Original Article

Nomogram model for predicting cancer-specific mortality in patients with early-onset colorectal cancer: a competing risk analysis insight from the SEER database and an external validation cohort

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Background: Early-onset colorectal cancer (EOCRC) is increasing in incidence and poses a growing threat. Urgent research is needed, especially in survival analysis, to enhance comprehension and treatment strategies. This study aimed to explore the risk factors associated with cancer-specific mortality (CSM) and other-cause mortality (OCM) in patients with EOCRC. Additionally, the study aimed to develop a nomogram predicting CSM using a competitive risk model and validate its accuracy through the use of training, using internal and external cohorts.

Methods: Data from EOCRC patients were collected from the Surveillance, Epidemiology, and End Results (SEER) database (2008–2017). EOCRC patients who were treated at a tertiary hospital in northeast China between 2014 and 2020 were also included in the study. The SEER data were divided into the training and validation sets at a 7:3 ratio. A univariate Cox regression model was employed to identify prognostic factors. Subsequently, multivariate Cox regression models were applied to ascertain the presence of independent risk factors. A nomogram was generated to visualize the results, which were evaluated using the concordance index (C-index), area under the curve (AUC), and calibration curves. The clinical utility was assessed via decision curve analysis (DCA).

Results: Multivariable Cox regression analysis demonstrated that factors such as race, tumor differentiation, levels of carcinoembryonic antigen (CEA), marital status, histological type, American Joint Committee on Cancer (AJCC) stage, and surgical status were independent risk factors for CSM in EOCRC patients. In addition, age, gender, chemotherapy details, CEA levels, marital status, and AJCC stage were established as independent risk factors for OCM in individuals diagnosed with EOCRC. A nomogram was developed using the identified independent risk factors, demonstrating excellent performance with a C-index of 0.806, 0.801, and 0.810 for the training, internal validation, and external validation cohorts, respectively. The calibration curves and AUC further confirmed the accuracy and discriminative ability of the nomogram. Furthermore, the DCA results indicated that the model had good clinical value.

Conclusions: In this study, a competing risk model for CSM was developed in EOCRC patients. The model demonstrates a high level of predictive accuracy, providing valuable insights into the treatment decision-making process.

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Keywords: Early-onset colorectal cancer (EOCRC); cancer-specific mortality (CSM); competing risk model; Surveillance, Epidemiology, and End Results database (SEER database); external validation

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Introduction

Colorectal cancer (CRC) is a prevalent form of malignancy worldwide, ranking third in terms of frequency. It is also the second most significant contributor to cancer-related deaths (1,2). Although the definition of early-onset colorectal cancer (EOCRC) remains controversial, it commonly encompasses CRC patients who are diagnosed before the age of 50 years (3,4). Recent studies have contributed to deepening our understanding of CRC, which has triggered shifts in multidisciplinary treatment strategies including early prevention, chemoradiotherapy, surgical intervention, targeted therapy, and immunotherapy. These changes have resulted in substantial improvements in both the morbidity and mortality of CRC (5). However, a contrasting trend was observed in the occurrence of EOCRC, evidenced by a significant rise in countries such as the United States (US), Canada, Australia, and various European nations (6-9). Similar patterns have also been observed in the Chinese population (10).

Highlight box

Key findings

- A nomogram predicting cancer-specific mortality (CSM) was established in patients with early-onset colorectal cancer (EOCRC) and underwent internal and external validation.

What is known and what is new?

- The levels of carcinoembryonic antigen, marital status, and American Joint Committee on Cancer staging were independent risk factors for both CSM and other-cause mortality (OCM).
- Chemotherapy was previously thought to increase the risk of other systems in tumor patients; however, our study shows that chemotherapy is a protective factor against OCM in patients with EOCRC.

What is the implication, and what should change now?

- The findings of this study enable a more precise understanding of survival expectations for patients with EOCRC, facilitating the formulation of personalized treatment plans.

Notably, EOCRC patients exhibit distinctive characteristics, including rapidly growing incidence in high-income countries, late detection, and high rates of delayed treatment (11,12). Furthermore, the majority of studies have indicated no significant difference in the prognosis of patients with EOCRC compared to that of older CRC patients (13-15). Nonetheless, the majority of young people diagnosed with CRC do not have significant risk factors (e.g., family history), and most patients with EOCRC are categorized as being at average risk according to current algorithms for screening and management of CRC (16). Delayed diagnosis in young people significantly affects prognosis.

Compared to a single parameter that solely reflects survival in EOCRC, prognostic analysis employs nomograms, which integrate multiple parameters, offering a more precise and convenient approach to identifying the factors that influence EOCRC prognosis. Previous studies have developed survival nomograms for EOCRC. These studies have examined various factors, including primary tumor site, race, clinical and pathological staging, treatment regimens, levels of carcinoembryonic antigen (CEA), presence of Kirsten rat sarcoma viral oncogene homolog (*KRAS*) mutations, and microsatellite instability (MSI), as well as other clinical and pathological factors (10,13,17). Several studies have indicated that emerging chemotherapeutic agents and immunotherapy, among other treatments, were effective in reducing tumor mortality. However, these treatments also have greater adverse events or carry an elevated risk of non-tumor-related mortality (18-21).

Non-tumor-related mortality factors in EOCRC have largely been overlooked in previous studies, even though analysis of the causes of non-tumor-related mortality is essential for assessing patient prognosis and guiding treatment options. Neglecting potential competing risks could impact the accuracy of the EOCRC prognosis assessment (22-24). To address this issue, the present study investigated EOCRC patients using data from the large-

scale Surveillance, Epidemiology, and End Results (SEER) database from the US and a single-center retrospective cohort from China. This study aimed to assess the influence of various causes of mortality on patients with EOCRC and develop a competing risk nomogram to quantitatively examine disparities in survival rates among EOCRC patients. We present this article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2023/rc).

Methods

Dataset description

Patients with EOCRC were collected from the SEER database, a project developed by the National Cancer Institute (NCI) in the US. The current extensive clinical investigation is conducted at the national level and encompasses over 28% of the US population (25). This study adhered to the research guidelines outlined by the SEER database. Moreover, patient data obtained from Chaoyang Central Hospital of China Medical University were also analyzed.

Data collection

Data from patients with a definitive pathological/histological diagnosis of EOCRC in 2008–2017 were extracted by SEERStat software (version 8.4.1.2; https://seer.cancer.gov/seerstat/). The exclusion criteria were cases involving other systemic tumors, incomplete information, non-primary site tumors, and post-mortem diagnoses. Furthermore, patients with a survival time of less than 1 month were also excluded as they could not be included in the competing risk model. Additionally, patients diagnosed with EOCRC at Chaoyang Central Hospital of China Medical University from August 2014 to August 2020 were also enrolled. Survival information was gathered through the Clinical Information System (CIS) and telephone follow-up. The data extraction process is illustrated in *Figure 1*.

Variable selection and description

The demographic information of the patients was collected, including the age at the time of diagnosis, gender, race, and marital status. In addition, clinical information about the disease was also retrieved, such as the primary tumor site, grade, American Joint Committee on Cancer (AJCC) staging, and histological type. Treatment-related variables encompassed the surgical status, radiation therapy details, and the quantity of lymph node dissections. The age at diagnosis was classified into 2 categories, namely "<35 years" and "≥35 years". Race was classified into 3 distinct groups: "White", "Black", and "Others", utilizing race recode codes [Race recode (W, B, AI, API)]. Furthermore, marital status at the time of diagnosis was divided into 2 categories: "Married" and "Unmarried", with the latter category comprising the statuses "Divorced", "Single", "Separated", and "Widowed". The primary tumor site was categorized into 4 groups, including "Left Colon", "Right Colon", "Transverse Colon", and "Rectum", using primary site codes (labeled as Primary Site). The tumor grade was categorized into 4 classes, namely "Well-differentiated", "Moderately differentiated", "Poorly differentiated", and "Undifferentiated" according to Grade recode. Moreover, the histological type of the tumor was classified as "Adenocarcinoma", "Mucinous adenocarcinoma", or "Other" based on the International Classification of Disease for Oncology. The tumor infiltration depth (T) was categorized as T0–1, T2, T3, and T4, according to the AJCC staging (6th edition). Lymph node staging (N) was classified into N0, N1, and N2 groups, whereas distant metastasis (M) was categorized as M0 or M1. In addition, the surgical status was divided into 2 groups, namely "No surgery (code 0)" and "Surgery (other codes)" based on RX Summ-Surg Prim Site (1998+). Chemotherapy analysis was categorized as "Chemotherapy" or "No chemotherapy/unknown" according to Chemotherapy recode (yes, no/unknown). Radiation therapy information was classified as "Radiation therapy" or "No radiation therapy", based on the Radiation recode. The number of lymph node dissections was grouped as "None", "<4", and "≥4" using RX Summ--Scope Reg LN Sur (2003+). Survival information included survival status, survival time, and 1-, 3-, and 5-year survival rates. The cancer-specific mortality (CSM) information was extracted from SEER's cause-specific death classification, whereas the other-cause mortality (OCM) information was extracted from SEER's other cause of death classification. Survival time was defined as the interval from the date of diagnosis to the date of death from any cause. An identical processing methodology was employed for external validation of the Chinese cohort data.

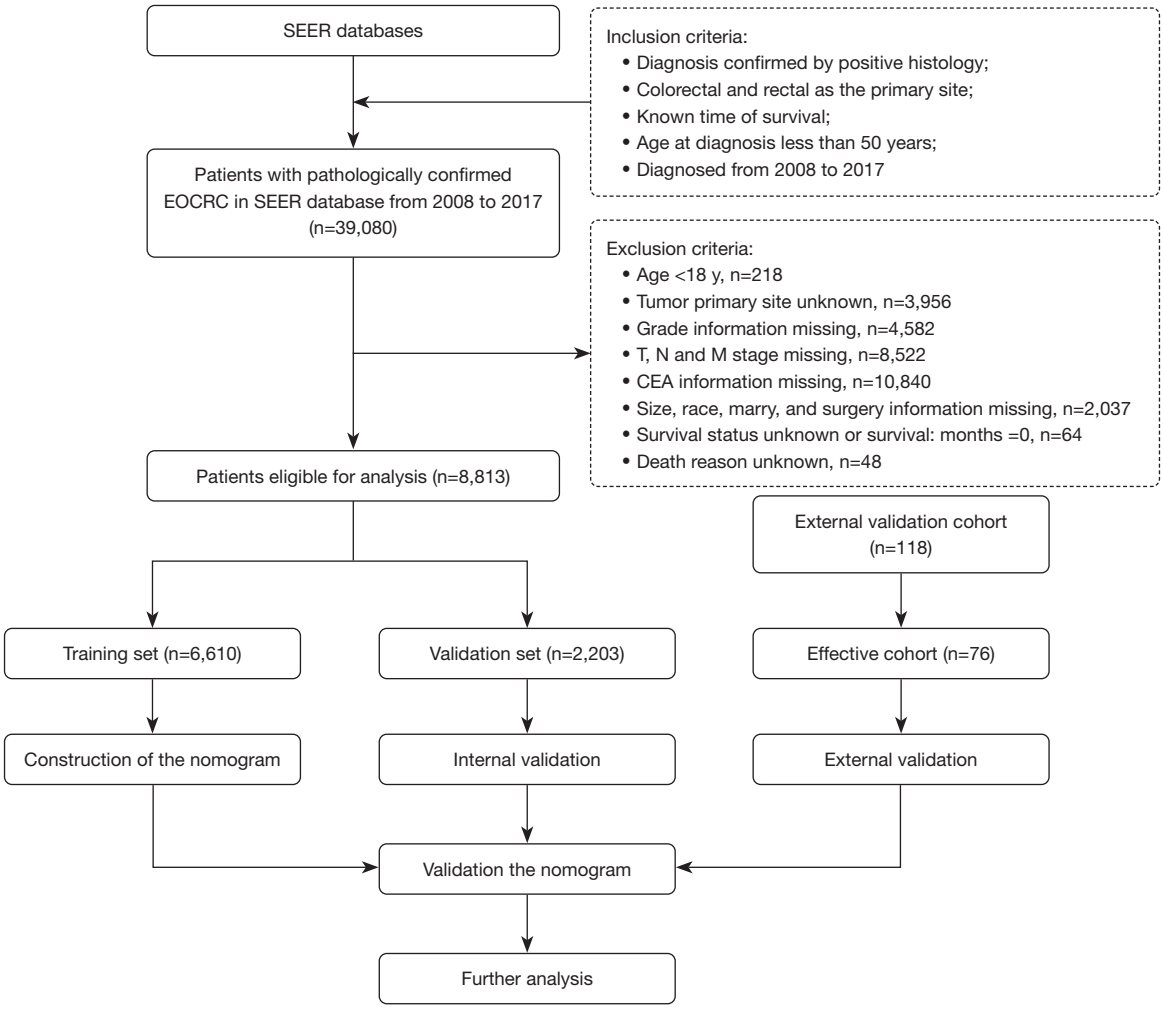

Figure 1 Flow chart of inclusion and exclusion of EOCRC patients. Patients in the training set were used to screen independent risk factors and establish a nomogram. The accuracy of the model was verified using a validation set and an external validation set. SEER, Surveillance, Epidemiology, and End Results; EOCRC, early-onset colorectal cancer; CEA, carcinoembryonic antigen; T, primary tumor; N, regional lymph node; M, distant metastasis.

Nomogram construction and validation

This study included a cohort of 8,813 patients diagnosed with EOCRC from the SEER database from the years 2008 to 2017. Using the R software (R Foundation for Statistical Computing, Vienna, Austria), a random assignment method was used to allocate the 8,813 patients into 2 cohorts, namely the training cohort (n=6,610) and the internal validation cohort (n=2,203) at a ratio of 7:3 (26-28). Cumulative incidence functions (CIFs) were calculated for the training group to assess the probabilities of experiencing various events at 1, 3, and 5 years. Subsequently, the data from the training group were utilized to develop competing risk models for CSM and OCM. CIFs were calculated for different causes of death to analyze the mortality rates. Additionally, CIF subgroup analyses were carried out using Gray's test to investigate variations among subgroups based on different variables (29).

Univariate Cox regression analysis was performed to screen influencing factors associated with CSM and OCM, and multivariate Cox regression analysis was carried out to identify independent risk factors. The independent risk factors were then used to construct nomograms to predict CSM at 1, 3, and 5 years in EOCRC patients. Subsequently, the

predictive performance of the nomogram was assessed by metrics such as the concordance index (C-index), receiver operating characteristic (ROC) curve, and calibration curves. Furthermore, data from a cohort of 118 Chinese EOCRC patients were collected, among which 76 patients were included for external validation after excluding patients with loss to follow-up and incomplete medical records. Both the validation cohort and the Chinese follow-up cohort were used for internal and external validation. Decision curve analysis (DCA) was performed to evaluate the potential clinical value of the nomogram's predictive model.

Statistical analysis

In this study, continuous variables were transformed into categorical variables. The chi-square test or non-parametric *U* test was used for between-group comparisons, whereas descriptive statistics and between-group comparisons for other categorical variables were typically conducted using the chi-square test. Moreover, Cox regression models were constructed to analyze risk factors associated with patient outcomes, and the log-rank test was used to assess differences in patient survival rates. Statistical analysis was conducted using R software version 4.3.0 (https://www.r-project.org/) and SPSS version 26.0 (IBM Corp., Armonk, NY, USA). R packages used in the analysis included "cmprsk", "RMS", "survival", "ggplot2", "car", and "ggDCA". In this study, P values less than 0.05 were considered statistically significant.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Chaoyang Central Hospital of China Medical University (2023 No. 16). The requirement for individual consent for this retrospective analysis was waived.

Results

Patient characteristics

This study included a total of 8,813 patients from the SEER database and 76 patients from Chaoyang Central Hospital of China Medical University. The 8,813 EOCRC patients from the SEER database were randomly divided into a training cohort (n=6,610) and a validation cohort (n=2,203) at a 7:3 ratio using R software. No significant differences in baseline characteristics were observed between the 2 groups. Among the patients in the SEER database, the majority of deceased patients succumbed to tumor-specific factors (32.3%), whereas a smaller proportion died of non-tumor-related causes (3.1%). The 35–49-year age group contained the highest number of participants, accounting for 88.5% of the total sample population. A considerable proportion of the patient population underwent chemotherapy (72.9%) and surgical interventions (94.9%), whereas a smaller percentage received radiation therapy (25.2%). Moderately differentiated (73.1%) adenocarcinoma (90.3%) accounted for the majority of cases, with stage III being the most prevalent AJCC staging (41.1%). In the Chinese cohort, most patients were married (97.4%) and of Asian ethnicity (100%). In terms of tumor characteristics, a greater percentage of patients in the Chinese cohort exhibited larger tumor diameters (53.9%), elevated levels of CEA (84.2%), and a relatively higher prevalence of mucinous adenocarcinomas (26.3%).

The detailed results are presented in *Table 1*. For the patients included in the training cohort (n=6,610), a univariate Cox regression analysis was first conducted to identify factors influencing CSM and OCM. The identified factors were then subjected to a multivariate Cox regression analysis to determine independent risk factors.

Independent risk factors for CSM and OCM in EOCRC patients

Univariate Cox regression analysis revealed that CSM in EOCRC patients was influenced by various risk factors. The variables evaluated in this study encompassed a range of factors, such as age, gender, race, differentiation, TNM stage, number of cleared lymph nodes, CEA levels, tumor size, marital status, pathological type, AJCC 6th edition staging, surgery, and chemotherapy information. The multivariate Cox regression analysis identified several independent risk factors that significantly influenced the risk of CSM. These factors included race, tumor grade, CEA levels, marital status, pathology type, AJCC staging, and surgery. Specifically, the analysis indicated that individuals of Black race had a higher risk of CSM compared to those of White race [hazard ratio (HR) =1.247; 95% confidence interval (CI): 1.105–1.251; P<0.001]. In addition, poorly differentiated and undifferentiated tumors were associated with a higher risk of CSM

Table 1 Demographics and clinicopathologic characteristics of the training and validation cohort

Variables	SEER databases (n=8,813)	Training cohort (n=6,610)	Internal validation cohort (n=2,203)	External validation cohort (n=76)	P value	
					¶T *vs.* ⊥IV	¶T *vs.* #EV
Death reason					0.10	0.97
Death by tumor	2,847 (32.3)	2,103 (31.8)	744 (33.8)	25 (32.9)		
Death by others	277 (3.1)	218 (3.3)	59 (2.7)	2 (2.6)		
Age					0.12	0.59
<35 years	1,017 (11.5)	783 (11.8)	234 (10.6)	11 (14.5)		
≥35 years	7,796 (88.5)	5,827 (88.2)	1,969 (89.4)	65 (85.5)		
Gender					0.09	0.54
Male	4,692 (53.2)	3,554 (53.8)	1,138 (51.7)	44 (57.9)		
Female	4,121 (46.8)	3,056 (46.2)	1,065 (48.3)	32 (42.1)		
M stage					0.46	–
M0	6,789 (77.0)	5,105 (77.2)	1,684 (76.4)	–		
M1	2,024 (23.0)	1,505 (22.8)	519 (23.6)	–		
Chemotherapy					0.37	0.82
No	2,386 (27.1)	1,773 (26.8)	613 (27.8)	19 (25.0)		
Yes	6,427 (72.9)	4,837 (73.2)	1,590 (72.2)	57 (75.0)		
Radiation therapy					0.71	0.02
No	6,589 (74.8)	4,935 (74.7)	1,654 (75.1)	66 (86.8)		
Yes	2,224 (25.2)	1,675 (25.3)	549 (24.9)	10 (13.2)		
CEA					0.89	<0.001
Negative	5,008 (56.8)	3,753 (56.8)	1,255 (57.0)	12 (15.8)		
Positive	3,805 (43.2)	2,857 (43.2)	948 (43.0)	64 (84.2)		
Size					0.84	0.002
≤5 cm	5,647 (64.1)	4,231 (64.0)	1,416 (64.3)	35 (46.1)		
>5 cm	3,166 (35.9)	2,379 (36.0)	787 (35.7)	41 (53.9)		
Marital status					0.66	<0.001
Unmarried†	3,584 (40.7)	2,679 (40.5)	905 (41.1)	2 (2.6)		
Married	5,229 (59.3)	3,931 (59.5)	1,298 (58.9)	74 (97.4)		
Surgery					0.15	0.79
No	449 (5.1)	350 (5.3)	99 (4.5)	3 (3.9)		
Yes	8,364 (94.9)	6,260 (94.7)	2,104 (95.5)	73 (96.1)		
Race					0.52	<0.001
White	6,593 (74.8)	4,935 (74.7)	1,658 (75.3)	–		
Black	1,116 (12.7)	852 (12.9)	264 (12.0)	–		
Others	1,104 (12.5)	823 (12.5)	281 (12.8)	76 (100.0)		

Table 1 (*continued*)

Table 1 (*continued*)

Variables	SEER databases (n=8,813)	Training cohort (n=6,610)	Internal validation cohort (n=2,203)	External validation cohort (n=76)	P value	
					¶T *vs.* ⊥IV	¶T *vs.* #EV
Primary tumor location					0.15	0.002
Left colon‡	3,875 (44.0)	2,934 (44.4)	941 (42.7)	21 (27.6)		
Right colon	2,026 (23.0)	1,483 (22.4)	543 (24.6)	17 (22.4)		
Transverse colon	2,349 (26.7)	1,762 (26.7)	587 (26.6)	3 (3.9)		
Rectum	563 (6.4)	431 (6.5)	132 (6.0)	35 (46.1)		
Grade					0.81	0.03
Well differentiated	529 (6.0)	390 (5.9)	139 (6.3)	1 (1.3)		
Mid differentiated	6,438 (73.1)	4,824 (73.0)	1,614 (73.3)	51 (67.1)		
Poorly differentiated	1,534 (17.4)	1,162 (17.6)	372 (16.9)	22 (28.9)		
Undifferentiated	312 (3.5)	234 (3.5)	78 (3.5)	2 (2.6)		
T stage					0.87	–
T1	724 (8.2)	552 (8.4)	172 (7.8)	–		
T2	976 (11.1)	734 (11.1)	242 (11.0)	–		
T3	5,331 (60.5)	3,989 (60.3)	1,342 (60.9)	–		
T4	1,782 (20.2)	1,335 (20.2)	447 (20.3)	–		
N stage					0.81	–
N0	3,540 (40.2)	2,664 (40.3)	876 (39.8)	–		
N1	3,049 (34.6)	2,289 (34.6)	760 (34.5)	–		
N2	2,224 (25.2)	1,657 (25.1)	567 (25.7)	–		
Lymph node dissection						
None	723 (8.2)	553 (8.4)	170 (7.7)	–	0.20	–
<4	137 (1.6)	95 (1.4)	42 (1.9)	–		
≥4	7,953 (90.2)	5,962 (90.2)	1,991 (90.4)	–		
Histology					0.23	<0.001
Adenocarcinoma	7,958 (90.3)	5,989 (90.6)	1,969 (89.4)	49 (64.5)		
Mucinous adenocarcinoma	635 (7.2)	460 (7.0)	175 (7.9)	20 (26.3)		
Others	220 (2.5)	161 (2.4)	59 (2.7)	7 (9.2)		
AJCC stage, 6th§					0.72	0.37
I	1,081 (12.3)	814 (12.3)	267 (12.1)	10 (13.2)		
II	2,085 (23.7)	1,581 (23.9)	504 (22.9)	24 (31.6)		
III	3,623 (41.1)	2,710 (41.0)	913 (41.4)	29 (38.2)		
IV	2,024 (23.0)	1,505 (22.8)	519 (23.6)	13 (17.1)		

Data are presented as the number (%). ¶T, training cohort; ⊥IV, internal validation cohort; #EV, external validation cohort. †, unmarried, including unmarried, separated, divorced and widowed; ‡, left colon including the sigmoid colon; §, AJCC stages, the 6th edition AJCC TNM staging system. SEER, Surveillance, Epidemiology, and End Results; M, distant metastasis; CEA, carcinoembryonic antigen; T, primary tumor; N, regional lymph node; AJCC, American Joint Committee on Cancer.

compared to well-differentiated tumors (HR =2.006, 95% CI: 1.590–2.531, P<0.001; HR =2.279, 95% CI: 1.705–3.048, P<0.001, respectively). CEA positivity was also associated with a significantly increased risk of CSM compared to CEA negativity (HR =1.655; 95% CI: 1.503–1.821; P<0.001). Conversely, being married was identified as a protective factor against CSM (HR =0.751; 95% CI: 0.688–0.820; P<0.001). Mucinous adenocarcinoma and other pathological types were associated with a higher risk of CSM compared to adenocarcinoma (HR =1.329, 95% CI: 1.132–1.561, P=0.001; HR =1.983, 95% CI: 1.689-2.329, P<0.001). Higher AJCC staging was also found to be a significant risk factor for CSM, particularly stage IV (HR =14.834, 95% CI: 11.012–19.982; P<0.001). Lastly, surgery was identified as a protective factor against CSM (HR =0.511; 95% CI: 0.385–0.678; P<0.001). Moreover, age, gender, race, primary site of the tumor, M staging, number of lymph nodes cleared, chemotherapy, CEA, marital status, and AJCC 6th edition staging were identified as risk factors for OCM in EOCRC patients. Multivariate Cox regression analysis revealed that age, gender, chemotherapy information, CEA levels, marital status, and AJCC 6th edition staging were independent risk factors for OCM in patients with EOCRC. Among them, a higher risk of OCM was observed in patients aged ≥35 years (HR =2.217; 95% CI: 1.262–3.894; P=0.006), and women showed a lower risk of OCM compared to men (HR =0.761; 95% CI: 0.581-0.998; P=0.04). Patients who received chemotherapy had a lower risk of OCM (HR =0.451; 95% CI: 0.320–0.636; P<0.001). CEA-positive patients had a higher risk of OCM (HR =1.570; 95% CI: 1.179–2.088; P=0.002). Additionally, being married was found to be a protective factor against OCM (HR =0.466; 95% CI: 0.356–0.610; P<0.001). Stage IV AJCC classification had a higher risk of OCM compared to stage I (HR =1.904; 95% CI: 1.110–3.265; P=0.01), whereas no significant trend was observed for stage III and stage II. Detailed findings are displayed in *Tables 2*,*3*.

CIF curves for CSM and OCM in EOCRC patients

Subsequently, Gray's test was employed to perform a subgroup analysis, investigating the association between CSM and OCM in patients with EOCRC. The CIFs are plotted in *Figure 2A-2K*. Among the various curves analyzed, EOCRC patients who tested positive for CEA demonstrated low differentiation or other differentiation types, underwent fewer than 4 lymph node dissections, received chemotherapy, had higher TNM staging according to the AJCC 6th edition staging system, did not undergo surgery, and exhibited higher cumulative incidence rates for CSM. In contrast, EOCRC patients 35 years or older and those with low differentiation exhibited elevated cumulative incidence rates for OCM (see *Figure 3A-3F* for CIFs under remaining variables).

Construction and validation of the nomograms

Nomograms predicting CSM in EOCRC patients were constructed using independent risk factors, including the degree of tumor differentiation, CEA, marital status, pathology type, AJCC staging, and surgery (*Figure 4*). Each variable was projected onto the upper 'Point' axis to determine the corresponding score, which was aggregated to yield a cumulative score. The total score was projected onto the '3-year CSM' and '5-year CSM' axes to estimate the 3- and 5-year CSM occurrence rates. For example, a patient with EOCRC who has not yet undergone surgery (29 points), is unmarried (11 points), is in AJCC stage III (46 points), tests positive for CEA (19 points), and has moderately differentiated adenocarcinoma (4 points), would accumulate a total of 109 points. This score would correspond to a projected 3-year CSM of 32.0% and a projected 5-year CSM of 48.0%. Additionally, the model was validated both internally and externally to assess its performance and reliability. The results revealed that the nomogram exhibited exceptional discriminatory capacity, with C-index values of 0.806, 0.801, and 0.810 for the training group, internal validation group, and external validation group, respectively. The area under the curve (AUC) performance of the nomogram was evaluated at 1-, 3-, and 5-year, yielding values of 0.875, 0.864, and 0.848, respectively. The AUC values were 0.867, 0.849, and 0.846 for the internal validation, and 0.870, 0.868, and 0.859 for the external validation, respectively. These results demonstrate the strong predictive ability of the nomogram (*Figure 5A-5C*). Furthermore, the calibration curves displayed a high level of agreement between the predicted and observed values for CSM in the training and internal and external validation groups (*Figure 6A-6F*).

Clinical application of nomograms

The results of DCA highlighted the good clinical utility of the nomograms (*Figure 7A-7C*). The curve demonstrated that the nomograms yielded advantageous net benefits for a majority of threshold probabilities at various time points.

Table 2 Univariate and multivariate analyses of CSM in the training cohort

Variables	CSM			
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age				
<35 years	1 (reference)		1 (reference)	
≥35 years	0.843 (0.742–0.957)	0.009	1.028 (0.902–1.172)	0.67
Gender				
Male	1 (reference)		1 (reference)	
Female	0.875 (0.802–0.954)	0.002	0.937 (0.859–1.023)	0.14
Race				
White	1 (reference)		1 (reference)	
Black	1.342 (1.194–1.508)	<0.001	1.247 (1.105–1.251)	<0.001
Others	1.039 (0.914–1.181)	0.55	1.098 (0.963–1.251)	0.16
Primary tumor location				
Left colon[†]	1 (reference)		–	–
Right colon	1.038 (0.937–1.151)	0.47	–	–
Transverse colon	0.989 (0.898–1.090)	0.82	–	–
Rectum	0.930 (0.777–1.112)	0.42	–	–
Grade				
Well differentiated	1 (reference)		1 (reference)	
Mid differentiated	0.593 (0.542–0.648)	<0.001	1.157 (0.928–1.442)	0.19
Poorly differentiated	1.965 (1.781–2.168)	<0.001	2.006 (1.590–2.531)	<0.001
Undifferentiated	1.892 (1.558–2.300)	<0.001	2.279 (1.705–3.048)	<0.001
T stage				
T1	1 (reference)		–	–
T2	0.314 (0.255–0.387)	<0.001	–	–
T3	0.708 (0.650–0.772)	<0.001	–	–
T4	3.001 (2.744–3.283)	<0.001	–	–
N stage				
N0	1 (reference)		–	–
N1	1.135 (1.039–1.240)	0.005	–	–
N2	2.77 (2.540–3.021)	<0.001	–	–
M stage				
M0	1 (reference)		–	–
M1	7.907 (7.243–8.633)	<0.001	–	–

Table 2 (*continued*)

Table 2 (*continued*)

Variables	CSM			
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Lymph node dissection				
None	1 (reference)		1 (reference)	
<4	1.390 (1.017–1.901)	0.03	1.147 (0.771–1.701)	0.49
≥4	0.393 (0.350–0.441)	<0.001	0.855 (0.660–1.109)	0.23
Chemotherapy				
No	1 (reference)		1 (reference)	
Yes	2.898 (2.547–3.297)	<0.001	1.040 (0.898–1.204)	0.60
Radiation therapy				
No	1 (reference)		1 (reference)	
Yes	1.028 (0.933–1.133)	0.57	0.855 (0.660–1.204)	0.23
CEA				
Negative	1 (reference)		1 (reference)	
Positive	3.056 (2.794–3.342)	<0.001	1.655 (1.503–1.821)	<0.001
Size				
≤5 cm	1 (reference)		1 (reference)	
>5 cm	1.189 (1.089–1.292)	<0.001	1.017 (0.930–1.111)	0.71
Marital status				
Unmarried[‡]	1 (reference)		1 (reference)	
Married	0.727 (0.668–0.793)	<0.001	0.751 (0.688–0.820)	<0.001
Histology				
Adenocarcinoma	1 (reference)		1 (reference)	
Mucinous adenocarcinoma	1.236 (1.055–1.447)	0.009	1.329 (1.132–1.561)	0.001
Others	3.662 (3.013–4.449)	<0.001	1.983 (1.689–2.329)	<0.001
AJCC stage, 6th[§]				
I	1 (reference)		1 (reference)	
II	0.257 (0.221–0.299)	<0.001	1.509 (1.108–2.054)	<0.001
III	0.647 (0.591–0.708)	<0.001	3.453 (2.565–4.648)	<0.001
IV	7.907 (7.243–8.633)	<0.001	14.834 (11.012–19.982)	<0.001
Surgery				
No	1 (reference)		1 (reference)	
Yes	0.209 (0.183–0.238)	<0.001	0.511 (0.385–0.678)	<0.001

[†], left colon including the sigmoid colon; [‡], unmarried, including unmarried, separated, divorced and widowed; [§], AJCC stages, the 6th edition AJCC TNM staging system. CSM, cancer-specific mortality; HR, hazard ratio; CI, confidence interval; T, primary tumor; N, regional lymph node; M, distant metastasis; CEA, carcinoembryonic antigen; AJCC, American Joint Committee on Cancer.

Table 3 Univariate and multivariate analyses of OSM in training cohort

Variables	OSM			
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age				
<35 years	1 (reference)		1 (reference)	
≥35 years	1.970 (1.128–3.443)	0.01	2.217 (1.262–3.894)	0.006
Gender				
Male	1 (reference)		1 (reference)	
Female	0.759 (0.579–0.995)	0.04	0.761 (0.581–0.998)	0.04
Race				
White	1 (reference)		–	–
Black	1.350 (0.941–1.939)	0.10	–	–
Others	0.643 (0.397–0.042)	0.07	–	–
Primary tumor location				
Left colon[†]	1 (reference)		–	–
Right colon	1.344 (0.999–1.810)	0.05	–	–
Transverse colon	0.863 (0.632–1.179)	0.35	–	–
Rectum	1.292 (0.798–2.093)	0.29	–	–
Grade				
Well differentiated	1 (reference)		–	–
Mid differentiated	0.958 (0.704–1.304)	0.87	–	–
Poorly differentiated	0.880 (0.632–1.304)	0.51	–	–
Undifferentiated	1.728 (0.918–3.251)	0.09	–	–
T stage				
T1	1 (reference)		–	–
T2	1.131 (0.774–1.655)	0.52	–	–
T3	0.810 (0.619–1.060)	0.12	–	–
T4	1.165 (0.821–1.654)	0.39	–	–
N stage				
N0	1 (reference)		–	–
N1	0.923 (0.696–1.226)	0.58	–	–
N2	0.981 (0.705–1.366)	0.90	–	–
M stage				
M0	1 (reference)		–	–
M1	1.691 (1.205–2.372)	0.002	–	–

Table 3 (*continued*)

Table 3 (*continued*)

Variables	OSM			
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Lymph node dissection				
None	1 (reference)		–	–
<4	2.027 (0.901–4.562)	0.08	–	–
≥4	0.845 (0.527–1.087)	0.48	–	–
Chemotherapy				
No	1 (reference)		–	–
Yes	0.589 (0.449–0.773)	<0.001	0.451 (0.320–0.636)	<0.001
Radiation therapy				
No	1 (reference)		–	–
Yes	0.829 (0.602–1.142)	0.25	–	–
CEA				
Negative	1 (reference)		–	–
Positive	1.628 (1.245–2.128)	<0.001	1.570 (1.179–2.088)	0.002
Size				
≤5 cm	1 (reference)		1 (reference)	
>5 cm	1.250 (0.953–1.639)	0.08	1.207 (0.915–1.207)	0.18
Marital status				
Unmarried[‡]	1 (reference)		–	–
Married	0.473 (0.362–0.618)	<0.001	0.466 (0.356–0.610)	<0.001
Histology				
Adenocarcinoma	1 (reference)		–	–
Mucinous adenocarcinoma	0.668 (0.354–1.259)	0.21	–	–
Others	1.518 (0.624–3.963)	0.35	–	–
AJCC stage, 6th[§]				
I	1 (reference)		–	–
II	0.906 (0.666–1.231)	0.52	0.880 (0.569–1.362)	0.56
III	0.737 (0.559–0.972)	0.03	1.161 (0.723–1.863)	0.53
IV	1.691 (1.205–2.372)	0.002	1.904 (1.110–3.265)	0.01
Surgery				
No	1 (reference)		–	–
Yes	1.315 (0.538–3.214)	0.54	–	–

[†], left colon including the sigmoid colon; [‡], unmarried, including unmarried, separated, divorced and widowed; [§], AJCC stages, the 6th edition AJCC TNM staging system. OSM, other-cause mortality; HR, hazard ratio; CI, confidence interval; T, primary tumor; N, regional lymph node; M, distant metastasis; CEA, carcinoembryonic antigen; AJCC, American Joint Committee on Cancer.

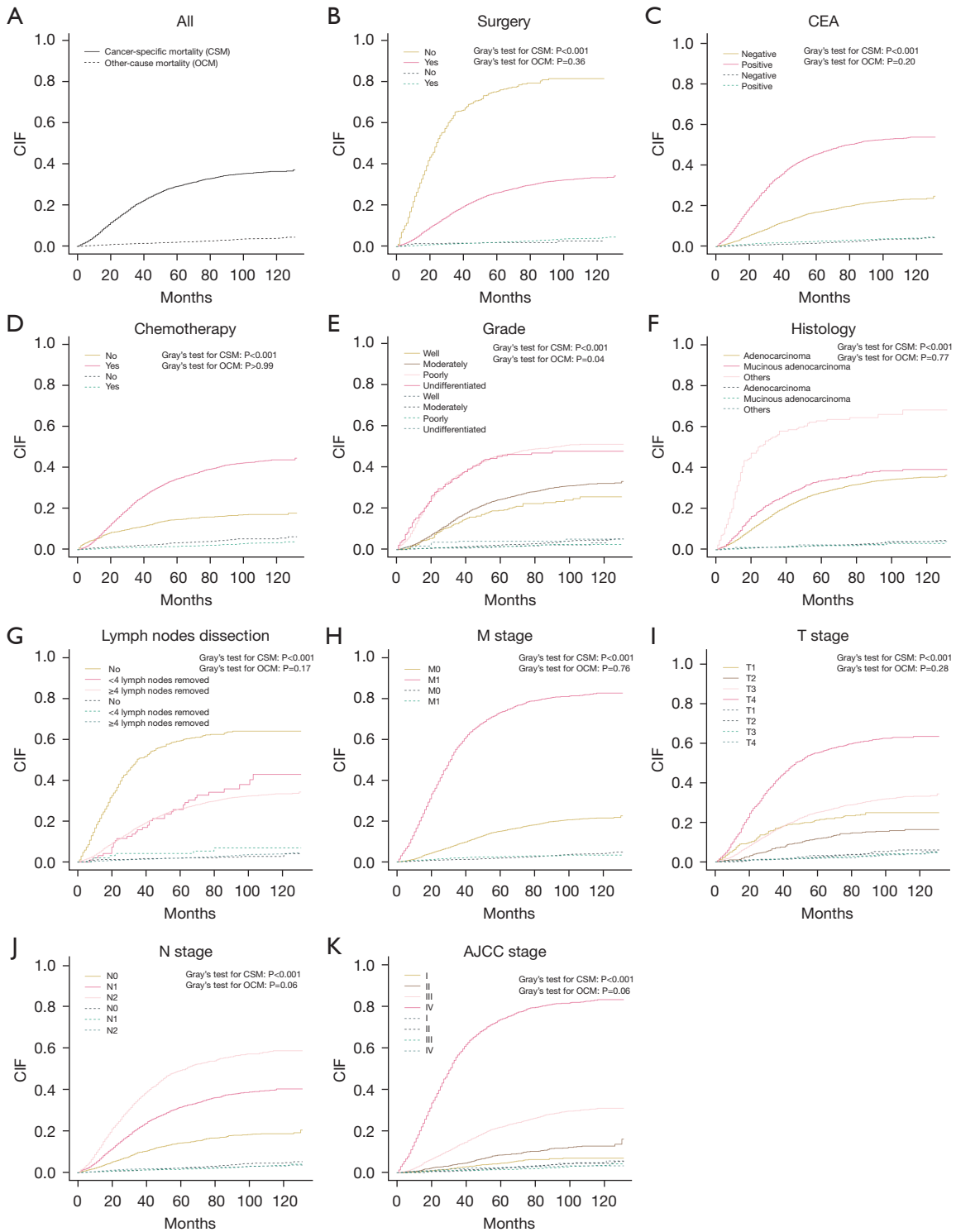

Figure 2 Cumulative incidence estimates of CSM and OCM in EOCRC patients based on (A) all variables; (B) surgery; (C) CEA; (D) chemotherapy; (E) grade; (F) histology; (G) lymph node dissection; (H) M stage; (I) T stage; (J) N stage; (K) AJCC stage; dotted line: OCM, solid line: CSM. CSM, cancer-specific mortality; OCM, other-cause mortality; EOCRC, early-onset colorectal cancer; CEA, carcinoembryonic antigen; T, primary tumor; N, regional lymph node; M, distant metastasis; AJCC, the American Joint Committee on Cancer; CIF, cumulative incidence function.

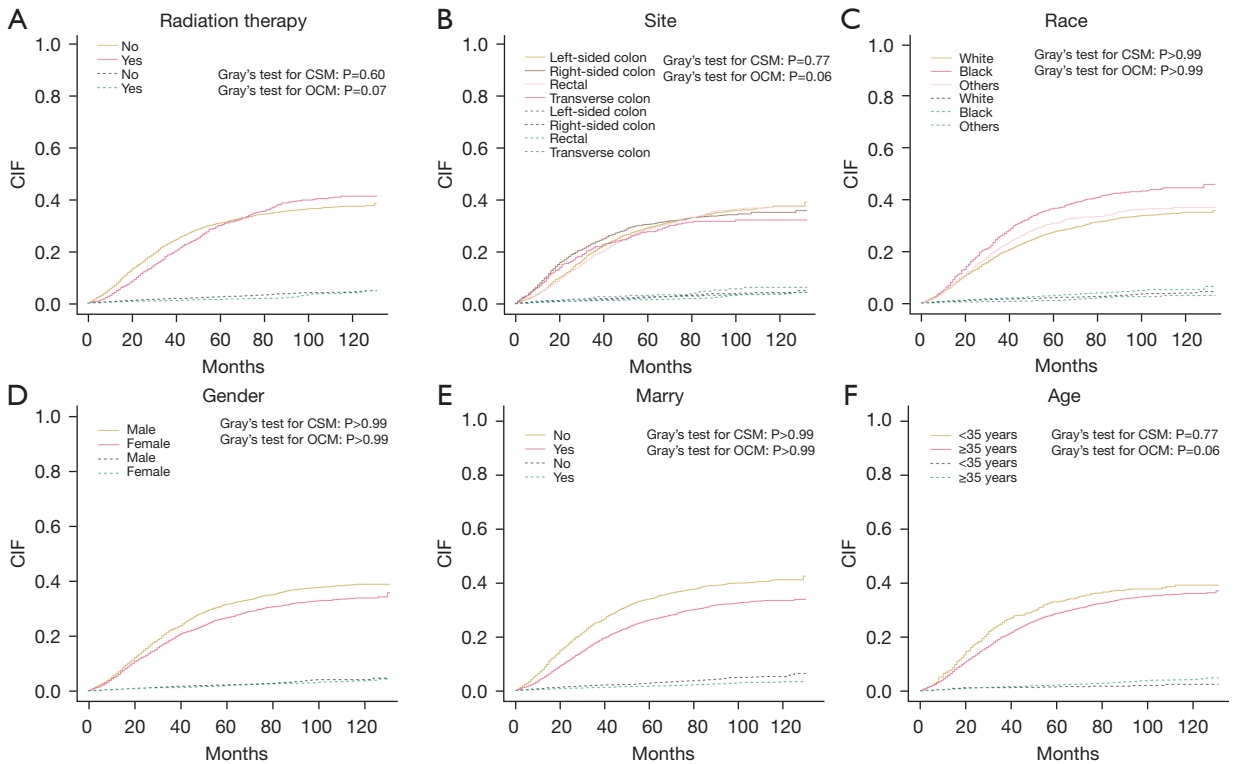

Figure 3 Cumulative incidence estimates of CSM and OCM in patients with EOCRC according to (A) radiation therapy; (B) site; (C) race; (D) gender; (E) marry; (F) age; dotted line: other-cause mortality, solid line: cancer-specific mortality. CSM, cancer-specific mortality; OCM, other-cause mortality; EOCRC, early-onset colorectal cancer; CIF, cumulative incidence function.

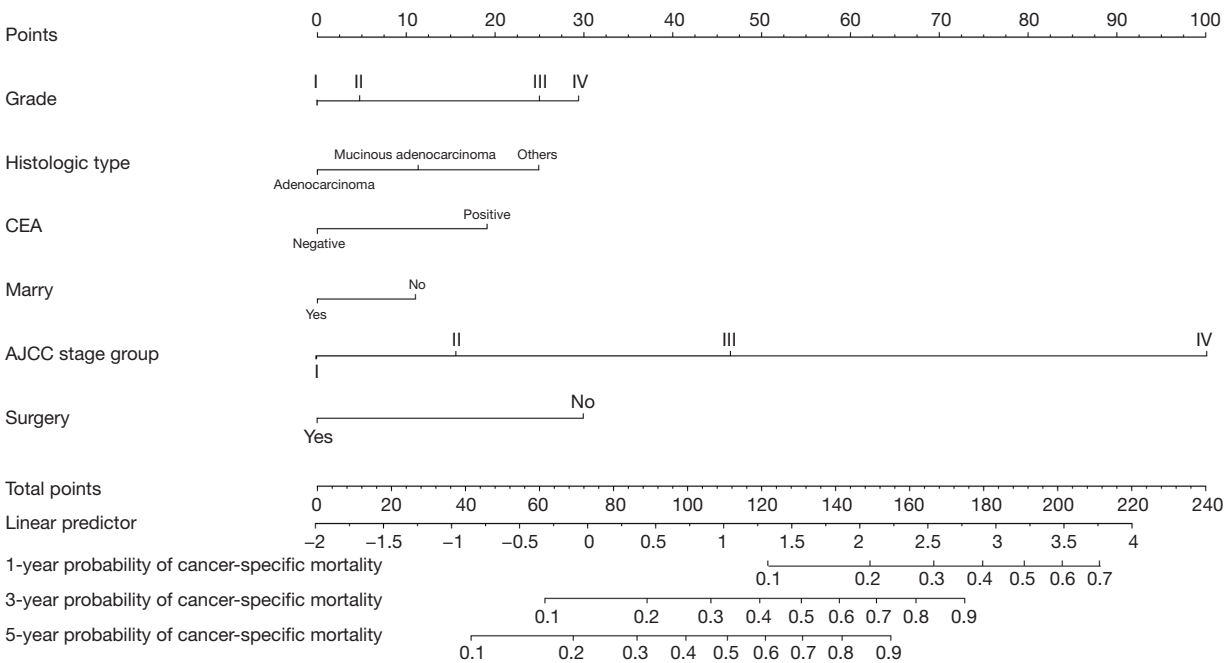

Figure 4 The nomograms for predicting 1-, 3-, and 5-year CSM in patients with EOCRC. CSM, cancer-specific mortality; EOCRC, early-onset colorectal cancer; CEA, carcinoembryonic antigen; AJCC, the American Joint Committee on Cancer.

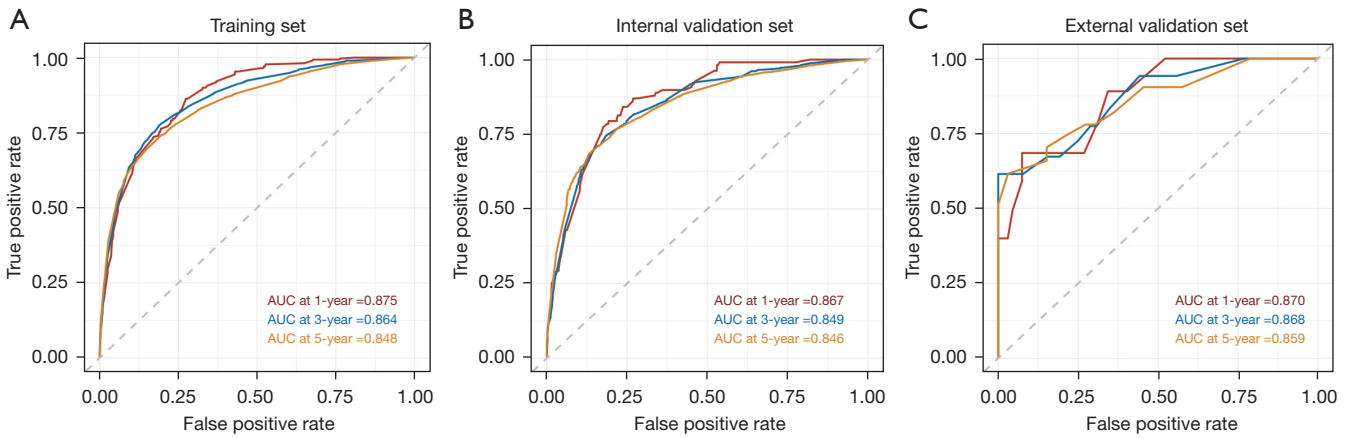

Figure 5 AUC for predicting 1-, 3-, and 5-year CSM in EOCRC patients. (A) The AUC for CSM in the training set. (B) The AUC for CSM in the internal validation set. (C) The AUC for CSM in the external validation set. AUC, area under the curve; CSM, cancer-specific mortality; EOCRC, early-onset colorectal cancer.

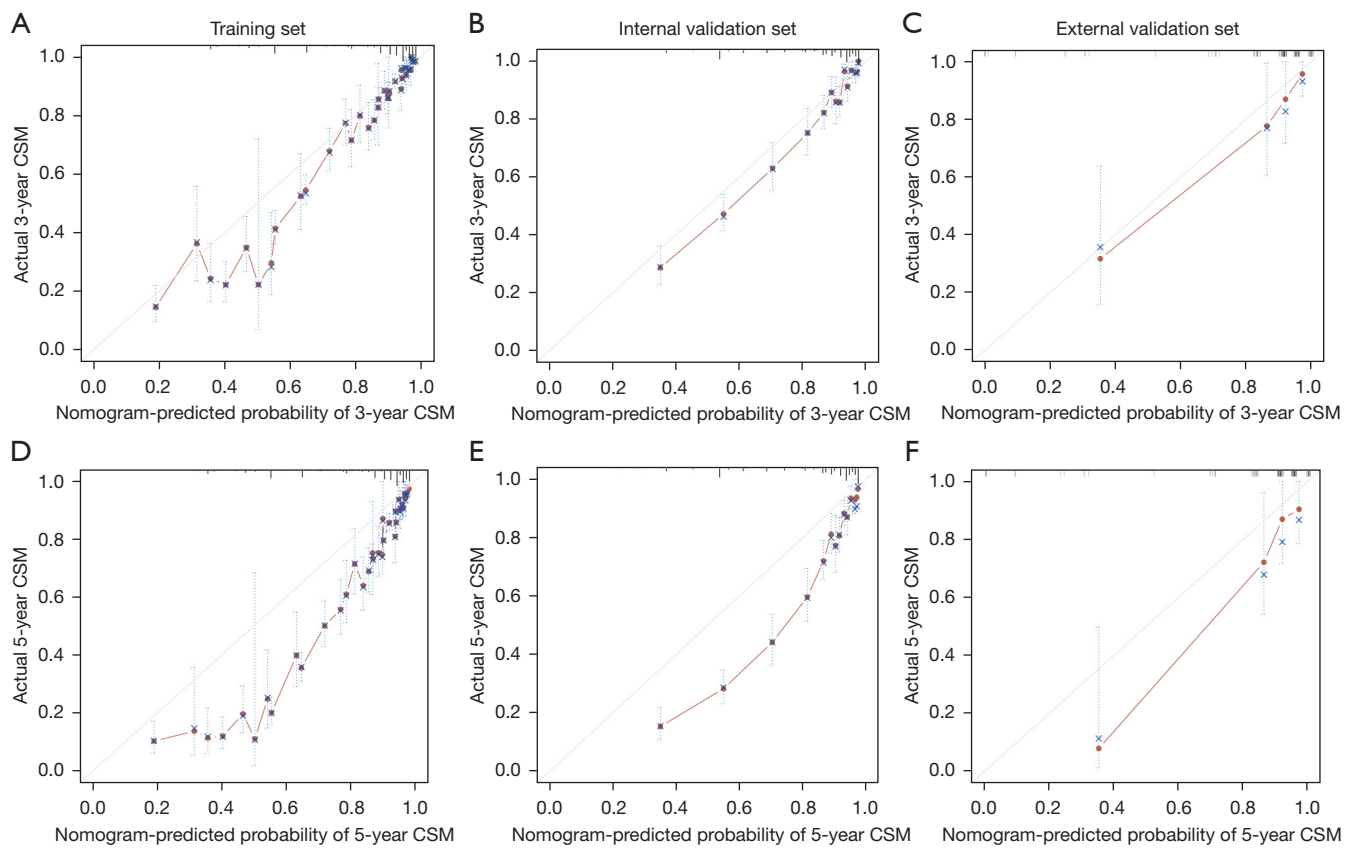

Figure 6 Calibration curve of the nomograms for predicting 3- and 5-year CSM in EOCRC patients. (A,D) Calibration curve of the nomograms for predicting 3- and 5-year CSM in the training set. (B,E) Calibration curve of the nomograms for predicting 3- and 5-year CSM in the internal validation set. (C,F) Calibration curve of the nomograms for predicting 3- and 5-year CSM in the external validation set. The horizontal axis is the predicted value in the nomogram, and the vertical axis is the observed value. CSM, cancer-specific mortality; EOCRC, early-onset colorectal cancer.

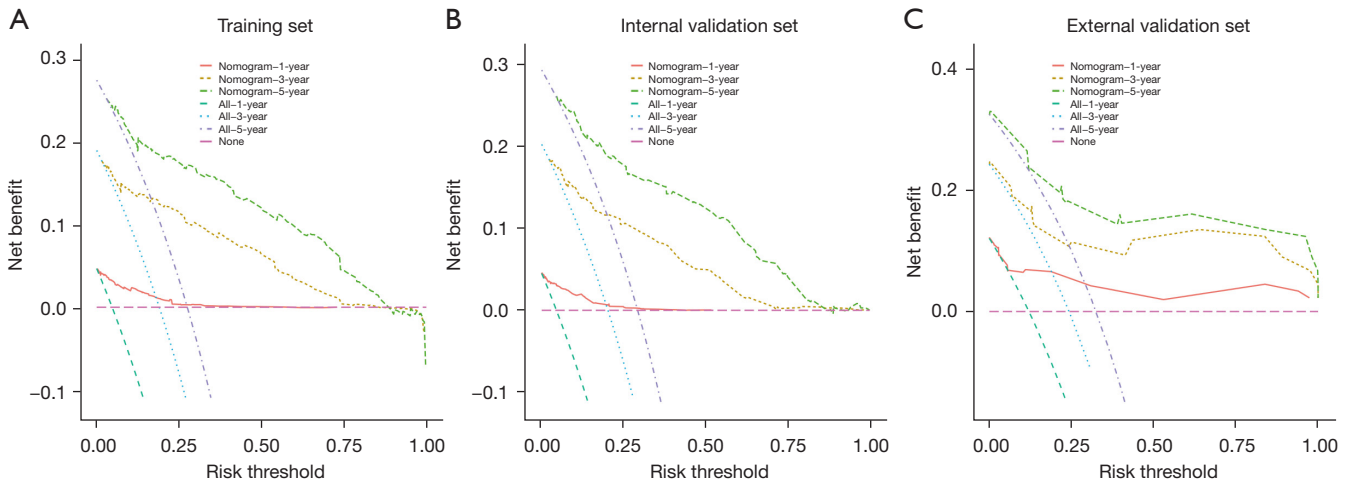

Figure 7 DCA of the nomograms for predicting 1-, 3-, and 5-year CSM. (A) The nomogram for CSM in the training set. (B) The nomogram for 1-, 3-, and 5-year CSM in the internal validation set. (C) The nomogram for 1-, 3-, and 5-year CSM in the external validation set. DCA, decision curve analysis; CSM, cancer-specific mortality.

The nomograms constructed using the competing risk model provide enhanced value compared to traditional survival analysis methods.

Discussion

EOCRC is increasingly prevalent worldwide, including countries such as the US. The US Preventive Services Task Force has issued a recommendation for CRC screening to commence at the age of 35 (30). The statement highlights the significance of researching on the causes, treatment, and prognosis of EOCRC.

EOCRC typically affects the left side of the colon (specifically, the distal colon and rectum) and exhibits advanced tumor staging, limited cell differentiation, loss of DNA methylation, and elevated mutation rates in the *KRAS* and cellular tumor antigen p53 (*TP53*) genes. Individuals with a family history of cancer syndrome have a higher risk of developing EOCRC (6,31,32).

The etiology of EOCRC remains incompletely understood. Research indicates that genetic mutations, such as breast cancer susceptibility gene 1 (*BRCA1*), *BRCA2*, partner and localizer of *BRCA2* (*PALB2*), ataxia telangiectasia-mutated gene (*ATM*), Nibrin gene (*NBN*), checkpoint kinase 2 gene (*CHEK2*), *BRCA1*-associated RING domain 1 gene (*BARD1*), and *BRCA1* interacting protein C-terminal helicase 1 (*BRIP1*), may play a role in the pathogenesis of EOCRC. The genetic predisposition to EOCRC seems to differ from that of late-onset disease. Younger patients show a significantly higher rate of variation in pathogenic lineage (17–35%) compared to older patients, with approximately 50% of these mutations occurring in DNA mismatch repair (MMR) genes that are linked to Lynch syndrome (33). A case-control study published in the *British Journal of Cancer* analyzed data from a sample of nearly 8,000 CRC patients and over 35,000 controls. The findings revealed a notable positive correlation between the duration of oral antibiotic exposure and the risk of colon cancer, particularly early-onset colon cancer ($P<0.05$). However, no significant association was observed between oral antibiotic exposure and the risk of rectal cancer (34).

When analyzing survival data, we often encounter situations where the endpoint event is not observed. This may be due to several reasons, such as loss to follow-up, continued survival, or voluntary withdrawal of the study participants. This inability to obtain specific survival times, only knowing that the survival time exceeds the observed time, is called right censoring. During the follow-up of cancer patients, it is possible that some observed patients may die from non-tumor-related causes, such as cardiovascular diseases, liver or kidney ailments, or infections. The direct inclusion of these data with outcome events in survival analyses can lead to an overestimation of the tumor-specific mortality rate. The use of traditional statistical methods to exclude data on patients with non-tumor-specific deaths also introduces selective bias, as factors such as advanced age and later tumor staging could simultaneously be risk factors for both OCM and CSM. In

such cases, using the competing risk approach proves to be an effective solution. This method allows for the analysis of survival data with various potential outcomes, with the CIFs often used as a primary endpoint measure (22,23).

In the present study, EOCRC patients from the SEER database were screened to identify prognostic factors. A nomogram based on these factors was developed to forecast the risk of CSM in EOCRC patients. The multivariate Cox regression analysis results indicated that several variables, including race, tumor grade, CEA levels, marital status, histologic type, AJCC staging, and surgical intervention, were independent risk factors for CSM. Moreover, age, gender, chemotherapy status, CEA levels, marital status, and AJCC 6th edition staging were determined to be significant independent risk factors for OCM in EOCRC patients.

It was found in a previous study that EOCRC patients diagnosed between the ages of 35 and 39 years had the highest survival, whereas those diagnosed at or below the age of 25 years showed the lowest survival (31). Meanwhile, Lieu *et al.* discovered a 19% (95% CI: 7–33%) higher risk of death in younger patients (around 18 years of age) compared to middle-aged patients (around 53 years of age) with metastatic CRC during follow-up (35). Our study findings indicated that individuals between the ages of 35 and 49 years have a higher risk of OCM compared to those between 18 and 34 years old, but this trend was not observed for CSM. At present, the reasons underlying this phenomenon remain unclear due to a lack of evidence.

The AJCC staging is a classical method for predicting tumor prognosis, with patients in advanced disease stages exhibiting a poorer prognosis (36). Our study provided evidence supporting this perspective. This factor indeed has the highest contribution coefficient in our nomogram. Additionally, a positive correlation was observed between patients with higher AJCC stages and an increased likelihood of non-tumor-related mortality. However, currently, due to a lack of sufficient understanding of EOCRC, young individuals tend to underestimate the importance of proactive cancer screening. Furthermore, the absence of clear familial tendencies in the genetics of EOCRC also contributes to many EOCRC patients being diagnosed at later stages (15,16). This significantly impacts the prognosis and survival of patients. In the past, some countries have lowered the screening age for CRC, and this study also supported such an approach (30).

Furthermore, the occurrence of various types of cancer is closely linked to race. Previous studies have reported that CRC patients of African descent exhibit a lower 5-year overall survival rate compared to individuals of Caucasian descent (37-39). A growing body of evidence suggests that the disparity in survival rates between Black and White older patients with CRC can be attributed to variations in tumor characteristics, such as tumor stage, grading, lymph node status, and comorbidities, rather than treatment disparities (38,39). Research has revealed that patients with EOCRC experience similar outcomes to those with CRC. Additionally, EOCRC patients from African American and minority ethnic backgrounds exhibited poorer outcomes compared to Caucasians (40). Our study results corroborated these findings, indicating a consistent pattern of poorer prognosis among ethnicities other than White, with Black individuals exhibiting the most unfavorable prognosis.

With the advent of fluorouracil-based combination regimens, the survival time and quality of life of patients with advanced metastatic disease have significantly improved. However, in our multifactorial analysis of CSM in EOCRC patients, we observed that the receipt of chemotherapy did not show a significant correlation (HR =1.040; 95% CI: 0.898–1.204; P=0.60). We speculate that this may be related to the fact that patients requiring chemotherapy are usually diagnosed at a later stage. Furthermore, studies have demonstrated that although chemotherapeutic agents enhance the prognosis of patients with CRC, they also lead to a higher rate of associated complications (19-21). Chemotherapy treatment is known to primarily induce excessive immune activation and can potentially cause direct harm to non-target organs, particularly the heart. Cardiovascular complications are the most common non-tumor related causes of death in CRC patients (41). In contrast, our results revealed that receiving chemotherapy is a protective factor for OCM (P<0.001). Yet, this result may also be affected by bias as our study analyzed data from the SEER database, which summarized radiotherapy information as either yes, no, or unknown. Therefore, there is a possibility of error in our study.

In recent years, a growing emphasis has been placed on determining the impact of socioeconomic factors such as cultural and social values, insurance status, educational level, and employment status on disease outcomes (42). In the present study, the marital status of individuals was found to be an independent risk factor for both CSM and OCM.

Furthermore, independent risk factors and existing literature were analyzed to identify indicators and construct the model. Considering the covariance between individual

TNM staging and AJCC staging among the independent risk factors for CSM, we chose the latter, which is more comprehensive, to be included in the model. However, due to significant racial differences between the external validation group and the training group, this variance was excluded.

A major strength of this study is the utilization of a substantial sample derived from the SEER database to construct a robust competitive risk model. Additionally, data from Chinese patients were obtained to serve as an external validation cohort. The C-index values in the training group, as well as the internal and external validation groups, all exceeded 0.80. A C-index or AUC value below 0.60 is indicative of inadequate discrimination, whereas a range of 0.60 to 0.75 suggests potentially beneficial discrimination. Values exceeding 0.75 indicate highly effective discrimination and are considered to possess robust validity and generalizability.

However, a higher percentage of individuals in the external validation cohort were of Asian ethnicity and married, with tumors exhibiting larger diameters and a higher rate of CEA positivity. This observation may be potentially attributed to relatively late tumor screening in China. All of the above factors can bias the external validation process. Nevertheless, the external validation cohort effectively confirmed the accuracy of the model, thereby demonstrating the applicability of the SEER database to Asian populations. This finding highlights the robustness and generalizability of the study's results.

Nevertheless, the limitations of the study should be acknowledged. Patients who had incomplete clinical and follow-up data were excluded, which may have introduced a certain level of bias in terms of the representativeness of the study sample. Moreover, the retrospective nature of the study introduces the possibility of selection bias. In addition, certain crucial prognostic factors related to tumors were not incorporated into the model due to their unavailability in the SEER database, such as surgical approach, chemotherapy regimens, *KRAS* mutations, *BRAF* mutations, MSI, TMB, and other relevant factors. Our study also does not provide a dynamic nomogram, thereby restricting its practical applicability. Finally, an analysis was conducted to identify independent risk factors for OCM, but no further modeling was performed as only 2 cases of non-tumor-related deaths (7.4%) were observed in the external validation group. For future research endeavors, our plan entails the development of a dynamic nomogram with a larger sample size in the external validation group. This will facilitate a more comprehensive analysis of OCM in EOCRC.

Overall, a nomogram was developed and validated using a competing risk model to forecast the CSM of EOCRC based on the SEER database as well as a Chinese cohort. Additionally, the DCA showed that our predictive model displayed favorable clinical utility.

Conclusions

This study successfully developed a nomogram model based on competing risk analysis of mortality in patients with EOCRC. The model exhibited strong predictive efficacy and was subjected to both internal and external validation processes. The C-index, calibration curves, and AUC values further demonstrated the accuracy and discriminative capability of the model. Additionally, DCA demonstrated the significant clinical utility of the model.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2023/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2023/dss

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2023/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2023/coif). The authors have no conflicts of interest to declare.

Ethical Statement: 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 conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Chaoyang Central Hospital of China Medical University (2023 No. 16) and the requirement for individual consent for this retrospective analysis was waived.

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