95	16	30.77	
NCP (%)	$< 75$	91	70.54	29	55.77	0.058
	$\geq 75$	38	29.46	23	44.23	
HGB (g/L)	$> 120$	62	48.06	29	55.77	0.349
	$\leq 120$	67	51.94	23	44.23	
PLT ( $\times 10^9/L$ )	$< 350$	105	81.4	42	80.77	0.922
	$\geq 350$	24	18.6	10	19.23	
CEA (ng/ml)	$< 5$	55	42.64	29	55.77	0.11
	$\geq 5$	74	57.36	23	44.23	
CA19-9 (U/ml)	$< 27$	82	63.57	38	73.08	0.222
	$\geq 27$	47	36.43	14	26.92	
Albumin (g/L)	$> 40$	56	43.41	25	48.08	0.569
	$\leq 40$	73	56.59	27	51.92	
Na (mmol/L)	$> 137$	94	72.87	37	71.15	0.816
	$\leq 137$	35	27.13	15	28.85	
K (mmol/L)	$> 3.5$	113	87.6	42	80.77	0.237
	$\leq 3.5$	16	12.4	10	19.23	
Ca (mmol/L)	$> 2.11$	114	88.37	41	78.85	0.099
	$\leq 2.11$	15	11.63	11	21.15	
Cl (mmol/L)	$> 99$	111	86.05	40	76.92	0.136
	$\leq 99$	18	13.95	12	23.08	

In the training cohort, over half were male ( $n = 69, 53.49\%$ ). The majority of patients in both group were elderly patients ( $\geq 60$  years,  $60.47\%$ ). Radical resection was performed in 2/3 of the patients ( $n = 86, 66.7\%$ ), the most common obstructive site was right colon ( $52, 40.31\%$ ), The majority of patients were chronic incomplete obstruction ( $120, 93.02\%$ ) (Table 1). The proportion of higher CEA level ( $\geq 5\text{ng/ml}$ ) in TNM staging is:  $50\%$  in phase I,  $42.22\%$  in phase II,  $53.49\%$  in phase III, and  $79.49\%$  in phase IV.

In the training cohort, 30 patients died, with a median follow-up of 18 months (ranging 1–40 months). In the validation cohort, 16 patients died, with a median follow-up of 19 months (ranging 1–56 months). The 1-year and 3-year OS of training cohort was 85.0% and 63.5% respectively, while 85.4% and 68.1% respectively of validation cohort.

## Independent Prognostic Factors Of Ocrc

Univariate analysis illustrated the NCP ( $p = 0.036$ ), CEA ( $p = 0.003$ ), CA19-9 ( $p = 0.02$ ), N stage ( $p < 0.001$ ), M stage ( $p = 0.001$ ), TNM stage ( $p < 0.001$ ) and surgical procedure ( $p < 0.001$ ) were significantly associated with a shorter OS of oCRC patients (**Table 2**). However, only CEA [ $p = 0.037$ , HR = 2.872 (1.065–7.740)], N stage [N1 vs. N0,  $p = 0.028$ , HR = 3.187 (1.137–8.938); N2 vs. N0,  $p = 0.010$ , HR = 4.098 (1.393–12.051)], and surgical procedure [ $p = 0.002$ , HR = 0.299 (0.139–0.643)] were shown to be significant independent prognostic factors for OS by multivariate Cox proportional hazard analyzes of univariate factors (**Table 2**). Survival curves were utilized to provide significant distinction of outcome between each risk factor within univariate analysis (Fig. 2).

## Nomogram Model For Ocrc

A Nomogram model incorporating significant predictors in the COX analysis was established to predict the prognosis of oCRC (Fig. 3). Each subtype within these variables was assigned a score on the points scale. After adding up the total score, a vertical line could be drawn downwards from the total points scale to obtain the probability of survival.

## Validation For Nomogram Model

The Nomogram model was validated by two procedures: internal ( $n = 129$ ) and external ( $n = 52$ ) validation. The internal validation showed that the Nomogram can precisely predict the OS with a C-index of 0.797. Similarly, the C-index was 0.703 in the external validation. The calibration plots showed a good agreement between the predicted and observed values for the 1- and 3-year OS in not only the training cohort but also the validation cohort (Fig. 4).

**Table 2** Univariate and multivariate COX regression analyses for OS of oCRC patients in the training cohort

Variables		Univariate analysis	p	Multivariate analysis	p
		HR(95%CI)		HR(95%CI)	
Sex	Male	1			-
	Female	0.878(0.428,1.800)	0.723	-	-
Age	<60	1		-	-
	≥ 60	1.555(0.712,3.398)	0.268	-	-
Obstructive type	Acute complete obstruction	1		-	-
	Chronic incomplete obstruction	2.252(0.307,16.536)	0.425	-	-
Obstructive site	Right colon	1		-	-
	Left colon	1.158(0.518,2.591)	0.721	-	-
	Rectum	1.099(0.410,2.942)	0.851	-	-
Surgical procedure	Palliative resection	1		1	
	Radical resection	0.199(0.094,0.422)	<0.001	0.299(0.139,0.643)	0.002
T stage	T2-3	1		-	-
	T4	2.229(0.304,16.366)	0.431	-	-
N stage	N0	1		1	
	N1	3.820(1.374,10.615)	0.01	3.187(1.137,8.938)	0.028
	N2	6.582(2.280,19.005)	<0.001	4.098(1.393,12.051)	0.01
M stage	M0	1		-	-
	M1	3.522(1.714,7.239)	0.001	-	-
TNM stage	III	1		-	-
	II	6.084(1.347,27.475)	0.019	-	-
	I	14.472(3.326,62.961)	<0.001	-	-
Histopathology	Adenocarcinoma	1		-	-
	Mucinous or signet ring adenocarcinoma	1.285(0.571,2.894)	0.544	-	-
WBC( $\times 10^9/L$ )	<9.5	1		-	-

	≥ 9.5	1.520(0.619,3.736)	0.361	-	-
NCP (%)	<75%	1		-	-
	≥ 75%	2.159(1.052,4.432)	0.036	-	-
HGB (g/L)	≤ 120	1		-	-
	>120	0.617(0.299,1.273)	0.192	-	-
PLT(×10 <sup>9</sup> /L)	<350	1		-	-
	≥ 350	1.043(0.426,2.555)	0.927	-	-
CEA(ng/ml)	<5	1		1	
	≥ 5	4.301(1.643,11.259)	0.003	2.872(1.065,7.740)	0.037
CA19-9(U/ml)	<27	1		-	-
	≥ 27	2.356(1.144,4.852)	0.02	-	-
Albumin(g/L)	>40	1		-	-
	≤ 40	0.783(0.382,1.602)	0.502	-	-
Na(mmol/L)	>137	1		-	-
	≤ 137	1.794(0.853,3.775)	0.123	-	-
K (mmol/L)	>3.5	1		-	-
	≤ 3.5	1.048(0.366,3.005)	0.93	-	-
Ca(mmol/L)	>2.11	1		-	-
	≤ 2.11	2.002(0.818,4.902)	0.129	-	-
Cl (mmol/L)	>99	1		-	-
	≤ 99	1.188(0.454,3.107)	0.726	-	-

## Discussion

CRC is one of the leading causes of cancer mortality worldwide. The TNM staging system are the most widely used to predict the clinical outcomes of CRC patients currently. The current National Comprehensive Cancer Network (NCCN) guidelines point out that bowel obstruction is one of the high-risk factors for recurrence. Colonic obstruction caused by malignant CRC lead to more complicated clinical problems[13]. Compared with CRC without obstruction, oCRC present unfavorable postoperative mortality rate in short- and long-term follow-ups[14]. Mohd et al reported that bowel obstruction were associated with poor disease survival in CRC[6].

Bowel obstruction is a poor prognostic factor of CRC. However, it is still lack of an appropriate method to predict the outcome of oCRC patients. In the present study, CEA, N stage and surgical procedures are considered as the independent risk factors for the prognosis of oCRC. Finally, using these risk factors, we developed a Nomogram to predict the probability of survival for oCRC patients. To our knowledge, this is the first study to focus on the prognosis of oCRC with the aim of building a Nomogram.

Tumor biomarkers have been widely used in clinical diagnosis[15]. CEA is one of the tumor biomarkers used for predicting recurrence, prognosis and therapeutic efficacy in CRC patients[16, 17]. In general, the high levels of CEA revealed larger tumor size, higher possibility of lymph node metastasis and poor differentiated[18]. In our study, results showed that patients with higher CEA level ( $\geq 5\text{ng/ml}$ ) have a significantly shorter survival period, and the level of CEA in patients of advanced stage was found mainly more than  $5\text{ng/ml}$ . CEA are meaningful both in univariate and multivariate regression and are eventually incorporated into the establishment of Nomogram model.

the AJCC/TNM staging system remains the basics tool for the evaluate the prognosis of CRC patients. However, survival heterogeneity is frequently occurred when patients with the same AJCC stages. Bowel obstruction may act as a major role to the survival heterogeneity. In this study, we identified TNM staging system (T stage, N stage, M stage and TNM stage) for oCRC patients, We found that only N stage was independent predictor of prognosis in patients with oCRC. Patients with more lymph node metastasis have a worse prognosis, which is consistent both in patients with or without bowel obstruction[19]. In general, distant metastasis is well-considered as a major predictor of poor prognosis in CRC, in our study, the absence of metastasis has a significantly longer survival period just in univariate analysis but not in multivariate analysis. It may due to the relatively high dropout rate, which is also the limitation of the article.

Surgical resection is a beneficial therapeutic option for oCRC patients, which include radical resection and palliative resection[20, 21]. Several studies reported that radical treatments of enterectomy or plus metastasectomy could prolong OS and PFS of CRC patients[22, 23]. The K-M curve about the surgical procedure in our study also showed the advantages of radical resection for oCRC patients. However, some patients with malignant bowel obstruction initially present with acute colonic obstruction and some patients even have advanced stage (locally advanced or distance metastases) at time of diagnosis, making them poor candidates for radical resection[24]. Frederico et al explored the outcome of an emergency surgery including bowel obstruction of CRC, suggesting that it has been possible to respect the principles of the radical resection in the emergency surgery for CRC[25]. In addition, colonic stents and stoma are also a bridge from emergency surgery to elective resection[26, 27]. Patients with significant response to conversion chemotherapy can be converted from unresectable to resectable status. According to the NCCN guidelines, chemotherapy for colorectal cancer with unresectable metastasis is recommended, when the patient has no tumor related symptoms, the first treatment option is chemotherapy, thereafter, surgery for the primary tumor and metastatic lesions is recommended if the metastatic lesions become resectable[28]. Diaconescu and his colleagues assessed the results of resection of hepatic and extrahepatic metastases in patients with hepatic and extrahepatic metastases, and demonstrated that complete resection of metastatic burden significantly prolong survival[29]. For advanced oCRC patients, we could firstly consider using

methods such as stoma or stent implantation to release the obstruction, give neoadjuvant or conversion therapy and seek radical resection.

From the above three parameters, we can see that CEA and N stage are associated with advanced disease, suggesting the importance of early diagnosis treatment. What's more, the surgical procedure is related to treatment, we propose that oCRC patients can benefit from radical surgery, which is also mentioned by Ishibe[24]. For oCRC, radical resection should be encouraged. If systemic or local conditions are not allowed, transitional procedures, such as neoadjuvant chemotherapy or stent placement, should be used as soon as possible to strive for radical resection.

The prognostic Nomogram, as a statistical model, can provide an accurate prediction by a simple graphical presentation. The model is easy to understand and easy to apply to clinical practice. In order to make the Nomogram model more accurate, the univariate and multivariate Cox proportional hazard methods were used to select the factors to develop the oCRC Nomogram model. Finally, the result of both internal and external validation shows it relatively accuracy, which was identified by C-index and calibration plots, in predicting the OS. In this study, we selected risk factors for prognosis in patients with oCRC through univariable and subsequent multivariable Cox regression analysis, the Nomogram based on the identified risk factors makes data to be more easily visualized. However, there may exist some potential limitations need to be mentioned. First, this is a retrospective research, the duration of the follow-up periods in both training cohort and validation cohort was short. Second, the number of participants is small. The above deficiency makes the model not reflect all factors affecting prognosis. Therefore, more patients with long time follow-ups should be recorded to improve the current conclusions of Nomogram model.

## Conclusions

In summary, the present study established and validated a Nomogram model to predict the prognosis of oCRC patients, the Nomogram model that incorporates CEA expression, N stage and surgical procedure has been internally and externally validated as a useful tool for risk assessments. Among the three pivotal parameters, only surgical procedure can be controlled by doctors. For oCRC patients, in order to prolong their survival, we should attempt to change the surgical procedure from non-radical resection to a radical status[30].

## Abbreviations

CRC colorectal cancer

oCRC obstructive colorectal cancer

CEA carcinoembryonic antigen

WBC white blood cell count

NCP neutrophil count percentage

Hb hemoglobin

PLT platelet

CA19-9 carbohydrate antigen 19 – 9

AJCC American Joint Committee on Cancer

NCCN National Comprehensive Cancer Network

HR hazard ratio

OS overall survival

PFS progression-free survival

## **Declarations**

### **Ethics approval and consent to participate**

This study was in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the Research Ethics Committee of Hebei Medical University, China. All patients provided written informed consent.

### **Consent for publication**

Not available

### **Availability of data and materials**

Additional data and materials may be requested from the corresponding author on reasonable request.

### **Conflict of Interest**

We declare that we have no competing interests. In addition, neither the entire paper nor any part of its content has been published or has been accepted elsewhere. It is not being submitted to any other journal.

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### **Authors' contributions**

ZXL and YTJ designed the research. JL, YYL, and GYD collected the data . JLH and PG analyzed the data. All authors wrote the manuscript. ZLZ, ZXL, JL and YNZ discussed the results and revised the final manuscript. All authors read and approved the final

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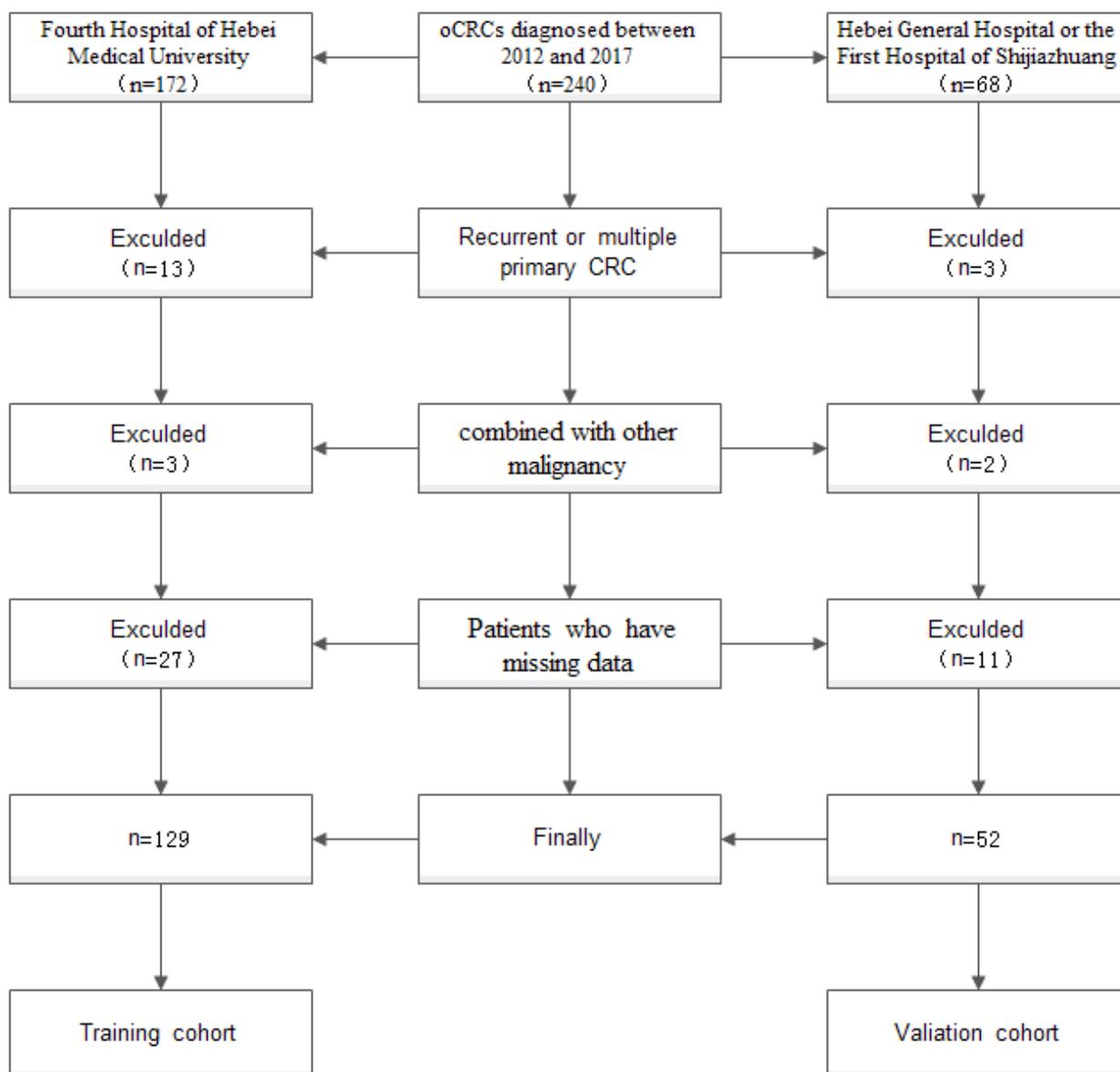
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## Figures

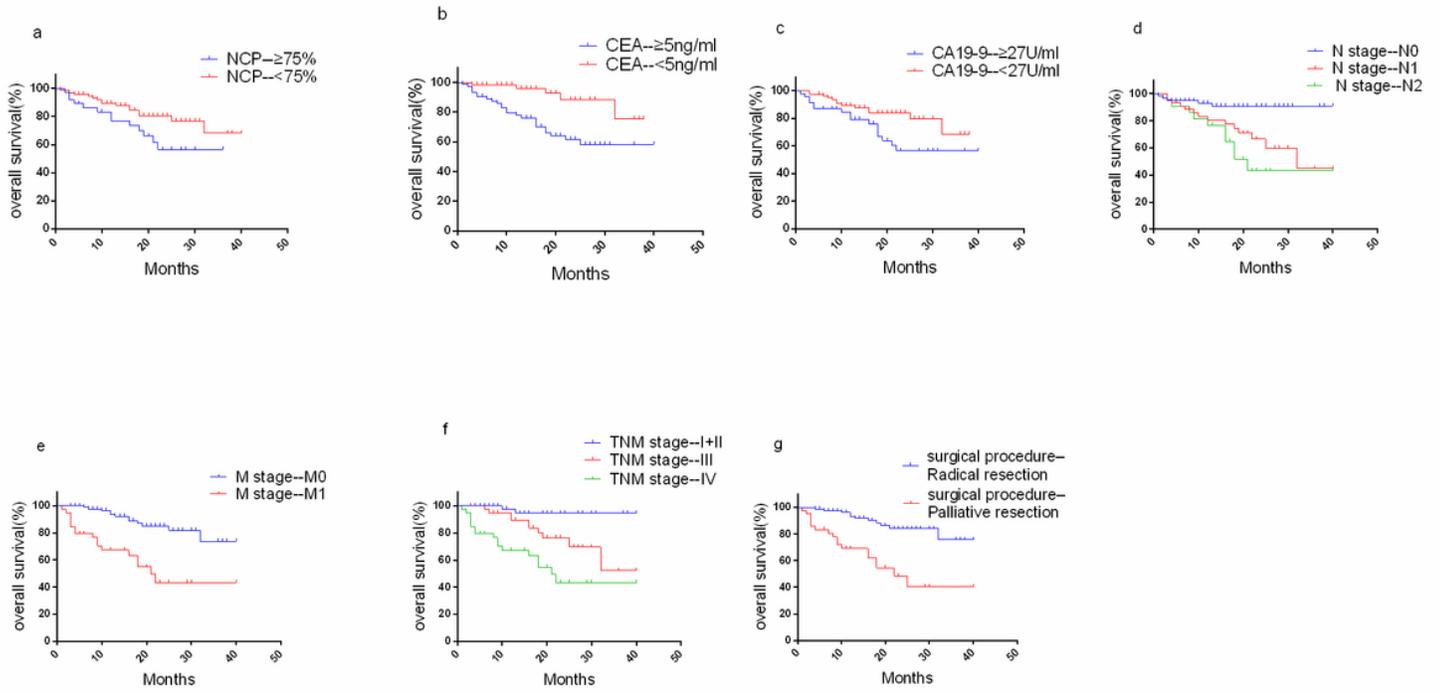
### Fig.1



**Figure 1**

Flow chart for the study on patients with oCRC according to exclusion criteria.

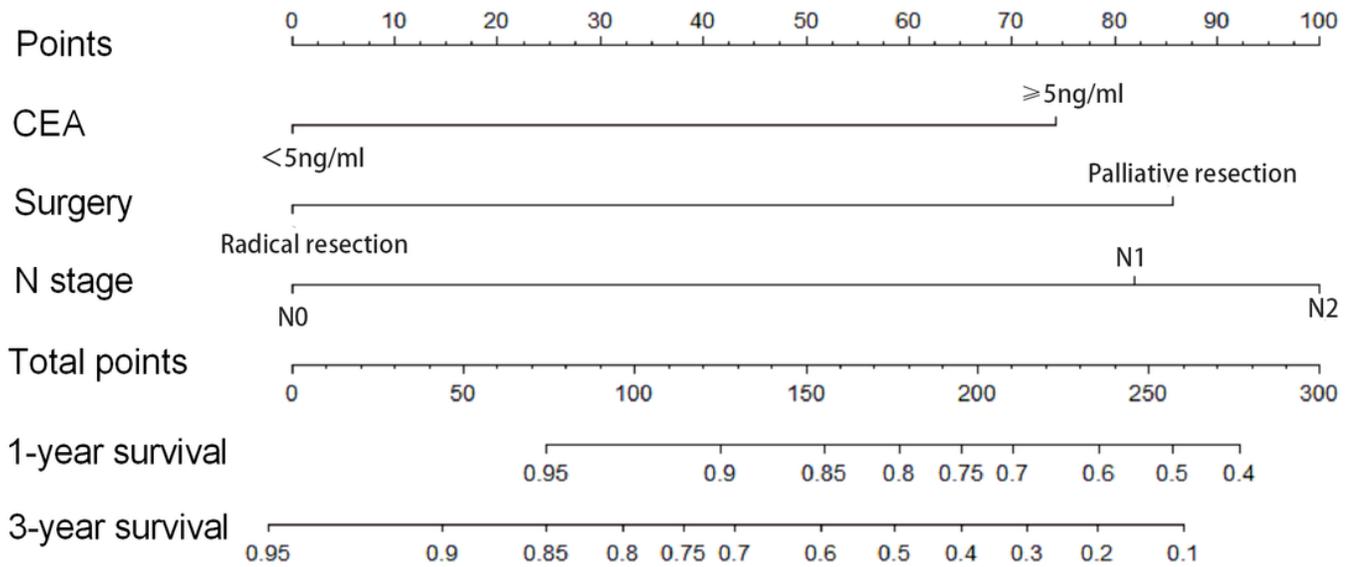
**Fig.2**



**Figure 2**

Kaplan-Meier curves of OS for patients with oCRC in the training cohort. (a) NCP; (b) CEA; (c) CA19-9; (d) N stage; (e) M stage; (f) TNM stage; (g) surgical procedure.

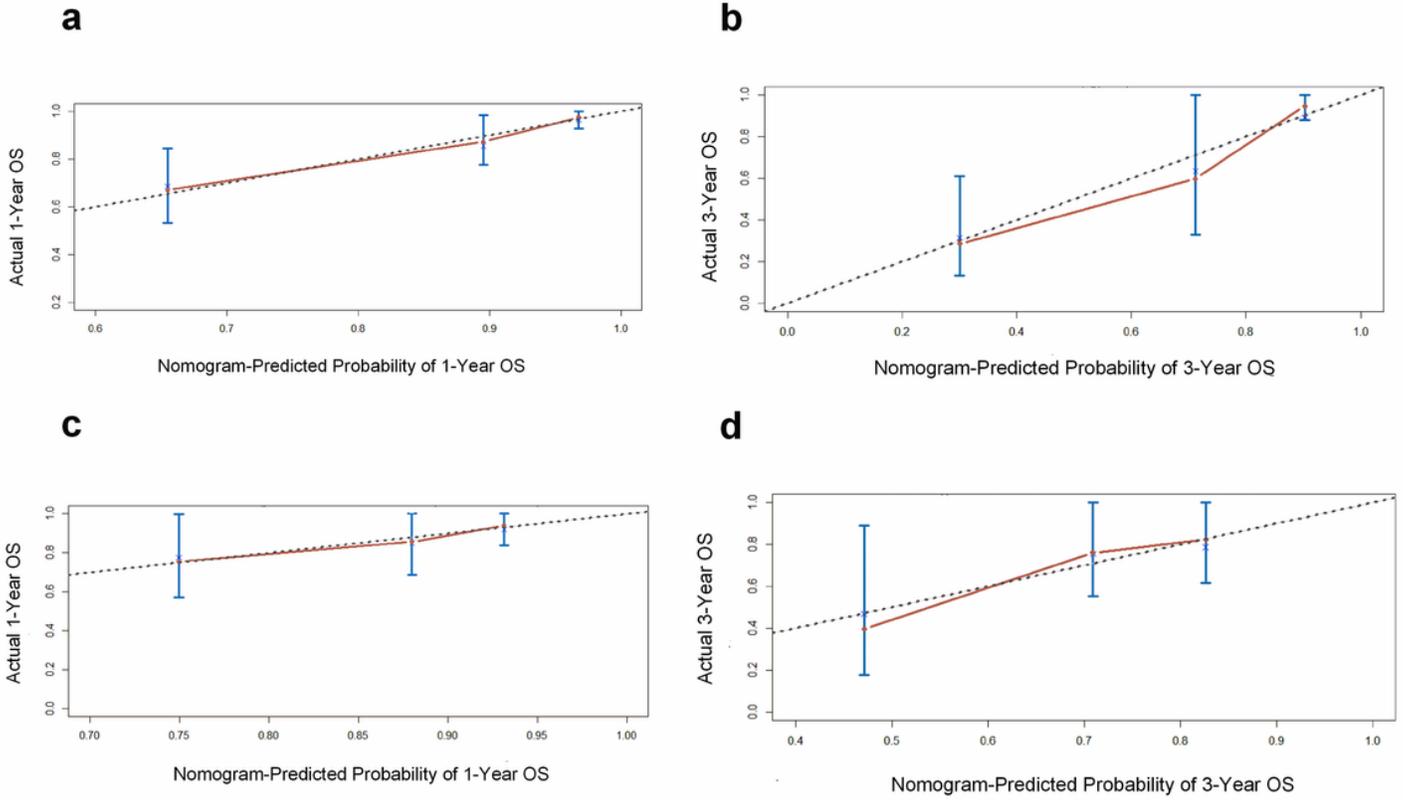
**Fig.3**



**Figure 3**

Nomogram model predicting the 1- and 3-year OS in oCRC patients. The nomogram was used summing the points identified on the points scale for each variable. The total points projected on the bottom scales indicate the probability of 1- and 3-year survival.

**Fig.4**



**Figure 4**

The calibration curves for predicting patient OS at (a) 1 year and (b) 3 years in the training cohort and (c) 1 year and (d) 3 years in the validation cohort. The nomogram model predicted OS is plotted on the x-axis, and the actual OS is plotted on the y-axis.