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ORIGINAL ARTICLE

Clinical and Translational Research

Analysis of cancer-specific survival in patients with metastatic colorectal cancer: A evidence-based medicine study

Yin-Jie Zhou, Zhi-E Tan, Wei-Da Zhuang, Xin-Hua Xu

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Abstract

BACKGROUND

Metastatic colorectal cancer (mCRC) is a common malignancy whose treatment has been a clinical challenge. Cancer-specific survival (CSS) plays a crucial role in assessing patient prognosis and treatment outcomes. However, there is still limited research on the factors affecting CSS in mCRC patients and their correlation.

AIM

To predict CSS, we developed a new nomogram model and risk grading system to classify risk levels in patients with mCRC.

METHODS

Data were extracted from the United States Surveillance, Epidemiology, and End Results database from 2018 to 2023. All eligible patients were randomly divided into a training cohort and a validation cohort. The Cox proportional hazards model was used to investigate the independent risk factors for CSS. A new nomogram model was developed to predict CSS and was evaluated through internal and external validation.

RESULTS

A multivariate Cox proportional risk model was used to identify independent risk

factors for CSS. Then, new CSS columns were developed based on these factors. The consistency index (C-index) of the histogram was 0.718 (95%CI: 0.712-0.725), and that of the validation cohort was 0.722 (95%CI: 0.711-0.732), indicating good discrimination ability and better performance than tumor-node-metastasis staging (C-index: 0.712-0.732). For the training set, 0.533, 95%CI: 0.525-0.540; for the verification set, 0.524, 95%CI: 0.513-0.535. The calibration map and clinical decision curve showed good agreement and good potential clinical validity. The risk grading system divided all patients into three groups, and the Kaplan-Meier curve showed good stratification and differentiation of CSS between different groups. The median CSS times in the low-risk, medium-risk, and high-risk groups were 36 months (95%CI: 34.987-37.013), 18 months (95%CI: 17.273-18.727), and 5 months (95%CI: 4.503-5.497), respectively.

CONCLUSION

Our study developed a new nomogram model to predict CSS in patients with synchronous mCRC. In addition, the risk-grading system helps to accurately assess patient prognosis and guide treatment.

Key Words: Colorectal tumor; Surveillance epidemiology and end results database; Nomogram analysis; Survival prognosis; Retrospective study

Core Tip: This study utilized an evidence-based approach to analyze cancer-specific survival (CSS) in patients with metastatic colorectal cancer (mCRC). By systematically collecting, integrating, and analyzing relevant data, we explored CSS in mCRC patients and its influencing factors to provide clinicians with more accurate prognostic assessments and treatment decision support. The importance of this study is that it can provide a basis for individualized treatment of mCRC patients and promote the maximization of treatment effects, thereby improving the quality of life and survival rate of patients.

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INTRODUCTION

Colorectal cancer (CRC) is one of the most common malignant neoplasms, ranking third in incidence (10.2%) and second in mortality (9.2%)[1-3]. In countries in Eastern Europe, Latin America, and Asia, the incidence and mortality of CRC are increasing annually[4]. There are no obvious signs or symptoms of CRC in the early stages, and more than one-fifth of patients have developed distant metastases at the time of diagnosis[5]. Among patients with CRC, patients with simultaneous metastases have lower survival rates than patients with heterochronous metastases[6]. The most common metastatic organs for CRC are the liver and lung, while bone metastases are rare, and brain metastases occur in only 1% of CRC patients[7]. Although metastatic CRC (mCRC) has the worst prognosis, there are large differences in survival outcomes between patients with different metastatic organs. The 1-year survival rate for patients with liver and lung metastases is greater than 80%, while the 1-year survival rates for patients with bone and brain metastases are 30% and 11%, respectively[8]. Therefore, accurate screening for different risk factors is critical for physicians to predict mCRC outcomes.

Currently, the American Joint Committee on Cancer (AJCC) staging system is the primary method for predicting survival outcomes in patients with mCRC[9]. However, the T stage, N stage, and M stage are the only factors for distinguishing different prognoses, and this scheme is far from satisfactory in terms of prediction accuracy[10]. A nomogram is a visual tool used to predict the probability of an endpoint occurring and to quantify survival risk. According to the different regression coefficients, the columniogram can include significant factors to improve the prediction accuracy. To date, nomograms have been successfully used to predict the prognosis of patients with CRC but have rarely been used for patients with mCRC[11].

Therefore, our goal was to develop a new nomographic model to predict tumor-specific survival for patients with simultaneous mCRC and to divide this model into different risk levels to accurately assess patient prognosis.

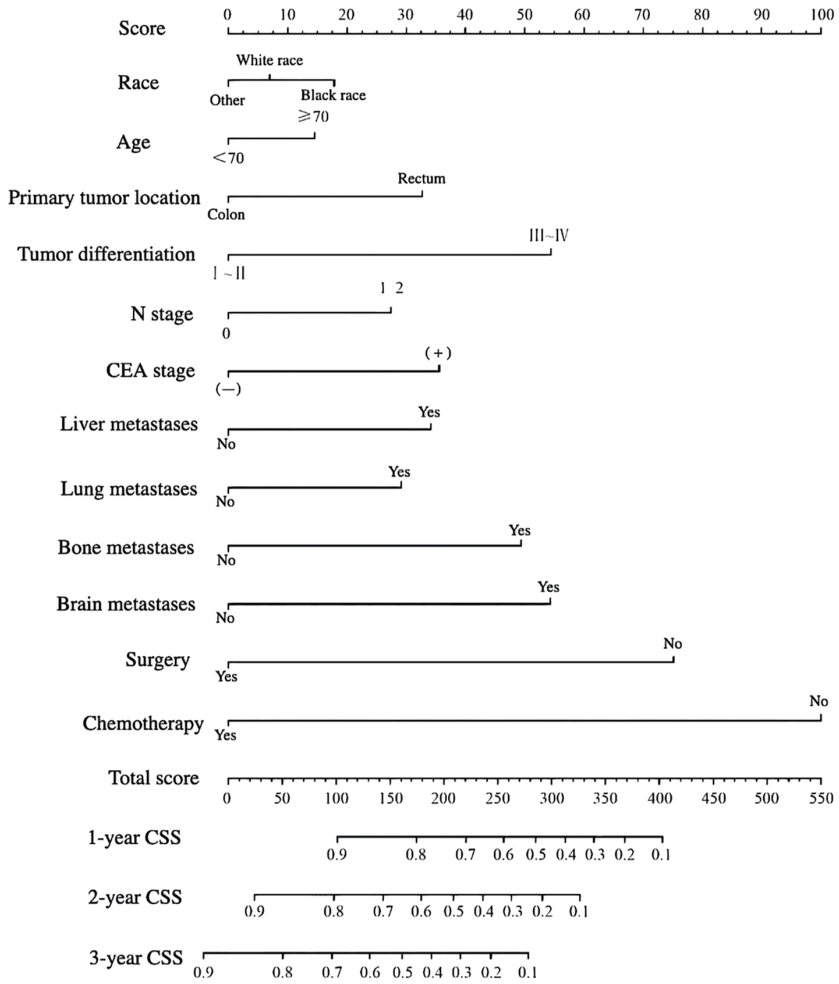

Figure 1 Nomogram for predicting the tumor-specific survival of patients with metastatic colorectal cancer. CEA: Carcinoembryonic antigen; CSS: Cancer-specific survival.

MATERIALS AND METHODS

Research subjects

This study obtained all the data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute using SEER Stat software (version 8.3.6). The data were collected and reported using data items and codes recorded by the North American Association of Central Cancer Registries. The inclusion criteria for patients were as follows: (1) Were diagnosed with CRC between 2018 and 2023; (2) were diagnosed with simultaneous metastasis; and (3) had a histological diagnosis. The exclusion criteria were as follows: (1) No patients with distant metastasis; and (2) unknown missing data, such as race, primary tumor site, T stage, N stage, carcinoembryonic antigen (CEA) status, surgical status, and survival time.

The following variables were collected: Race, sex, age at diagnosis, primary site, grade, T stage, N stage, CEA status, distant metastatic status (liver, lung, bone, brain), surgery (primary tumor resection), chemotherapy, cancer-specific survival (CSS), and survival time. CSS was assessed by 1-, 2-, and 3-year survival rates, defined as the time from the date of diagnosis to the date of death or study due to CRC, according to the eighth edition of the AJCC tumor-node-metastasis staging system.

Research method

All eligible patients were randomly divided into training and validation groups (at a ratio of 7:3). The Pearson chi-square test was used to examine demographic differences between all coqueues, training coqueues, and validation coqueues. A multivariate Cox proportional risk model was used to explore independent risk factors for CSS, and a predictive nomogram model was built using a training cohort. The C-index, calibration curve, and decision curve analysis (DCA) were used for internal and external verification.

Nomogram analysis

X-tile software was used to determine the optimal critical value according to the total score of the column graph to establish a risk grading system, and all patients were divided into low-, medium-, and high-risk groups. Kaplan-Meier (K-M) curves of CSS were constructed and compared with a logarithmic rank test. Statistical analysis was performed

Table 1 Demographic characteristics, *n* (%)

Variable	Total cohort (*n* = 15838)	Training cohort (*n* = 11088)	Validation cohort (*n* = 4750)	χ^2	*P* value
Race				1.36	0.507
Black people	2303 (14.5)	1590 (14.3)	713 (15.0)		
White race	12075 (76.2)	8480 (76.5)	3595 (75.7)		
Other	1460 (9.2)	1018 (9.2)	442 (9.3)		
Sex				0.027	0.869
Male	8560 (54.0)	5988 (54.0)	2572 (54.1)		
Female	7278 (46.0)	5100 (46.0)	2178 (45.9)		
Age at diagnosis (yr)				1.73	0.188
< 70	10 735 (67.8)	7480 (67.5)	3255 (68.5)		
≥ 70	5103 (32.2)	3608 (32.5)	1495 (31.5)		
Primary tumor location				0.264	0.607
Colon	7063 (44.6)	4930 (44.5)	2133 (44.9)		
Rectum	8775 (55.4)	6158 (55.5)	2617 (55.1)		
Tumor differentiation				0.014	0.906
I-II	11127 (70.3)	7793 (70.3)	3334 (70.2)		
III-IV	4711 (29.7)	3295 (29.7)	1416 (29.8)		
T staging				0.08	0.777
1-2	2079 (13.1)	1461 (13.2)	618 (13.0)		
3-4	13759 (86.9)	9627 (86.8)	4132 (87.0)		
N stage				0.576	0.448
0	4209 (26.6)	2966 (26.7)	1243 (26.2)		
1-2	11629 (73.4)	8122 (73.3)	3507 (73.8)		
CEA status				2.721	0.099
Masculine	12378 (78.2)	8705 (78.5)	3673 (77.3)		
Feminine	3460 (21.8)	2383 (21.5)	1077 (22.7)		
Liver metastases				0.286	0.593
No	4731 (29.9)	3298 (29.7)	1433 (30.2)		
Yes	11107 (70.1)	7790 (70.3)	3317 (69.8)		
Lung metastases				2.202	0.138
No	12673 (80.0)	8838 (79.7)	3835 (80.7)		
Yes	3165 (20.0)	2250 (20.3)	915 (19.3)		
Bone metastases				0.724	0.395
No	15226 (96.1)	10669 (96.2)	4557 (95.9)		
Yes	612 (3.9)	419 (3.8)	193 (4.1)		
Brain metastases				1.032	0.31
No	15682 (99.0)	10973 (99.0)	4709 (99.1)		
Yes	156 (1.0)	115 (1.0)	41 (0.9)		
Surgical				0.014	0.906
No	3495 (22.1)	2444 (22.0)	1051 (22.1)		
Yes	12343 (77.9)	8644 (78.0)	3699 (77.9)		
Chemotherapy				0.026	0.872

None/unknown	4235 (26.7)	2969 (26.8)	1266 (26.7)
Yes	11603 (73.3)	8119 (73.2)	3484 (73.3)

CEA: Carcinoembryonic antigen.

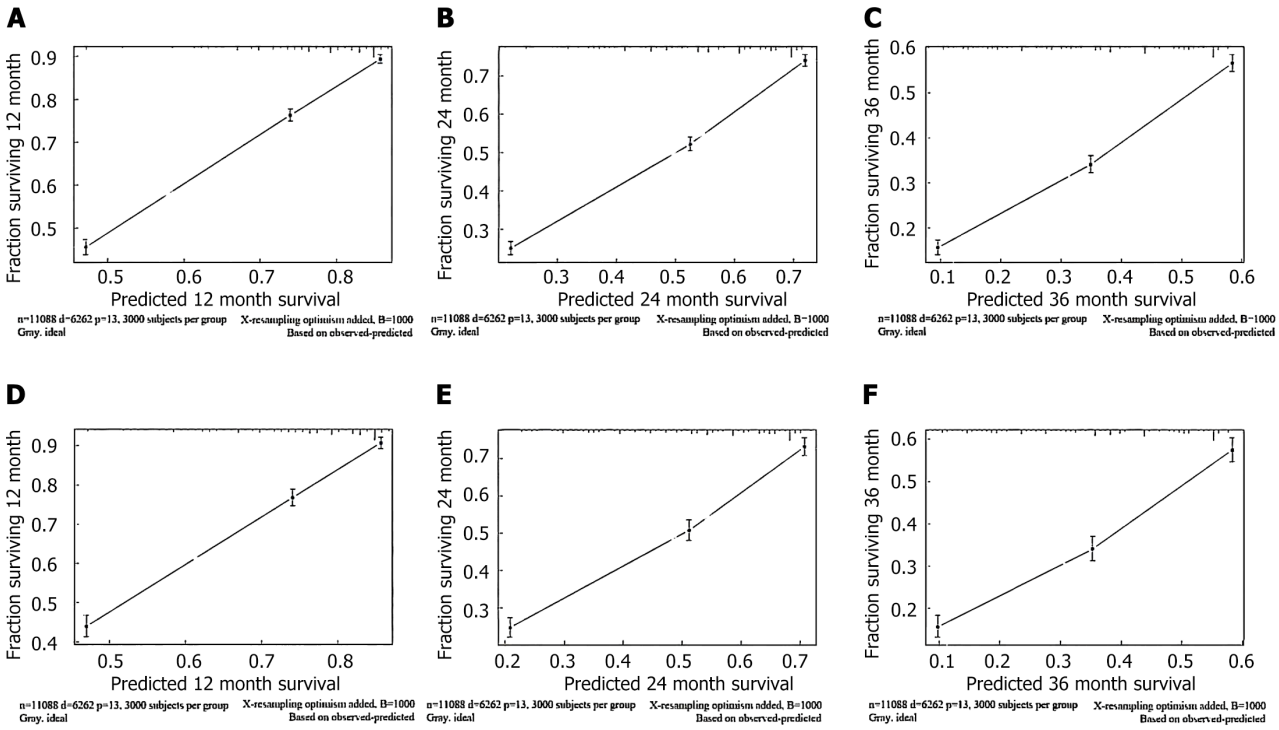

Figure 2 Calibration curves based on cancer-specific survival for metastatic colorectal cancer patients. A-C: Calibration curves based on 1-, 2-, and 3-year cancer-specific survival (CSS) of the training cohort; D-F: Calibration curves based on 1-, 2-, and 3-year CSS of the validation cohort.

using SPSS 21.0 statistical software (IBM SPSS Statistics for Windows; Armonk, NY, United States), GraphPad Prism 6 (GraphPad Software), X-Tile software (Yale University), and R Statistical Software 3.6.2 (www.r-project.org/).

Statistical analysis

SPSS 23.0 statistical software was used for analysis. The χ^2 test was used for comparison of counting data, and the t test was used for comparison of measurement data. The survival rate was calculated by the life table method, the survival curve was plotted by the K-M method, and comparisons were performed by the log-rank method. Multiple factor analysis was performed by the Cox proportional risk regression model, and $P < 0.050$ was considered to indicate statistical significance.

RESULTS

Baseline population information

According to the inclusion criteria, a total of 15838 patients eligible for inclusion were included in this study, among whom 11088 (70.0%) patients were randomly assigned to the training cohort and 4750 (30.0%) patients were randomly assigned to the verification cohort. The demographic characteristics of this study population are shown in Table 1.

In this study, there were 8560 males (54.0%) and 7278 females (46.0%), of which the majority were white (76.2%), 13759 (86.9%) were T3-4, 11629 (73.4%) were N1-2, and CEA was positive (78.2%). The incidence of distant metastasis in the liver, lung, bone, and brain was 11107 (70.1%), 3165 (20.0%), 612 (3.9%), and 156 (1.0%), respectively. A total of 12343 patients (77.9%) received surgery, and 11603 patients (73.3%) received chemotherapy. There was no significant difference between the training cohort and the verification cohort ($P > 0.05$).

Prediction factor determination

The Cox proportional hazards model was used to identify independent risk factors for CSS. Multivariate analysis revealed that the independent risk factors in the training cohort were race, age at diagnosis, primary site, tumor grade, N stage, CEA status, liver metastasis, lung metastasis, bone metastasis, brain metastasis, surgery, and chemotherapy

(Table 2).

Based on the significant risk factors for CSS, a predictive nomogram model of CSS was established (Figure 1). The regression coefficients and estimates of the training queue are shown in Table 3. The nomogram was evaluated with internal and external validation. The C-index of the column chart was 0.718 (95%CI: 0.712-0.725), and the C-finger number of the verification set was 0.722 (95%CI: 0.711-0.732), indicating good identification ability and better performance than TNM staging (C-index: Training set, 0.533, 95%CI: 0.525-0.540; verification set, 0.524, 95%CI: 0.513-0.535). A calibration diagram of the CSS showed good agreement between the predicted and actual values of the training and validation samples, with 1000 bootstrap samples (Figure 2). The DCA curve showed a large net gain between most threshold probabilities at different time points, indicating good potential clinical validity for predicting CSS (Figure 3).

Establishment of the risk classification system

In addition, X-Tile software was used to determine the optimal cutoff value and establish a risk classification system (Figure 4). All patients were classified as low risk (5852/11088, 52.78%, score: 0-164), medium risk (3487/11088, 31.45%, score: 165-247) or high risk (1749/11088, 15.77%, score: 248-524). In theory, the total score ranges from 0 to 524. K-M curves showed that the risk grading system had good layering and differentiation ability for different CSS groups (Table 4, Figure 5).

DISCUSSION

The prognosis of mCRC patients is significantly worse than that of non-mCRC patients. mCRC mortality varies widely from patient to patient, suggesting the importance and necessity of reclassifying the exact risk level based on the AJCC staging system[12-14]. However, due to the limitations of the included factors, the existing prediction models lack individualization and comprehensive evaluation, and the sample sizes of most studies[15-17] are small, which also limits their universal applicability. In this study, we developed a new CSS predictive nomogram based on simultaneous mCRC data from large population cohorts.

We identified predictors of CSS that were consistent with previous studies, including race, age at diagnosis, primary site, grade, N stage, CEA status, liver metastasis, lung metastasis, bone metastasis, brain metastasis, surgery, and chemotherapy[18]. For patients with mCRC, both surgery and chemotherapy are important for improving outcomes, as recommended by the United States National Comprehensive Cancer Network (NCCN) guidelines and the European Society of Medical Oncology guidelines[19]. Modest suggested that the effective rate of first-line systemic treatment is 38% to 65%, and the disease control rate is 81% to 90%[20]. Compared to earlier studies, this column chart is the first to include chemotherapy status as a risk predictor for predicting CSS. The highest score of mCRC patients who did not receive chemotherapy was 100, which was greater than that of mCRC patients who did not receive surgery, indicating that the regression coefficient of the effect of chemotherapy on CSS was greater than that of surgery[21-23]. In addition, patients who did not receive chemotherapy or who did not receive chemotherapy were not separately recorded in the SEER database as confounding risk factors in this study, which may reduce the actual regression coefficient of not receiving chemotherapy[24-26]. According to previous studies[27-29], chemotherapy is positively associated with survival benefits in patients with mCRC, and our study further highlights the unique advantages of simultaneous mCRC chemotherapy.

In addition to chemotherapy, our study revealed that primary tumor resection is also important for prognosis. Several studies[30-32] support this idea in mCRC, especially in patients with liver or lung metastases. The NCCN guidelines recommend that patients with mCRC should be evaluated by a multidisciplinary team and, if possible, that the metastatic disease and primary tumor should be removed. Therefore, primary tumor resection remains controversial for mCRC patients whose metastases cannot be resected. Studies[33-35] have shown that primary tumor resection significantly extends overall survival (OS) in mCRC patients with unresectable metastases (median OS: 13.8 months *vs* 6.3 months, $P = 0.0001$). Another study[36] also supported the idea that primary tumor removal resulted in better survival for mCRC patients with unresectable metastases (2-year CSS: 50.2% *vs* 28.1%, $P < 0.001$). In conclusion, primary tumor resection has a positive impact on patient survival. As mentioned above, the liver and lungs are the most common sites of CRC metastasis, and bone and brain metastases are very rare. In addition, the prognostic significance of different metastatic organs was inconsistent. The occurrence of brain metastases is often associated with the worst survival, and studies[37-39] have reported that the median survival of CRC patients with brain metastases is 3 to 6 months, that of CRC patients with bone metastases is 5 to 7 months, that of CRC patients with liver metastases is 22.8 months, and that of CRC patients with lung metastases is 36.2 to 49 months. Another study confirmed this idea, with brain metastases having the largest coefficient of impact among the four metastatic organs of CRC. Our study showed that the regression coefficients of CSS in descending order were brain metastasis, bone metastasis, liver metastasis, and lung metastasis. Due to the presence of the blood-brain barrier (BBB) and blood–cerebrospinal fluid barrier (CSF), brain metastases are often the ultimate organs of metastasis for CRC, while other extracranial metastases occur in areas such as the liver and lungs. The BBB and CSF also hinder chemotherapy efficacy, which may be another reason for the poor prognosis.

On the basis of multiple regression analysis, we developed a new nomograph to integrate multiple predictors and help accurately predict the survival of patients with synchronous mCRC. One study constructed a nomogram for predicting the survival of CRC patients. Another study also developed an OS nomogram model for predicting mCRC with strong consistency. Compared to existing predictive models, our column charts integrate more predictive variables, such as chemotherapy and surgery, to provide comprehensive predictions for CSS. In addition, through X-Tile software, we established a risk classification system with an optimal cutoff value that is more accurate and reliable. This approach

Table 2 Multivariate analysis of COX based on training cohorts

Variable	Multivariate analysis	
	HR (95%CI)	*P* value
Race		
Black people	1	
White race	0.894 (0.834-0.959)	0.002
Other	0.835 (0.752-0.928)	0.001
Sex		
Male	1	
Female	0.965 (0.918-1.015)	0.17
Age at diagnosis (yr)		
< 70	1	
≥ 70	1.162 (1.099-1.228)	< 0.001
Primary tumor location		
Colon	1	
Rectum	0.715 (0.678-0.754)	< 0.001
Tumor differentiation		
I-II	1	
III-IV	1.721 (1.630-1.817)	< 0.001
T staging		
1-2	1	
3-4	1.085 (0.999-1.179)	0.053
N stage		
0	1	
1-2	1.304 (1.226-1.386)	< 0.001
CEA status		
Masculine	1	
Feminine	0.699 (0.655-0.746)	< 0.001
Liver metastases		
No	1	
Yes	1.406 (1.326-1.490)	< 0.001
Lung metastases		
No	1	
Yes	1.341 (1.260-1.426)	< 0.001
Bone metastases		
No	1	
Yes	1.621 (1.438-1.827)	< 0.001
Brain metastases		
No	1	
Yes	1.718 (1.370-2.155)	< 0.001
Surgical		
No	1	
Yes	0.459 (0.429-0.492)	< 0.001

Chemotherapy		
None/unknown	1	
Yes	0.368 (0.348-0.390)	< 0.001

CEA: Carcinoembryonic antigen; HR: Hazard ratio.

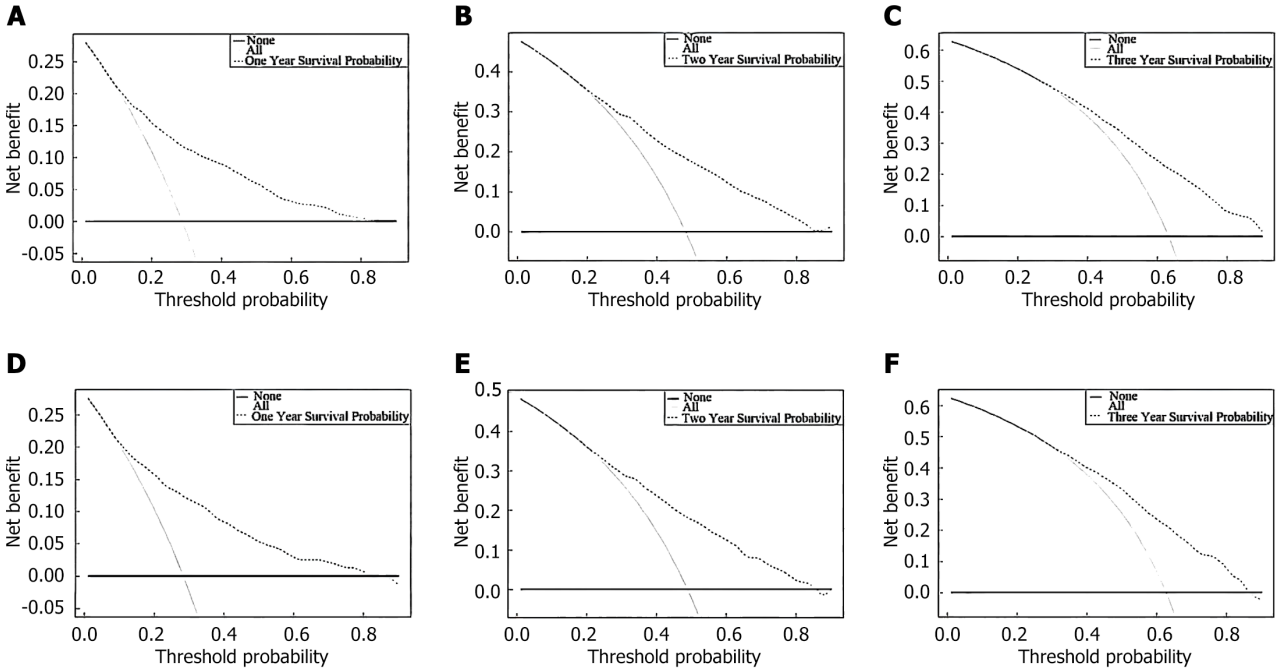

Figure 3 The nomogram model predicts the clinical decision curve of cancer-specific survival in metastatic colorectal cancer patients. A-C: Clinical decision curves based on 1-, 2-, and 3-year cancer-specific survival (CSS) in the training cohort; D-F: Clinical decision curves based on 1-, 2-, and 3-year CSS in the validation cohort.

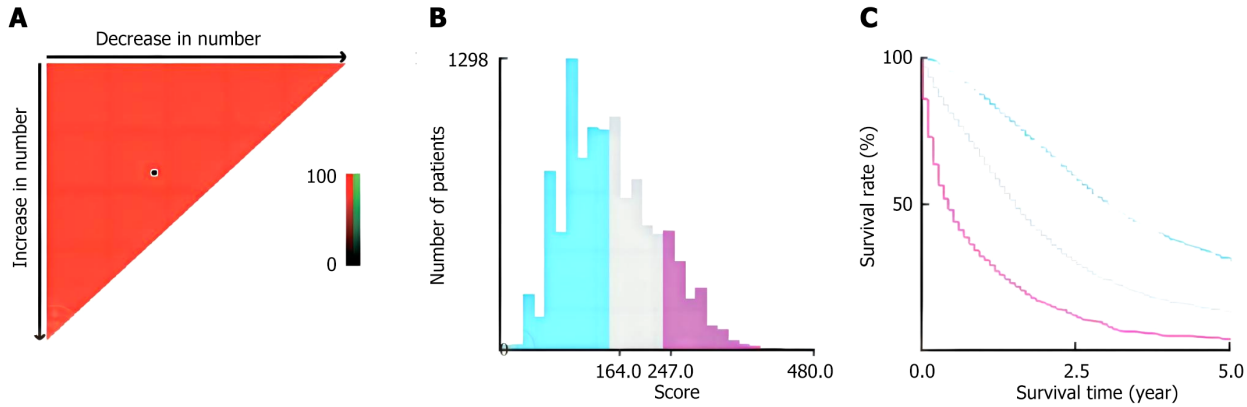

Figure 4 X-tile software was used to calculate the optimal truncation value and establish a risk classification system. A and B: The optimal cutoff values of the predicted total scores, including the low-risk group (score: 0-164), medium-risk group (score: 165-247) and high-risk group (score: 248-480); C: Kaplan-Meier curves for different risk levels according to the cancer-specific survival of the training cohort.

helps to assess the level of risk in patients with mCRC, allowing for individualized treatment and an accurate prognosis. In addition, we provide estimated points for each important prognostic factor to improve clinical application[40].

There are several limitations to our study. First, this study is a retrospective analysis of existing selection bias. Furthermore, the SEER database does not contain detailed information on chemotherapy regimens or targeted therapies, which hinders further subgroup analysis. Then, the SEER data are used to verify the validity of the column graph prediction, which lacks the verification of real data.

Table 3 Regression coefficients and estimated scores for building a Nomogram prediction model based on a training cohort

Variable	Nomogram	
	Regression coefficients	Estimated score
Race		
Black people	17.846261	18
White race	6.960746	7
Other	0	0
Age at diagnosis (yr)		
< 70	0	0
≥ 70	14.55836	15
Primary tumor location		
Colon	32.76881	33
Rectum	0	0
Tumor differentiation		
I-II	0	0
III-IV	54.39289	54
N stage		
0	0	0
1-2	27.38794	27
CEA status		
Masculine	35.56051	36
Feminine	0	0
Liver metastases		
No	0	0
Yes	34.12213	34
Lung metastases		
No	0	0
Yes	29.0965	29
Bone metastases		
No	0	0
Yes	49.30787	49
Brain metastases		
No	0	0
Yes	54.35879	54
Surgical		
No	75.074	75
Yes	0	0
Chemotherapy		
None/unknown	100	100
Yes	0	0
Range	0-524.474061	0-524
Score	531.434807	531

CEA: Carcinoembryonic antigen.

Table 4 Analyzes tumor-specific survival rates in patients with different risk classes, %

Variable	Low-risk group	Medium-risk group	High-risk group
	(*n* = 8140)	(*n* = 4737)	(*n* = 2013)
1 yr CSS	86.10	63.00	31.50
2 yr CSS	67.30	38.00	16.10
3 yr CSS	49.70	24.60	8.90
5 yr CSS	31.30	14.20	4.30
Median CSS	36 months	18 months	5 months
95%CI	34.987-37.013	17.273-18.727	4.503-5.497

CSS: Cancer-specific survival.

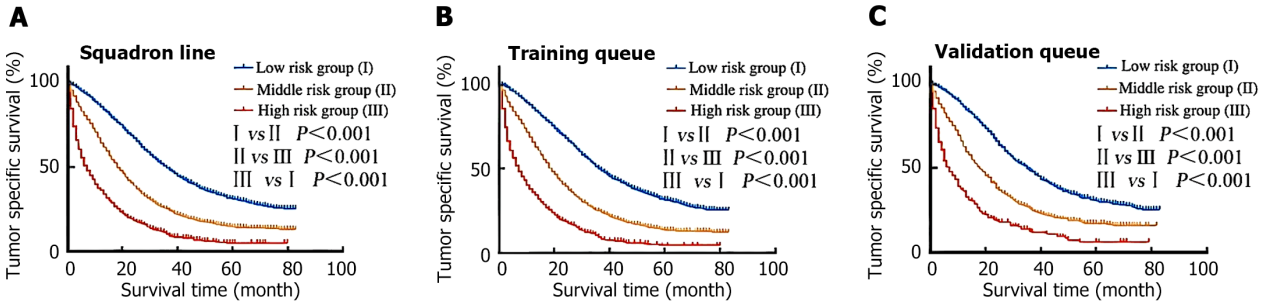

Figure 5 Kaplan-Meier survival curves for patients with different risk levels were drawn according to their cancer-specific survival. A: Platoon line; B: Training queue; C: Authentication queue.

CONCLUSION

In summary, we developed a new nomogram model to predict CSS in patients with synchronous mCRC. The verification of the model showed that the model has good discriminability and consistency. The risk grading system can grade the risk level of mCRC patients, accurately evaluate patient prognosis, and guide treatment.

FOOTNOTES

Author contributions: Zhou YJ wrote the manuscript; Tan ZE and Zhuang WD collected the data; and Xu XH guided the study; All authors reviewed, edited, and approved the final manuscript and revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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