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Construction of a nomogram to predict overall survival for patients with M1 stage of colorectal cancer: A retrospective cohort study

Hua Ge[a,*], Yan Yan[b], Ming Xie[c], Lingfei Guo[a], Dai Tang[a]

[a] Department of Gastrointestinal Surgery, The First People's Hospital of Zunyi, Third Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou, People's Republic of China
[b] Quality Control Department, The First People's Hospital of Zunyi, Third Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou, People's Republic of China
[c] Department of Gastrointestinal Surgery, Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou, People's Republic of China

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ABSTRACT

Background: The M1 stage of colorectal cancer (CRC) has a poor prognosis. The aim of this study is to develop a reliable tool for the prediction for CRC patients with M1 stage, thus assisting the strategy of clinical diagnosis and treatment.

Methods: CRC patient information collected in the Surveillance, Epidemiology, and End Results (SEER) database between 2004 and 2015 was extracted and evaluated. Multivariate analysis with Cox proportional hazards regression identified risk factors that predicted overall survival (OS) and the results were used to construct a nomogram to predict 3-, and 5-year OS in CRC patients with M1 stage. The Kaplan-Meier curve was plotted to evaluate OS differences.

Results: A total of 19,796 patients from the SEER database were included for analysis. All patients were randomly allocated to 2 cohorts, the training cohort (n = 13,860) and the validation cohort (n = 5936). Patients' age at diagnosis; gender; race; tumor site; tumor grade; T and N stage; brain, lung, bone, and liver metastasis status; marital status; and therapy were associated with survival in the multivariate models. All these factors were incorporated to construct a nomogram. Additionally, we divide all 19,796 patients into high-risk group and low-risk group according to our nomogram, and plotted Kaplan-Meier curve. The result indicated that patients with higher risk had worse survival outcomes.

Conclusions: Our predictive model has the potential to provide an individualized risk estimate of survival in CRC patients with M1 stage.

1. Background

Colorectal cancer (CRC) is the third most frequent cancer worldwide [1]. In the United States, colon cancer is the second leading cause of cancer death, and it remains a major public health problem [2]. The majority of cases occur in more developed regions, which point to the importance of environmental risk factors in carcinogenesis, such as improper dietary habits, insufficient physical activity, excessive body weight, smoking and alcohol consumption [1]. CRC is not a single type of tumor, its pathogenesis and characteristics correlated with the location of the tumor and differs between right side and left side of the colon [3]. Depending on the position, CRCs behave differently in terms of disease progression and overall survival [4]. Although therapeutic strategies and technologies have been developed in recent decades, the overall survival (OS) of CRC patients with M1 stage still remains unsatisfactory. Therefore, there is an urgent to estimate the prognosis of the patient with CRC, thus facilitating individualization and optimization of patient treatment.

The American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system is widely used for prognostic assessment for patients with CRC. In this classification system, patients are stratified according to depth of invasion (T), number of metastasis lymph-nodes (N), and presence of distant metastases (M) [5]. However, other factors such as age, sex, race, tumor size, tumor site, differentiation and marital status can also influence patient outcomes [6,7]. Thus, further research to identify predictors that could affect patient long-term survival is essential. Constructing a quantitative prognostic model for remote metastasis from CRC would be more beneficial in forecasting the prognosis for this patient population. As a simple statistical prediction tool, nomograms have been widely used in clinical practice for cancer prognosis in recent years [8,9]. In this study, we used the Surveillance, Epidemiology, and End Results (SEER) database to construct a clinical

* Corresponding author.
E-mail address: zyyyhuage@126.com (H. Ge).

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nomogram and evaluate the clinicopathologic characteristics of the long-time survival of CRC patients with M1 stage.

2. Materials and methods

2.1. Data source

This retrospective study was based on the SEER database, which is a population based cancer registry covering approximately 30% of the population across the USA. We obtained information of patients diagnosed with M1 stage colorectal cancer between 2010 and 2015 after obtaining permission to access research data files with the reference number 18655-Nov2017. Relevant data were extracted using SEER*Stat software version 8.3.5 (https://seer.cancer.gov/seerstat/). All procedures performed in our study were in line with the STROCSS criteria [10].

2.2. Eligibility criteria

The inclusion criterias were as follows: (1) patients pathologically diagnosed with M1 stage of CRC among 2010 and 2015; (2) no history of other primary malignant tumor; (3) complete follow-up information is available. Patients were excluded if the clinicopathological information was incomplete.

2.3. Data extraction

Individual data retrieved for each case included age at diagnosis, gender, race, year of diagnosis, grade, TNM stage, marital status, site-specific metastasis, surgery, cause-specific death classification, vital status and survival months. The primary tumor site was classified as the left side colon (including the splenic flexure and the descending and sigmoid colons), the right side colon (including the cecum, the ascending colon, the hepatic flexure and the transverse colon), and the rectum.

2.4. Statistical analysis

We randomly divided all these included patients into 7:3 training and validating groups. Multivariable Cox proportional hazards models were determined to evaluate prognostic factors; hazard ratios with 95% confidence intervals (CIs) were calculated. A nomogram based on possible prognostic factors associated with overall survival (OS) was established using R software, on the basis of the Cox regression model. The performance of the nomogram was assessed with respect to discrimination and calibration both in training and validation cohort. The discriminative abilities of prognostic models were evaluated with Harrell's concordance index (C-index). The C-index measures discrimination and valued from 0.5 to 1.0, with 1 indicating perfect concordance, 0.5 indicating no better concordance than chance, and larger C-index values indicated a better prognostic model. The Kaplan-Meier curve was plotted and log rank (Mantel-Cox) test was applied to evaluate OS differences. All tests were two-sided; $P < 0.05$ was considered significant. All analyses were conducted using R (version 3.5.2; R Foundation).

3. Results

3.1. Patient characteristics

A total of 19,796 patients from the SEER database were included according to our inclusion criteria. The population consisted of 10,704 (54.1%) males and 9092 (45.9%) females. Of those, 13,860 patients were in the training cohort and 5936 were in the validation cohort. The majority of patients in both cohorts were elderly (≧60 years), married, and white. The most common tumor site was the right side colon. In both cohorts, most patients had grade II, T3 stage, N1 stage and received surgery. For remote metastasis, most patients had liver metastasis, while fewer patients with brain metastasis, lung metastasis and bone metastasis. Detailed demographic features and clinicopathological characteristics are summarized in Table 1.

Table 1
Clinicopathological characteristics of included patients.

Clinicopathological Characteristics	All patients n = (19796)	Training cohort n = (13860)	Validation cohort n = (5936)
	No (%)	No (%)	No (%)
Age			
< 30	168 (0.1)	125 (0.1)	43 (0.7)
30-39	683 (3.5)	469 (3.4)	214 (3.6)
40-49	2390 (12.1)	1679 (12.1)	711 (12.0)
50-59	4599 (23.2)	3239 (23.4)	1360 (22.9)
60-69	5326 (26.9)	3730 (26.9)	1596 (26.9)
70-79	3894 (19.7)	2705 (19.5)	1189 (20.0)
≥80	2736 (12.0)	1913 (13.8)	823 (13.9)
Gender			
Male	10704 (54.1)	7495 (54.1)	3209 (54.1)
Female	9092 (45.9)	6365 (45.9)	2727 (45.9)
Race			
White	15204 (76.8)	10664 (76.9)	4540 (76.5)
Black	2833 (14.3)	1981 (14.3)	852 (14.4)
Other	1759 (8.9)	1215 (8.8)	544 (10.1)
Tumor site			
Left side colon	5963 (30.1)	4251 (30.7)	1712 (31.8)
Right side colon	8566 (43.3)	5931 (42.8)	2635 (44.4)
Rectum	5267 (26.6)	3678 (26.5)	1589 (26.8)
Grade			
I	883 (4.5)	623 (4.5)	260 (4.4)
II	13040 (65.9)	9136 (65.9)	3904 (65.8)
III	4822 (24.4)	3347 (24.1)	1475 (24.8)
IV	1051 (5.3)	754 (5.5)	297 (5.0)
T stage			
T1	1804 (9.1)	1275 (9.2)	529 (8.9)
T2	617 (3.1)	422 (3.0)	195 (3.3)
T3	9833 (49.7)	6914 (49.9)	2919 (49.2)
T4	7542 (38.1)	5249 (37.9)	2293 (38.6)
N stage			
N0	4831 (24.4)	3373 (24.3)	1458 (24.6)
N1	7517 (38.0)	5276 (38.1)	2241 (37.8)
N2	7448 (37.6)	5211 (37.6)	2237 (37.7)
Brain metastasis			
Yes	180 (0.9)	125 (1.0)	55 (0.9)
No	19616 (99.1)	13735 (99.0)	5881 (99.1)
Lung metastasis			
Yes	3963 (20.0)	2754 (19.9)	1209 (20.4)
No	15833 (80.0)	11106 (80.1)	4727 (79.6)
Bone metastasis			
Yes	709 (3.6)	469 (3.4)	240 (4.0)
No	19087 (96.4)	13391 (96.6)	5696 (96.0)
Liver metastasis			
Yes	13972 (70.6)	9757 (70.4)	4215 (71.0)
No	5824 (29.4)	4103 (29.6)	1721 (29.0)
Surgery			
Yes	16033 (81.0)	11188 (80.7)	4845 (81.7)
No	3763 (19.0)	2672 (19.3)	1091 (18.3)
Marital status			
Married	10523 (53.2)	7371 (53.2)	3152 (53.1)
Unmarried	8355 (42.2)	5867 (42.3)	2488 (41.9)
Unknown	918 (4.6)	622 (4.5)	296 (5.0)

3.2. Nomogram construction

For the training cohort, data on the patients' age at diagnosis; gender; race; tumor site; tumor grade; T and N stage; brain, lung, bone, and liver metastasis status; marital status; and surgery were collected. As shown in Table 2, multivariate analyses demonstrated that all of these variables were independent risk factors for OS. A nomogram including all significant independent factors for predicting 3 year OS and

Table 2
Multivariate Cox analysis of the training cohort.

Clinicopathological Characteristics	Hazard ratio (95% CI)	P value
Age		
< 30	Reference	
30-39	0.940(0.715–1.235)	0.656
40-49	0.906(0.706–1.163)	0.438
50-59	1.065(0.834–1.361)	0.613
60-69	1.283(1.005–1.637)	0.046
70-79	1.672(1.309–2.136)	< 0.001
≥80	2.564(2.006–3.278)	< 0.001
Gender		
Male	Reference	
Female	0.918(0.879–0.960)	< 0.001
Race		
White	Reference	
Black	1.176(1.107–1.250)	< 0.001
Other	0.996(0.921–1.076)	0.912
Tumor site		
Left side colon	Reference	
Right side colon	1.274(1.210–1.342)	< 0.001
Rectum	0.885(0.832–0.941)	< 0.001
Grade		
I	Reference	
II	1.101(0.988–1.228)	0.083
III	1.671(1.491–1.872)	< 0.001
IV	1.754(1.528–2.014)	< 0.001
T stage		
T1	Reference	
T2	0.729(0.627–0.848)	< 0.001
T3	0.795(0.728–0.866)	< 0.001
T4	1.125(1.030–1.229)	0.009
N stage		
N0	Reference	
N1	1.048(0.987–1.111)	0.116
N2	1.391(1.308–1.480)	< 0.001
Brain metastasis		
Yes	Reference	
No	0.428(0.350–0.523)	< 0.001
Lung metastasis		
Yes	Reference	
No	0.804(0.762–0.848)	< 0.001
Bone metastasis		
Yes	Reference	
No	0.578(0.519–0.643)	< 0.001
Liver metastasis		
Yes	Reference	
No	0.773(0.736–0.811)	< 0.001
Surgery		
Yes	Reference	
No	2.087(1.949–2.236)	< 0.001
Marital status		
Married	Reference	
Unmarried	1.252(1.197–1.309)	< 0.001
Unknown	1.026(0.923–1.141)	0.636

5 year OS was established based on patient's characteristics with hazard ratios (Fig. 1). Each variable was given a score on a points scale, by adding the scores of each selected variable, we could easily estimate the probability of 3 and 5 year OS of an individual patient.

3.3. Nomogram validation

Based on internal validation via the training cohort demonstrated that the C-index for the nomogram to predict OS was 0.689 (95% CI, 0.683–0.695). Likewise, the C-index for prediction of OS in the validation cohort was also 0.689. Then we did the calibration of the nomogram internally with bootstrap sampling for 1000 times and Fig. 2 was plotted, and showed a good agreement between the prediction by the nomogram and actual observation in both the training and validation cohorts. In addition, we divide all 19,796 patients into high-risk group and low-risk group according to our nomogram, and plotted Kaplan-Meier curve. As shown in Fig. 3, compared with lower risk group, patients with higher risk had worse survival outcomes. These results meant that our nomogram model well fitted both the randomly assigned training and validating cohorts and there was no difference in utilization of the model between the training and validating groups.

4. Discussion

The Tumour Node Metastasis (TNM) staging classification system is the foundation of prognostication in colorectal cancer. However, variation in survival exists within stage groupings [11,12]. Some patients eventually die from recurrence and metastasis of cancer following surgery, whereas other patients with a similar stage do not. Clinicians are continually challenged as to how to best incorporate established and novel prognostic information alongside anatomic stage into an individualized estimate of outcome. The nomogram is a graphical presentation of a statistical prediction model [13]. Recent years, nomograms have been developed and shown to be more accurate than the conventional staging systems for predicting prognosis in some cancers [14,15]. Additionally, the nomogram enables individualized predictions that clinicians can use for assessing their patients for participation in clinical trials. Therefore, it is of great significance to establish effective nomogram models, which will accurately display the prognosis of CRC patients with M1 stage and provide the basis for decisions of individualized treatment.

In this study, we compared the relationship between clinicopathologic characteristics and survivals in CRC patients with M1 stage, and found thirteen independent prognostic factors from routine clinical practice: age; gender; race; tumor site; tumor grade; T and N stage; brain, lung, bone, and liver metastasis status; marital status; and therapy. Based on our result, we constructed a nomogram model in the training cohort that might facilitate individualized prediction of OS in CRC patients with M1 stage.

Age at diagnosis was identified as one of the independent prognostic factors in our study. Although it has been reported that age associated with patients' survival in certain tumors [16–18], the specific mechanism remains unclear. However, many age related factors, such as higher levels of chronic inflammation or lower immune response may affect survival of metastasis [19,20]. Our result indicated that compared with the younger population, patients older than 60 years have a worse OS. Consistent with us, Hu reported that younger patients have a better chance than older patients of receiving chemotherapy, radiation therapy, and surgery [21]. In addition, our study found that different sites of colon cancer had significantly different prognosis, and left side colon cancer exhibited better survival outcomes than right side colon cancer and rectum cancer. The reason for the observed difference in the prognosis for patients with different sites of colon cancer is not clear. However, studies have suggested that the disease biology is different between different sites of colon cancer, such as difference in microsatellite instability and gene expression [22–24]. Additionally, our study of racial differences among included patients showed that the OS of black patients is lowest. Evidence indicated that the risk of mortality of black patients with gallbladder cancer is higher than that of other patients, and black patients are associated with poor prognosis, which is consistent with us [25].

In this paper, we found that surgery was an independent prognostic factor for stage IV CRC. Compared to patients with surgery, the hazard ratio for patients who didn't receive surgery was 2.087 (95% CI: 1.949–2.236). Surgery is considered as a palliative treatment for stage IV CRC patients, and the benefits of surgery is still broadly discussed in clinicians. Miyoshi N et al. reported 103 patients diagnosed with synchronous liver and/or lung metastatic CRC followed by curative resection of the primary and metastatic lesions, the median OS of patients with synchronous liver and lung metastases was 20.7 months [26]. Another study showed that CRC patients treated with primary tumor resection had better OS than those without tumor resection (median OS 13.8 vs 6.3 months), and patients treated with D3 LND showed a

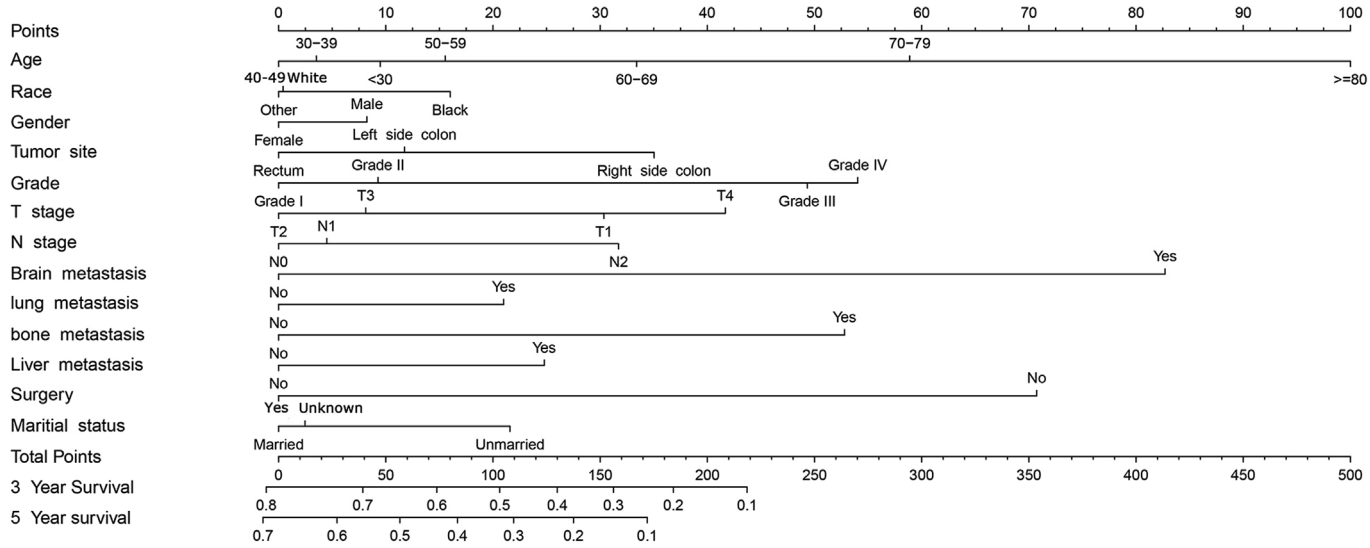

Fig. 1. Nomogram for predicting 3-year and 5-year overall survival.

significantly better OS than those with less extensive LND (median OS 17.2 vs 13.7 months) [27]. However, some studies also reported that the advantage of primary resection or metastasectomy is still unclear [28,29].

TNM staging has some limitations in the prediction of individualized prognosis. For instance, patients with the same stage according to TNM staging may have identical prognosis. Therefore, clinicians have to assess the prognosis of different patients based on their clinical experience under this circumstances. Compared to TNM staging, our model is easy to use and provides a quantitative prognosis assessment for individual patients. For example, consider 2 white male patients (T2N2M1) with liver metastasis and both received surgery (approximately 66.5 points): one patient aged 50year (15 points), with tumor location of the rectum (0 point), grade I (0 point)and married (0 point); one patient aged 60 year (33 point), with tumor location of the right side colon (55 point), grade IV (55 point) and unmarried (22 point). According to our nomogram, the two patients have 3-year OS probabilities of 58% and 13%, respectively. Therefore, doctors will be better able to make beneficial and individualized treatment and follow-up plans for patients with different prognosis according to their scores.

There are several potential limitations should be considered when interpreting the results of this study. First, it is a retrospective study and selection bias may be virtually brought in. Second, treatment variables such as information on surgical procedures, chemotherapy regimens,

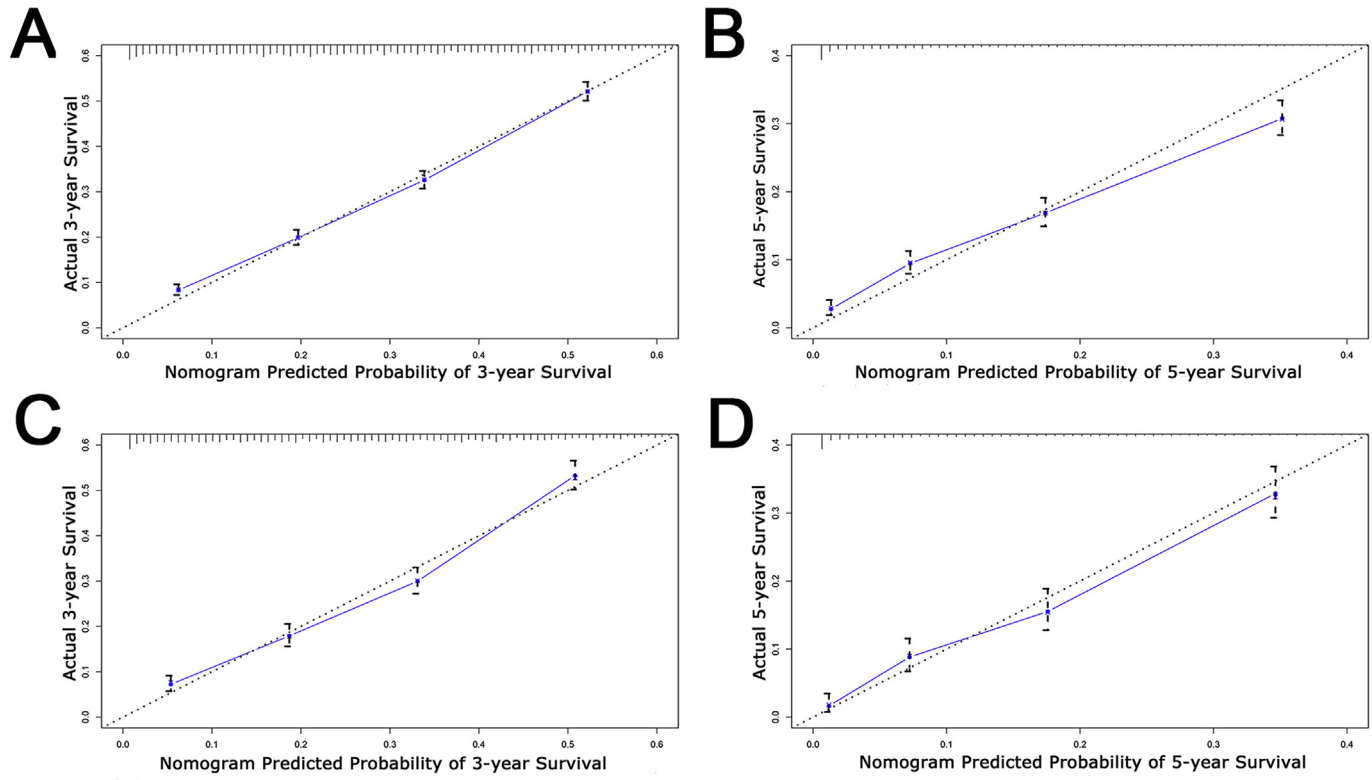

Fig. 2. Calibration plots. (A) 3-year and (B) 5-year OS nomogram calibration curves for training cohort; (C) 3-year and (D) 5-year OS nomogram calibration curves for validation cohort.

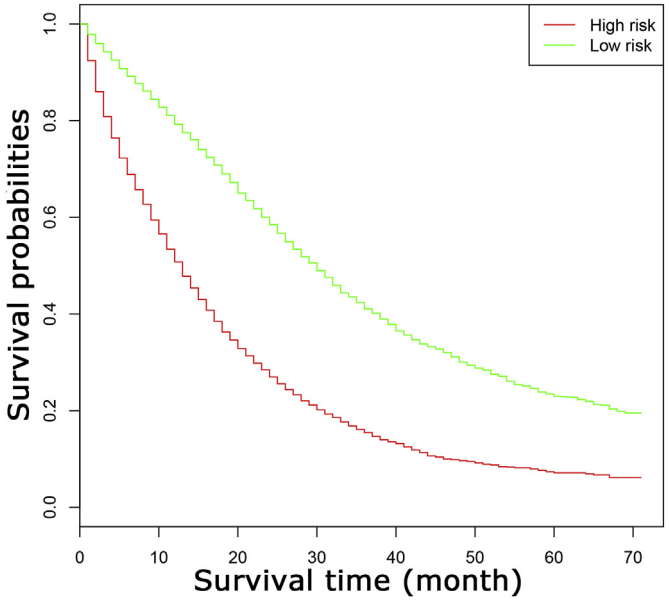

Fig. 3. Kaplan-Meier estimate of overall survival in all included patients divides by risk score.

and radiation dose/technology that influenced prognosis are not reported in the SEER database. Third, the information of serum carcinoembryonic antigen, the most widely used tumor biomarker for CRC, was unavailable due to missing data. Therefore, it is necessary for a prospective evaluation of the presented nomogram and its applicability in clinical application.

5. Conclusions

We found that 13 factors were associated with survival of CRC patients with M1 stage, and these factors were used to build a nomogram predicting 3- and 5-year OS for these patients. The C-index was good in both the training and validation cohort. The presented prognostic model has the potential to improve clinicians' abilities to predict individualized survival and to make treatment recommendations.

Ethical approval

The data of our study was derived from SEER database. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The SEER Program collects data from population-based cancer registries with anonymous information. The SEER is a publicly available database, thus no ethical approval is required.

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Author contribution

Hua Ge: Study design, data collections, data analysis, and writing.
Yan Yan: Data collections, data analysis, and writing.
Ming Xie: Data analysis.
Lingfei Guo: Data analysis.
Dai Tang: Study design and writing.

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Hua Ge.

Provenance and peer review

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Data statement

The raw data of this study are derived from the SEER database, which is a publicly available database. All detailed data included in the study are available upon request by contact with the corresponding author.

CRediT authorship contribution statement

Hua Ge: Conceptualization, Methodology, Software, Formal analysis, Writing - original draft, Writing - review & editing, Supervision, Project administration, Funding acquisition. **Yan Yan:** Methodology, Software, Validation, Formal analysis, Writing - original draft, Writing - review & editing. **Ming Xie:** Methodology, Validation, Investigation, Resources, Visualization, Supervision. **Lingfei Guo:** Validation, Investigation, Resources, Data curation, Writing - review & editing. **Dai Tang:** Investigation, Data curation, Writing - review & editing, Visualization, Supervision.

Declaration of competing interest

The authors report no conflicts of interest in this work.

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Appendix A. Supplementary data

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