Nomograms Predicting Long-Term Survival in Patients With *De Novo* Metastatic Colon Cancer: A Population-Based Analysis

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AIM: Our study aims to evaluate the overall survival (OS) and cancer-specific survival (CSS) of patients with colon cancer who present with distant metastasis, and to construct a prognostic nomogram for forecasting long-term survival outcomes.
METHODS: This population-based cohort analysis involved patients identified with *de novo* metastatic colon cancer between 2010 and 2015, utilizing data from the Surveillance Epidemiology and End Results (SEER) database.
RESULTS: The analysis comprised 6857 individuals diagnosed with *de novo* metastatic colon cancer and divided evenly into training and validation sets. Results from multivariate Cox regression analysis revealed that both OS and CSS were independently influenced by histological grade, patient age, T and N stage, presence of distant metastasis, perineural invasion, levels of carcinoembryonic antigen (CEA), receipt of chemotherapy, and surgery. Additionally, race emerged as a predictive factor for CSS but not for OS. The investigation successfully crafted a predictive nomogram capable of estimating personalized long-term survival probabilities, with a concordance index (C-index) of approximately 0.72 in both training and validation cohorts. By incorporating various clinicopathological characteristics, this nomogram effectively stratifies patients into distinct risk groups, each with a unique prognostic outlook.
CONCLUSIONS: This investigation sheds light on prognostic factors that impact the survival of patients with newly diagnosed metastatic colon cancer. Nomograms also enable accurate prediction of individual long-term survival for patients with *de novo* metastatic colon cancer.

Keywords: colon cancer; distant metastasis; surgery; SEER

Introduction

Colorectal cancer ranks as the third most prevalent form of cancer, leading to the deaths of approximately 52,980 individuals annually [1,2]. A significant portion of colorectal cancer patients presents with metastatic disease at diagnosis, with about 20% displaying distant metastases [3]. Around 22% of colorectal cancers undergo metastasis during their course. Synchronous liver and lung metastases are reported in 13.8% and 3.7% of colon cancer cases, respectively [3]. The presence of distant metastases significantly contributes to the high mortality associated with colon cancer, as the 5-year survival rate plummets from 64.4% to 14.2% upon the occurrence of metastasis [4]. Consequently, gaining a comprehensive insight into the potential risk and protective factors for colon cancer is imperative.

In recent years, the nomogram has emerged as a popular predictive tool in oncology [5–7]. Creating a precise prognostic nomogram holds the potential to transform clinical practices, facilitating tailored treatment approaches that enhance patients' quality of life and increase survival rates. To achieve this, the nomogram must account for a comprehensive range of factors, including tumor characteristics, patient demographics, and the intricacies of systemic and surgical interventions [6]. By integrating these diverse elements, the nomogram can offer clinicians valuable insights into individual patient prognosis, empowering them to make informed decisions regarding treatment strategies. This personalized approach not only optimizes patient care but also fosters advancements in oncological management, ultimately leading to improved outcomes and enhanced patient well-being.
Hence, this study aimed to meticulously assess the potential risk factors for patients with *de novo* metastatic colon cancer and to devise nomograms utilizing data from the Surveillance Epidemiology and End Results (SEER) database.

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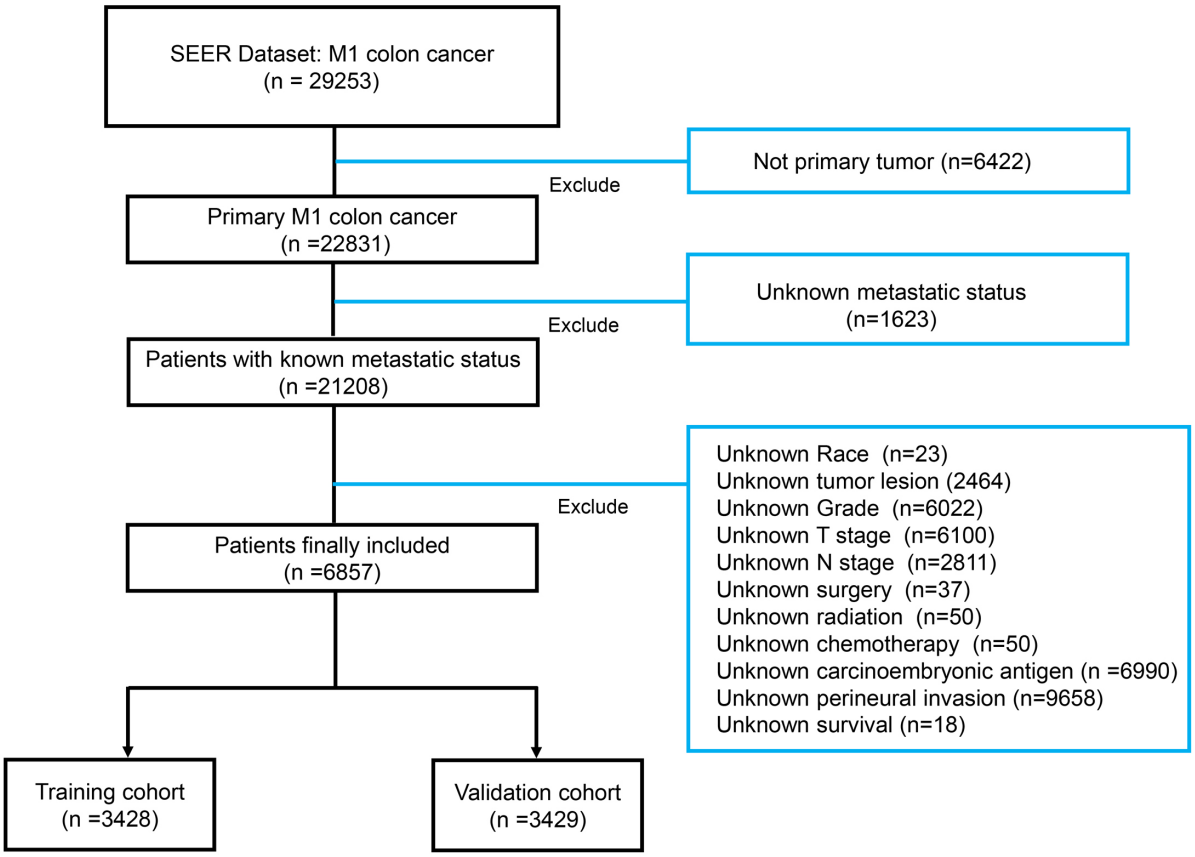

Fig. 1. A flowchart depicting the process for patient selection. SEER, Surveillance Epidemiology and End Results.

Methods

Participant Selection

The data for this research were obtained from the SEER database, underwritten by the National Cancer Institute, encompassing roughly 28% of the U.S. population. It aggregates data on cancer incidence and survival from 20 regional registries. The focus of this investigation was on subjects identified with *de novo* metastatic colon cancer between 2010 and 2015.

Patients included were those with colon cancer (categorized under Primary site codes: C18.0, C18.2–18.9). Exclusion criteria were: (1) No primary tumors; (2) lack of data on distant metastasis; (3) missing information on race, tumor location, grade, TNM classification, carcinoembryonic antigen (CEA) levels, perineural invasion, and records of surgery, chemotherapy, or radiotherapy. In addition, patients with any missing data were not included. This decision was made to ensure the completeness and accuracy of the statistical models. Following these exclusions, 6857 eligible patients were selected (Fig. 1). Subsequently, these participants were equally divided into training and validation groups, maintaining a 1:1 ratio. The training cohort was crucial for developing the nomogram, which underwent evaluation in the validation group. The primary outcomes measured were overall survival (OS) and cancer-specific survival (CSS).

Statistical Methodology

The investigation employed descriptive statistical methods to summarize demographic and clinicopathologic features. Cohort differences in demographic and clinicopathologic variables were examined using the Pearson chi-square (χ^2) test. The Kaplan–Meier curve and a two-tailed log-rank test were utilized for survival analyses. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated through both univariate and multivariate Cox regression analyses. Additionally, prognostic nomograms for forecasting 1-year, 3-year, and 5-year OS were developed. In our statistical analysis, we have examined the relationship between the independent variables to ensure that multicollinearity is not present. The Variance Inflation Factors (VIFs) for all variables are below the threshold of 10, indicating that multicollinearity is not a concern (**Supplementary Table 1**).

To evaluate the accuracy of the nomogram's predictions, calibration plots were employed, comparing anticipated against observed survival proportions. Descriptive metrics, Pearson's χ^2 examination, and Cox regression analysis were conducted using SPSS version 24.0 software (IBM Corp, Armonk, NY, USA). Kaplan–Meier survival assessments and nomogram generation were completed using R software (version 4.0.0; R Foundation for Statistical Computing, Vienna, Austria), leveraging the "rms" and "sur-

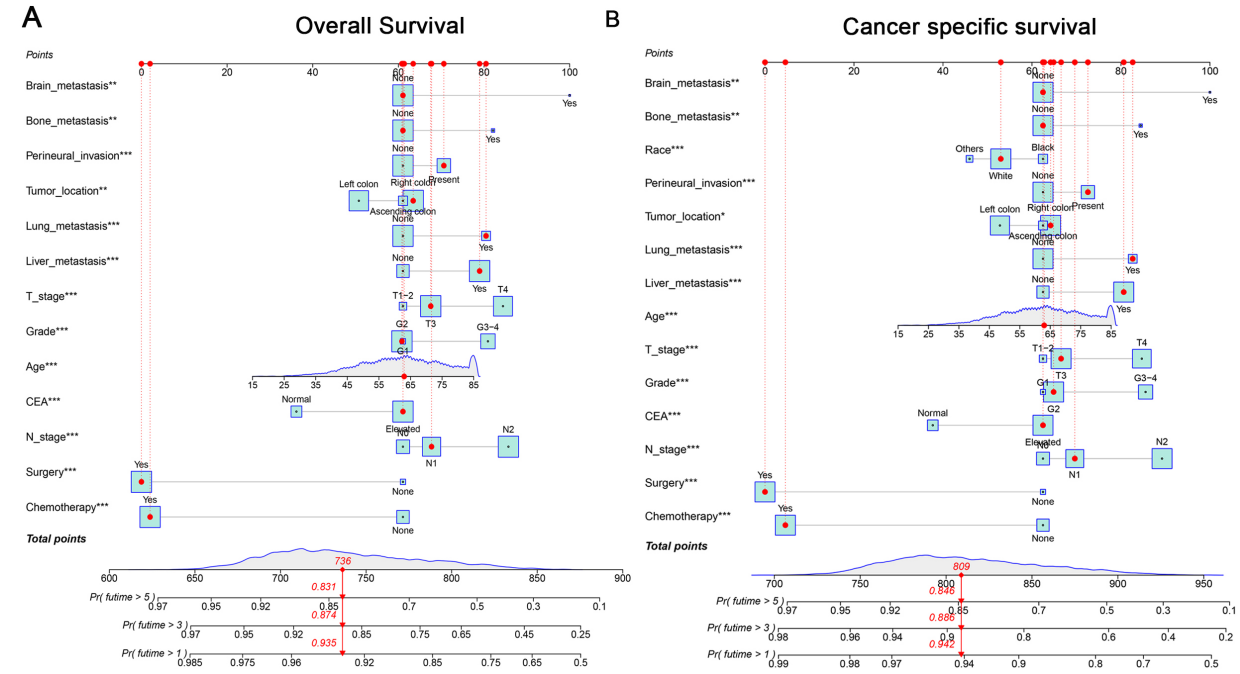

Fig. 2. Nomogram designed for predicting the OS (A) and CSS (B) probability. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$. CEA, carcinoembryonic antigen; OS, overall survival; CSS, cancer-specific survival.

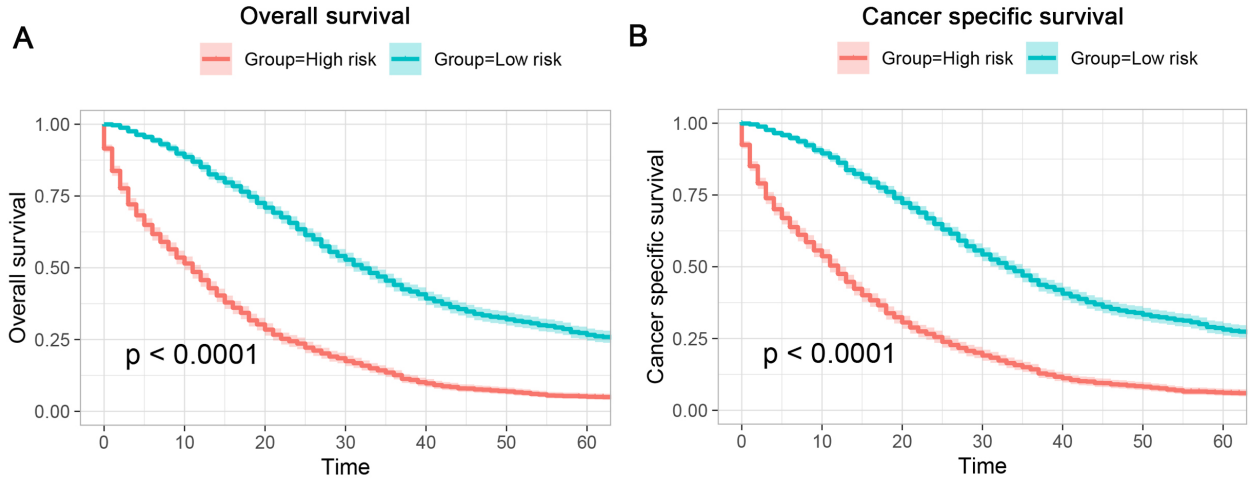

Fig. 3. Kaplan–Meier curve of OS (A) and CSS (B) for patients with high or low risk stratified by nomogram.

vival" libraries. Two-tailed p values less than 0.05 were considered statistically significant.

Results

Baseline Characteristics and Survival Analysis

Overall, 6857 patients with *de novo* metastatic colon cancer were included in current study. The entire patient group was split into two cohorts, a training set and a validation set, with an even distribution (Fig. 1). Upon analyzing the baseline characteristics, no significant statistical differences were found between the cohorts (Table 1). Subsequently, both univariate and multivariate Cox regression analyses were conducted to identify factors significantly associated with OS and CSS in patients with distant metastases (Tables 2,3). The analysis showed that advanced age (older than 65 vs. under 45; Hazard ratio [HR] = 1.52; $p < 0.001$), higher histological grade (grade 3–4 vs. grade 1; HR = 1.42; $p < 0.001$), larger primary tumors (T4 vs. T1–2; HR = 1.40; $p < 0.001$), more lymph node metastases (N2 vs. N0; HR = 1.52; $p < 0.001$), elevated CEA (elevated vs. normal; HR = 1.47; $p < 0.001$), perineural invasion (present vs. none; HR = 1.14; $p < 0.001$), bone metastasis (HR = 1.44; $p < 0.001$), liver metastasis (HR = 1.33; $p < 0.001$), lung metastasis (HR = 1.35; $p < 0.001$), and brain metastasis (HR = 1.79; $p < 0.001$) predicted worse OS. On the other hand, higher OS was predicted by tumor location in the left colon (left colon vs. right colon, HR = 0.79; $p < 0.001$), as well as having surgery (HR = 0.37; $p < 0.001$) or

Table 1. Demographic and clinicopathologic characteristics of the training and validation cohorts.

Characteristic	Training cohort No. (%)	Validation cohort No. (%)	χ^2 value	*p* value
Age			5.11	0.078
<45	324 (9.5)	280 (8.2)		
45–65	1659 (48.4)	1733 (50.5)		
>65	1445 (42.2)	1416 (41.3)		
Race			1.73	0.422
White	2583 (75.4)	2553 (74.5)		
Black	551 (16.1)	551 (16.1)		
Others	294 (8.6)	325 (9.5)		
Sex			0.27	0.604
Female	1695 (49.4)	1674 (48.8)		
Male	1733 (50.6)	1755 (51.2)		
Histological grade			0.38	0.826
1	144 (4.2)	134 (3.9)		
2	2184 (63.7)	2194 (64.0)		
3–4	1100 (32.1)	1101 (32.1)		
Tumor location			2.43	0.296
Right colon	1626 (47.4)	1690 (49.3)		
Ascending colon	322 (9.4)	317 (9.2)		
Left colon	1480 (43.2)	1422 (41.5)		
T stage			0.71	0.701
T1–2	231 (6.7)	215 (6.3)		
T3	1708 (49.8)	1705 (49.7)		
T4	1489 (43.4)	1509 (44.0)		
N stage			0.10	0.952
N0	642 (18.7)	645 (18.8)		
N1	1242 (36.2)	1230 (35.9)		
N2	1544 (45.0)	1554 (45.3)		
Surgery			0.09	0.768
None	214 (6.2)	220 (6.4)		
Yes	3214 (93.8)	3209 (93.6)		
Radiotherapy			0.77	0.381
None	3321 (96.9)	3309 (96.5)		
Yes	107 (3.1)	120 (3.5)		
Chemotherapy			0.07	0.793
None	941 (27.5)	951 (27.7)		
Yes	2487 (72.5)	2478 (72.3)		
Bone metastasis			0.08	0.772
None	3333 (97.2)	3330 (97.1)		
Yes	95 (2.8)	99 (2.9)		
Liver metastasis			0.10	0.751
None	932 (27.2)	944 (27.5)		
Yes	2496 (72.8)	2485 (72.5)		
Lung metastasis			0.38	0.538
None	2878 (84.0)	2860 (83.4)		
Yes	550 (16.0)	569 (16.6)		
Brain metastasis			1.30	0.255
None	3401 (99.2)	3393 (99.0)		
Yes	27 (0.8)	36 (1.0)		
CEA			0.84	0.360
Normal	759 (22.1)	728 (21.2)		
Elevated	2669 (77.9)	2701 (78.8)		
Perineural invasion			0.03	0.861
None	2378 (69.4)	2372 (69.2)		
Present	1050 (30.6)	1057 (30.8)		

Abbreviations: CEA, carcinoembryonic antigen.

Table 2. Cox regression analysis for the overall survival (OS) of colon cancer with distant metastasis.

	Univariate analysis		Multivariate analysis	
Variables	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age		<0.001		<0.001
<45	Reference		Reference	
45–65	1.20 (1.05–1.36)	0.008	1.17 (1.07–1.29)	0.001
>65	1.79 (1.57–2.05)	<0.001	1.52 (1.38–1.68)	<0.001
Race		0.066	NA	
White	Reference			
Black	1.04 (0.95–1.15)	0.399		
Others	0.87 (0.76–0.99)	0.041	NA	
Sex				
Female	Reference			
Male	1.02 (0.95–1.10)	0.588		
Histological grade		<0.001		<0.001
1	Reference		Reference	
2	1.03 (0.86–1.23)	0.787	1.01 (0.89–1.15)	0.874
3–4	1.51 (1.26–1.82)	<0.001	1.42 (1.24–1.62)	<0.001
Tumor location		<0.001		<0.001
Right colon	Reference		Reference	
Ascending colon	0.93 (0.85–1.02)	0.108	0.97 (0.89–1.07)	0.579
Left colon	0.70 (0.66–0.73)	<0.001	0.79 (0.75–0.83)	<0.001
T stage		<0.001		<0.001
T1–2	Reference		Reference	
T3	0.84 (0.75–0.93)	0.001	1.02 (0.91–1.15)	0.713
T4	1.21 (1.09–1.35)	<0.001	1.40 (1.24–1.58)	<0.001
N stage		<0.001		<0.001
N0	Reference		Reference	
N1	1.04 (0.96–1.11)	0.362	1.16 (1.07–1.25)	<0.001
N2	1.38 (1.29–1.48)	<0.001	1.52 (1.41–1.65)	<0.001
Surgery				
None	Reference		Reference	
Yes	0.50 (0.46–0.56)	<0.001	0.37 (0.33–0.42)	<0.001
Radiotherapy				
None	Reference		NA	
Yes	1.03 (0.89–1.18)	0.713		
Chemotherapy				
None	Reference		Reference	
Yes	0.37 (0.35–0.39)	<0.001	0.37 (0.35–0.39)	<0.001
Bone metastasis				
None	Reference		Reference	
Yes	1.83 (1.58–2.13)	<0.001	1.44 (1.24–1.67)	<0.001
Lung metastasis				
None	Reference		Reference	
Yes	1.36 (1.27–1.46)	<0.001	1.35 (1.26–1.44)	<0.001
Liver metastasis				
None	Reference		Reference	
Yes	1.09 (1.03–1.16)	0.002	1.33 (1.26–1.42)	<0.001
Brain metastasis				
None	Reference		Reference	
Yes	1.88 (1.46–2.43)	<0.001	1.79 (1.38–2.32)	<0.001
CEA				
Normal	Reference		Reference	
Elevated	1.46 (1.37–1.56)	<0.001	1.47 (1.37–1.56)	<0.001
Perineural invasion				
None	Reference		Reference	
Present	1.17 (1.11–1.24)	<0.001	1.14 (1.08–1.21)	<0.001

Abbreviations: HR, Hazard ratio; CI, confidence interval; NA, not applicable.

Table 3. Cox regression analysis for the cancer-specific survival (CSS) of colon cancer with distant metastasis.

	Univariate analysis		Multivariate analysis	
Variables	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age		<0.001		<0.001
<45	Reference		Reference	
45–65	1.21 (1.10–1.34)	<0.001	1.15 (1.05–1.27)	0.004
>65	1.78 (1.61–1.96)	<0.001	1.47 (1.33–1.63)	<0.001
Race		<0.001		<0.001
White	Reference		Reference	
Black	1.05 (0.98–1.12)	0.206	1.13 (1.05–1.21)	0.001
Others	0.85 (0.77–0.93)	<0.001	0.86 (0.78–0.94)	0.001
Sex				
Female	Reference		NA	
Male	1.02 (0.96–1.07)	0.556		
Histological grade		<0.001		<0.001
1	Reference		Reference	
2	1.00 (0.88–1.15)	0.951	1.01 (0.89–1.15)	0.874
3–4	1.50 (1.31–1.73)	<0.001	1.42 (1.24–1.62)	<0.001
Tumor location		<0.001		<0.001
Right colon	Reference		Reference	
Ascending colon	0.93 (0.85–1.02)	0.126	0.97 (0.89–1.07)	0.569
Left colon	0.69 (0.66–0.73)	<0.001	0.79 (0.75–0.84)	<0.001
T stage		<0.001		<0.001
T1–2	Reference		Reference	
T3	0.83 (0.75–0.93)	0.001	1.01 (0.90–1.15)	0.825
T4	1.22 (1.09–1.36)	<0.001	1.41 (1.24–1.60)	<0.001
N stage		<0.001		<0.001
N0	Reference		Reference	
N1	1.05 (0.98–1.14)	0.172	1.18 (1.09–1.28)	<0.001
N2	1.43 (1.33–1.54)	<0.001	1.59 (1.46–1.72)	<0.001
Surgery				
None	Reference		Reference	
Yes	0.49 (0.44–0.54)	<0.001	0.35 (0.31–0.40)	<0.001
Radiotherapy				
None	Reference		NA	
Yes	1.03 (0.89–1.19)	0.663		
Chemotherapy				
None	Reference		Reference	
Yes	0.38 (0.36–0.40)	<0.001	0.37 (0.35–0.40)	<0.001
Bone metastasis				
None	Reference		Reference	
Yes	1.86 (1.60–2.16)	<0.001	1.47 (1.26–1.71)	<0.001
Lung metastasis				
None	Reference		Reference	
Yes	1.38 (1.29–1.47)	<0.001	1.36 (1.27–1.46)	<0.001
Liver metastasis				
None	Reference		Reference	
Yes	1.11 (1.05–1.18)	0.001	1.35 (1.27–1.43)	<0.001
Brain metastasis				
None	Reference		Reference	
Yes	1.80 (1.37–2.35)	<0.001	1.71 (1.30–2.24)	<0.001
CEA				
Normal	Reference		Reference	
Elevated	1.47 (1.38–1.57)	<0.001	1.47 (1.37–1.57)	<0.001
Perineural invasion				
None	Reference		Reference	
Present	1.19 (1.13–1.26)	<0.001	1.16 (1.09–1.23)	<0.001

Abbreviations: HR, Hazard ratio; CI, confidence interval.

chemotherapy (HR = 0.37; $p < 0.001$). In addition, similar relationships were observed for CSS, except that race was also identified as a significant predictor (Table 3).

Nomogram and Risk Stratifications

To improve the accuracy of survival rate predictions for colon cancer patients with distant metastases, prognostic nomograms for OS and CSS were created. These models integrate several independent prognostic factors, such as age, tumor grade, location, T and N stage, CEA levels, perineural invasion, distant metastasis status, and treatment approaches like surgery and chemotherapy. As illustrated in Fig. 2, the nomograms enable to calculate a total score for each patient by mapping their specific attributes to corresponding points on a scale. This approach provides transparent predictions of OS and CSS probabilities at 1, 3, and 5 years, as depicted in Fig. 2A,B. For instance, the clinical data of a representative patient resulted in a score of 736, translating to predicted 1-, 3-, and 5-year OS rates of 93.5%, 87.4%, and 83.1%, respectively. A higher total score indicated a poorer prognosis for the patient. The Harrell's concordance index (C-index), which assesses the nomogram's prediction precision for OS, showed values of 0.715 for the training cohort and 0.717 for the validation cohort. The C-index for CSS was 0.713 and 0.716 for the training and validation cohorts, respectively. Furthermore, analysis of calibration curves revealed an excellent correlation between the survival rates predicted by the nomogram and the actual outcomes, as seen in **Supplementary Fig. 1**. Based on median risk scores from the nomogram, patients were categorized into low- and high-risk groups. Fig. 3 shows that the survival rate for individuals in the high-risk group was significantly lower than that of those in the low-risk group.

Discussion

Our research offers an in-depth analysis of outcomes in patients with colon cancer and distant metastases. We pinpointed multiple independent factors predictive of both OS and CSS in individuals with newly diagnosed metastatic colon cancer. In line with prior studies, variables such as advanced age, a higher grade of histology, a larger size of the primary tumor, and more extensive lymph node involvement were closely linked to decreased OS [8–11]. Likewise, factors like increased levels of CEA, the occurrence of perineural invasion, and metastases to bones, liver, lungs, and brain were identified as negative prognostic indicators [12]. These results highlight the aggressive behavior of colon cancer in the presence of such factors, which is consistent with established markers of cancer progression [13]. It was also noted that race is the predictive factor for the colon cancer-specific survival but not the OS, which may be related to financial income, genetic differences, diet, among others.

Conversely, the analysis indicated that tumors located in the left side of the colon and therapeutic measures including surgery and chemotherapy are linked to better survival rates. The notable survival benefit of left-sided tumors is partly due to the fact that right-sided tumors, because symptoms are less pronounced, are often larger and at a more advanced stage [14,15]. This observation supports the emerging data on the biological distinctions between colon cancers on the right and left sides, which may affect the response to treatment and prognosis [16].

Like with other metastatic cancers [17,18], creating prognostic nomograms that incorporate variables such as age, tumor grade, and treatment methods marks a major leap forward in tailored medicine for metastatic colon cancer. These tools have been shown to accurately predict OS and CSS, as validated by Harrell's C-index, offering precise prognostic estimates that can significantly guide clinical decisions, customizing treatments based on the patient's specific situation. Recognizing key prognostic factors enables patient stratification into different risk groups, thereby allowing for more individualized therapeutic strategies. For instance, identifying patients as high-risk could justify the adoption of more intensive treatment options, including innovative drugs or combined therapies.

However, this study is not without its limitations. Its retrospective design and exclusion of cases with missing data could lead to selection bias and hinder causal inference. Moreover, despite thorough statistical assessments, the presence of unaccounted confounding factors that might have affected the results cannot be ruled out. Also, being based on data from a single country might restrict the generalizability of the findings across different healthcare systems or in populations with distinct genetic predispositions. Future research should aim at validating these prognostic nomograms in prospective studies and varied demographic groups to confirm their wide-ranging relevance. Integrating these insights into clinical practice will necessitate a collaborative effort across disciplines to refine treatment modalities and enhance the prognosis for patients suffering from metastatic colon cancer.

Conclusions

This investigation sheds light on prognostic factors that impact the survival of patients with newly diagnosed metastatic colon cancer, offering valuable tools for predicting individual patient outcomes. Through a deeper understanding of the disease mechanisms, our research and the developed nomograms can significantly enhance personalized care and the optimization of treatment for patients.

Availability of Data and Materials

The data generated and/or analyzed during the current study are available in the SEER database (https://seer.cancer.gov/).

Author Contributions

RW and XW designed the research study. RW, JC, WZ and XW analyzed the data. RW, JC and XW wrote the

manuscript. All authors revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.62713/aic.3345.

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