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Original Article

Development and validation of survival nomograms in colorectal cancer patients with synchronous liver metastases underwent simultaneous surgical treatment of primary and metastatic lesions

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Abstract: Colorectal cancer patients with synchronous liver metastases (CRSLM) can be treated by simultaneous surgery, that is the primary tumor and liver metastasis are removed at the same time. However, criteria for simultaneous surgery are underwent continuously modified and expanded. An appropriate selection of adequate candidates for simultaneous surgery is vital to get best benefits. A retrospective study including CRSLM patients underwent simultaneous surgical treatment was conducted. CRSLM patients from SEER database were screened as development set, while CRSLM patients in Harbin (China) were enrolled as validation set. Overall survival (OS) and cancer-specific survival (CSS) were applied as end-point. Variables were screen by LASSO-Cox regression, then Cox regression was applied to construct 1-, 3- and 5-year OS, and CSS nomograms. Nomograms were compared to TMN stage for survival prediction and evaluated by concordance indexes (C-indexes), Time-dependent receiver operating characteristic (ROC) curves, Decision Curve Analysis (DCA). 1347 and 112 CRSLM patients were included in the development set and validation set respectively. Nine factors were found associated with OS and CSS, i.e., Age, Primary Site, Differentiation grade, Histology type, T stage, N stage, Tumor size, Chemotherapy, CEA. Compared to the TNM stage, OS nomogram in development set and validation set got C-indexes values of 0.701 vs 0.641, 0.670 vs 0.557 respectively. Meanwhile, compared to the TNM stage, CSS nomogram in development set and validation set got C-indexes values of 0.704 vs 0.649, 0.677 vs 0.569 respectively. AUC values of the OS and CSS nomograms were higher than the TNM stage, DCA showed the OS and CSS nomograms got more clinical net benefit than the TNM stage, in both the development set and validation set. Our nomograms for predicting survival might be helpful to identify the right CRSLM patients who can get most benefit from simultaneous surgery.

Keywords: Survival nomogram, SEER, colorectal cancer, liver metastases

Introduction

Globally, colorectal cancer is still a malignancy with third morbidity and second mortality in all cancers [1]. The most common metastatic organ of colorectal cancer is the liver. 15-25% of colorectal cancer patients accompanied by simultaneous liver metastasis when be diagnosed for the first time [2]. For patients with colorectal cancer synchronous liver metastases (CRSLM), radical resection of the primary site plus resection of liver metastases remains the most effective treatment, which give patients the greatest possibility of being cured [3, 4]. Simultaneous surgical treatment is of great significance for reducing patients suffering, medical insurance costs, and length of hospitalization [5]. However, 65% of these patients encounter recurrence within 3 years after simultaneous surgery [6-8]. Although NCCN guidelines recommend that the primary tumor and liver metastasis can be removed at the same time, but criteria for simultaneous surgery are underwent continuously modified and expanded [9]. To get the largest benefit from simultaneous hepatic resection, an appropriate selection of adequate candidates for simultaneous surgery is vital.

At present, the prognosis and survival prediction of colorectal cancer liver metastases (CRLM) patients mainly rely on the American Joint Committee on Cancer (AJCC) TNM stage and clinical experience [10]. However, the TNM stage only considers a few factors, and many clinical factors associated with prognosis are often ignored. These clinical factors include age, sex, CEA level, radiotherapy and chemotherapy, surgery type, differentiation grade, etc. Therefore, the TNM stage is one-sidedly and inaccurate to predict the prognosis of CRLM. A more scientific and accurate method taken full consideration of the above multiple clinical factors is needed.

Currently, among all the survival prediction models, the nomogram constructed based on several independent prediction factors show better accuracy and intuition for clinical application [11-13]. The nomograms show better predictive ability than the TNM stage in many studies [14-17]. Although some research [18-23] had reported using a survival model to predict the survival of CRLM patients, however, there is currently a lack of survival prediction studies for colorectal cancer synchronous liver metastases (CRSLM) patients, whose primary and metastatic tumors were treated simultaneously. Besides, these studies lacked independent external validation, and model evaluation methods were not comprehensive and haven't shown the clinical utility of the model. Therefore, the purpose of this study is to design a simple and accurate nomogram to predict the overall survival (OS) and cancer-specific survival (CSS) of CRSLM patients who underwent simultaneous surgical treatment of primary and metastatic lesions. We have built the nomogram base on the development set, then validated it in the development set and validation set. The development set of patients were screened from the Surveillance, Epidemiology, and End Results (SEER) database, while the validation set of patients were recruited from the First Affiliated Hospital and Third Affiliated Hospital of Harbin Medical University in China.

Methods

Patients

CRSLM patients underwent simultaneous surgical treatment of primary and liver metastatic lesions in the SEER database were included as development set. SEER Stat 8.3.6 was applied for SEER database patients screening as follow: 1. Patients came from the database of 'Incidence-SEER 18 Regs Custom Data (with additional treatment fields), Nov 2018 Sub (1975-2016 varying)'. 2. The International Classification of Diseases for Oncology (ICD-O-3) was used to CRSLM definition. 3. 'Site recode ICD-O-3/WHO 2008' was used to record tumor location information, including Ascending Colon, Hepatic Flexure, Transverse Colon, Splenic Flexure, Descending Colon, Sigmoid Colon, Rectosigmoid Junction, Cecum. 4. According to 'Histologic Type ICD-O-3', the following pathological types were included in this study: AdenoCA (8140), Adenocarcinoma arising in a polyp (8210), adenocarcinoma in tubulovillous adenoma (8263), Mucinous/colloid adenocarcinoma (8480), Adenosquamous carcinoma (8560). 5. 'Year of diagnosis' was set to 2010-2015.

The following options were used for TNM stage and other variable information: derived AJCC TNM stage group 7th ed. (2010-2015), CS tumor size (2004-2015), RX Summ--Surg Oth Reg/Dis (2003+), SEER Combined Mets at DX-liver (2010+), Chemotherapy record, CS site-specific factor 1 (2004+ varying by the schema), CS site-specific factor 8 (2004+ varying by the schema). We obtained survival information from the following options: SEER cause-specific-death classification, Survival months, vital status recode.

The exclusion criteria were as follows: (1) Colorectal was not diagnosed as the only primary site of cancer for the patients. (2) Patients were diagnosed with no-positive histology and not only from a death certificate or autopsy. (3) Patients were less than 20 years old and older than 85 years old. (4) Patients had missing or incomplete clinic pathological information (tumor size, differentiation grade, CEA, T stage, N stage, histologic type, chemotherapy, perineural invasion, survival month, follow-up months, and final cause of death).

We enrolled CRSLM patients who were treated in the First Affiliated Hospital of Harbin Medical University and the Third Affiliated Hospital of Harbin Medical University from 2010 to 2017 as an independent external validation set for this study. These patients have undergone surgery for the primary site and liver metastases

at the same time, and all of them met the "2010 WHO diagnostic criteria". The included criteria are as follows: (1) The age was between 20 and 85 years old. (2) The primary site of the tumors was in the colon or rectum, with no other primary site. (3) Patients with complete demographic data, clinical parameters, diagnosed with positive histology, TNM stage information, and full follow-up results.

Data collection

Four preoperative and seven postoperative predictor variables were evaluated. These variables included age (<50, ≥50), sex (Male, Female), primary site (Colon, Rectum), tumor size (>5 cm, ≤5 cm), CEA (Positive, Negative), T stage (T1, T2, T3, T4), N stage (N0, N1, N2), differentiation grade (Grade I, Grade II, Grade III, Grade IV), histologic type (Adenocarcinoma, Others), chemotherapy (Yes, No), perineural invasion (Yes, No). The survival time and the final cause of death in the development set were obtained through the SEER database. The survival time and the final cause of death in the validation set were obtained through follow-up. OS and CSS were applied as endpoints.

Statistical analysis

Categorical variables were presented as a number with percentage and compared with chi-square test and Fisher's exact test. In this study, LASSO regression was applied to screen out the variables from many clinical variables [24-27]. We applied Cox regression to perform multi-factor survival analysis and finally constructed a nomogram. Time-dependent receiver operating characteristic (ROC) curves and areas under the curves (AUCs) at 1-, 3- and 5-years were generated to assess prognostic accuracy. The concordance index (C-index) was also used to evaluate the accuracy of model prediction like ROC [28]. The calibration curve was applied to determine whether the predicted survival probability of the nomogram was consistent with 1000 bootstrap resampling. Decision curve analysis (DCA) was employed to evaluate the net benefit and clinical utility of the nomogram model developed in the development set. The x-axis of the decision curve was the threshold of the predicted probability. The y-axis showed the clinical decision net benefit for patients based on the classification result in this threshold. All statistical methods were performed by SPSS version 25 and R software version 3.13 (http://www.rproject.org) with rms, tidyverse, survivalROC, and glmnet data packages. $P \leq 0.05$ was considered to have significant statistical significance in all analyses.

Results

Patient characteristics

Finally, 1459 CRSLM patients who underwent simultaneous surgical treatment of primary and metastatic lesions were included in this study (**Table 1**) including 1347 patients in the development set (**Figure 1A**) and 112 patients in the validation set (**Figure 1B**). Of these patients, 55.8% were males. 74.9% of these patients were older than 50 years old, 75.3% of tumors were in the colon. Among the differentiation grade, 75.5% of tumors were classified as Grade II. CEA-positive patients accounted for 76.7%. 93.1% of patients were diagnosed with Adenocarcinoma. 30.9% of patients had perineural Invasion. 87.3% of patients received chemotherapy. For the TNM stage classification, 64.9% of the tumor were classified as T3, 43.1% of the tumor were classified as N2. Result (**Table 1**) shows the clinical case information of all patients. In all patients, the Overall survival rate was 47.0%, Cancer specific survival rate was 48.5%.

Nomogram construction

LASSO regression was applied to analyze the correlation between variables and OS (**Figure 2A**, **2B**). All the eleven variables with non-zero coefficients were selected for multivariate analysis, included Age (≥50), Sex (Male), Primary Site (Rectum), Differentiation grade (Grade III and Grade IV), Histology type (Others), T stage (T2, T3 and T4), N stage (N1 and N2), Tumor size (≥5 cm), Chemotherapy (Yes), CEA (Positive), Perineural Invasion (Yes). After multivariate analysis of the eleven factors, nine factors were found associated with OS ($P \leq 0.05$) which is summarized in **Table 2**. The nine independent prognostic factors are: Age (<50, HR 0.768), Primary Site (Colon, HR 1.408), Differentiation grade (Grade I, HR 0.497 and Grade II, HR 0.590), Histology type (Adenocarcinoma, HR 0.715), T stage (T2, HR 0.574 and T3, HR 0.755), N stage (N0, HR 0.502 and N1, HR 0.732), Tumor size (>5 cm,

Table 1. Patient demographics and pathological characteristics

Variable	All Patients (n = 1459)		Development set (n = 1347)		Validation set (n = 112)		*P* Value
	No.	%	No.	%	No.	%	
Age							0.022
<50	366	25.1	348	25.8	18	16.1	
≥50	1093	74.9	999	74.2	94	83.9	
Sex							0.275
Male	814	55.8	746	55.4	68	60.7	
Female	645	44.2	601	44.6	44	39.3	
Primary site							0.328
Colon	1098	75.3	1018	75.6	80	71.4	
Rectum	361	24.7	329	24.4	32	28.6	
Tumor size							0.727
>5 cm	609	41.7	564	41.9	45	40.2	
≤5 cm	850	58.3	783	58.1	67	59.8	
CEA							<0.001
Positive	1119	76.7	1049	77.9	70	62.5	
Negative	340	23.3	298	22.1	42	37.5	
Perineural invasion							0.024
No	1008	69.1	920	68.3	88	78.6	
Yes	451	30.9	427	31.7	24	21.4	
Differentiation grade							0.117
Grade I	50	3.4	46	3.4	4	3.6	
Grade II	1102	75.5	1012	75.1	90	80.3	
Grade III	241	16.5	223	16.6	18	16.1	
Grade IV	66	4.6	66	4.9	0	0	
T stage							<0.001
T1	31	2.1	31	2.3	0	0	
T2	51	3.5	47	3.5	4	3.6	
T3	947	64.9	853	63.3	94	83.9	
T4	430	29.5	416	30.9	14	12.5	
N stage							<0.001
N0	290	19.9	233	17.3	57	50.9	
N1	629	43.1	596	44.2	33	29.5	
N2	540	37	518	38.5	22	19.6	
Histology type							0.027
Adenocarcinoma	1359	93.1	1249	92.7	110	98.2	
Others	100	6.9	98	7.3	2	1.8	
Chemotherapy							<0.001
Yes	1274	87.3	1188	88.2	86	76.8	
No	185	12.7	159	11.8	26	23.2	
Overall Survival							0.064
Dead	774	53.0	724	53.7	50	44.6	
Alive	685	47.0	623	46.3	62	55.4	
Cancer-Specific Survival							0.132
Dead of cancer	751	51.5	701	52.0	50	44.6	
Others	708	48.5	646	48.0	62	55.4	

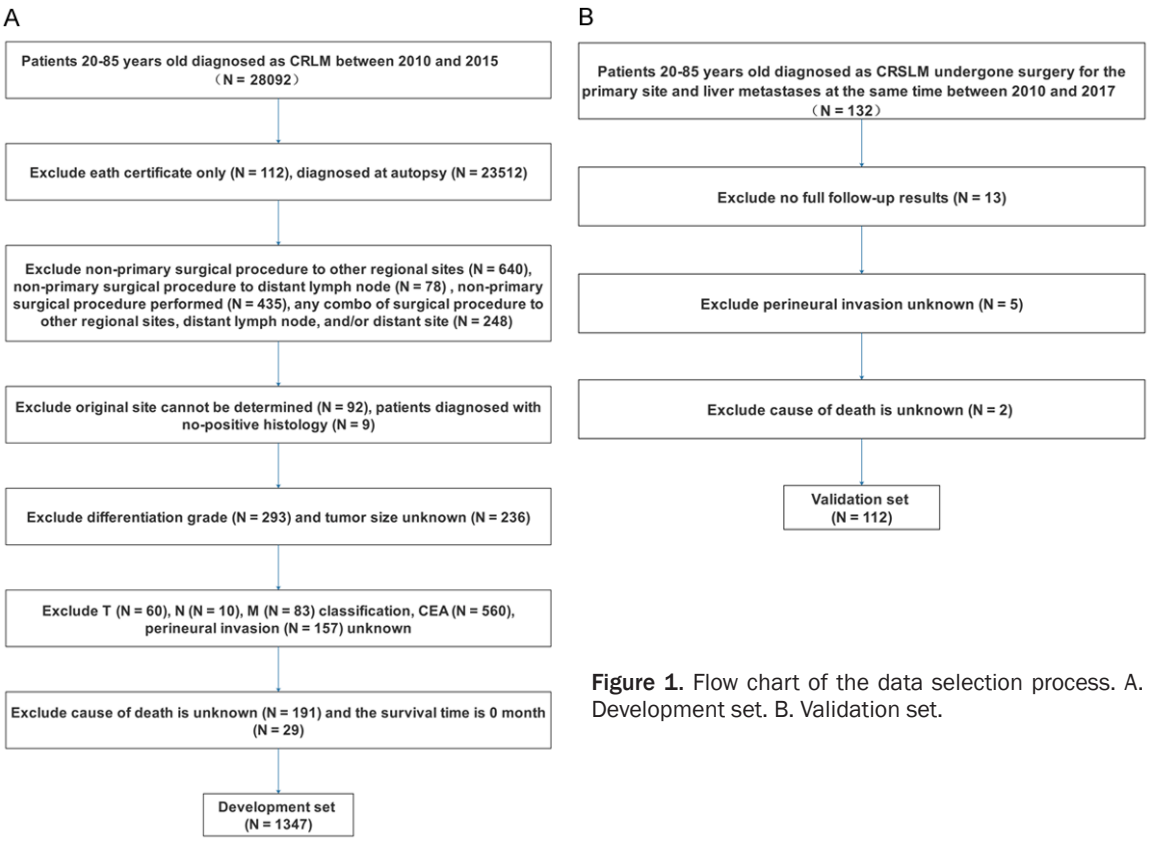

Figure 1. Flow chart of the data selection process. A. Development set. B. Validation set.

HR 1.203), Chemotherapy (No, HR 4.187), CEA (Negative, HR 0.630). Finally, we used these nine factors to construct a 1-, 3- and 5-year OS nomogram (**Figure 3A**).

LASSO regression was also applied to analyze the correlation between eleven variables and CSS (**Figure 2C**, **2D**). The final relevant factors include eleven factors, which were identical as CSS. After multivariate analysis, nine factors were associated with CSS (P≤0.05, **Table 2**). The nine independent prognostic factors were: Age (<50, HR 0.783), Primary Site (Colon, HR 1.401), Differentiation grade (Grade I, HR 0.518 and Grade II, HR 0.590), Histology type (Adenocarcinoma, HR 0.706), T stage (T2, HR 0.598 and T3, HR 0.749), N stage (N0, HR 0.476 and N1, HR 0.722), Tumor size (>5 cm, HR 1.211), Chemotherapy (No, HR 4.184), CEA (Negative, HR 0.620). Finally, we used these nine factors to construct a 1-, 3- and 5-year CSS nomogram (**Figure 3B**).

Validation of nomogram

The OS nomogram acquired a C-index of 0.701 (95% CI = 0.679-0.723) for the development set, demonstrating good accuracy for OS prediction. The C-indexes of the OS nomogram in the development and validation set were also higher than those based on the TNM stage (**Table 3**). The calibration plot indicated that the OS nomogram was well-calibrated, which mean predicted probabilities for each subgroup close to observed probabilities (**Figure 4A-F**). Meanwhile, CSS nomogram acquired a C-index of 0.704 (95% CI = 0.682-0.726) for the development set. Moreover, compared with the TNM stage, the nomogram showed significantly higher C-indexes values, which indicated a more accurate CSS prediction (**Table 3**). The calibration plots also confirmed an optimal agreement between CSS prediction and the actual observations for the development set (**Figure 5A-C**), and the validation set (**Figure 5D-F**).

The time-dependent receiver operating characteristic (ROC) curve is essential for further evaluating the accuracy of the prediction model. The Time-dependent ROC results showed that the prediction accuracy of the OS nomogram was better than the TNM stage in both development and validation set. OS nomogram in

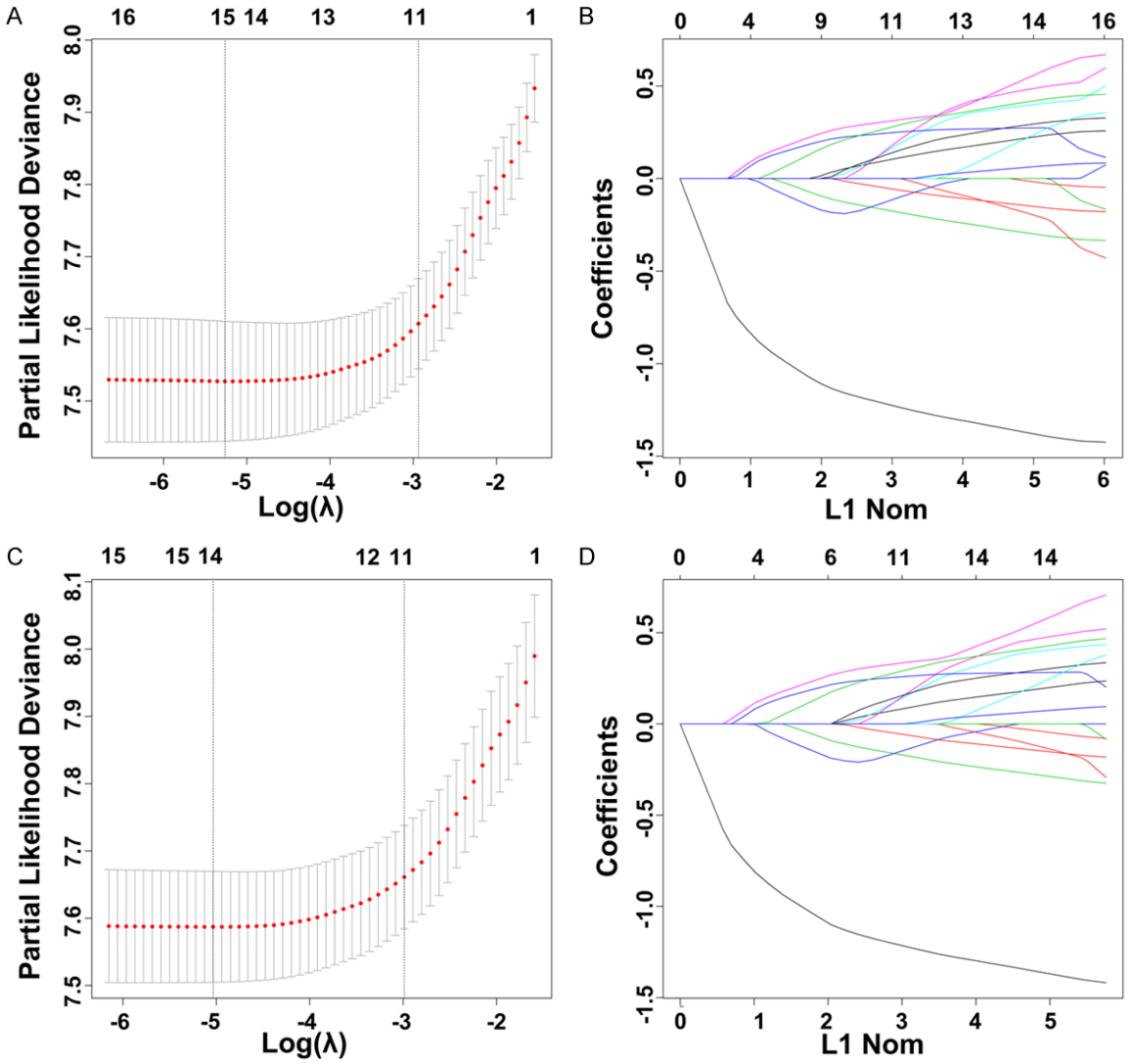

Figure 2. LASSO-Cox regression plot. A. Plot of LASSO coefficient profiles of OS. B. Plot of partial likelihood deviance of OS. C. Plot of LASSO coefficient profiles of CSS. D. Plot of partial likelihood deviance of CSS. Each colorful curve represents the LASSO coefficient profile of a feature against the log (lambda) sequence.

Table 2. Multivariate analyses of overall survival and cancer-special survival in the development set

Variable	OS		CSS	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age				
<50	0.768 (0.643-0.918)	0.004	0.783 (0.654-0.937)	0.008
≥50	Reference		Reference	
Tumor size				
>5 cm	1.203 (1.035-1.397)	0.016	1.211 (1.040-1.410)	0.014
≤5 cm	Reference		Reference	
Perineural Invasion				
No	0.917 (0.783-1.072)	0.277	0.904 (0.771-1.060)	0.216
yes	Reference		Reference	
Differentiation grade				
Grade I	0.497 (0.290-0.852)	0.011	0.518 (0.301-0.889)	0.017

Grade II	0.590 (0.434-0.802)	0.001	0.590 (0.433-0.805)	0.001
Grade III	0.905 (0.650-1.261)	0.556	0.915 (0.655-1.280)	0.605
Grade IV	Reference		Reference	
T stage				
T1	0.941 (0.521-1.699)	0.840	0.897 (0.484-1.660)	0.728
T2	0.574 (0.337-0.978)	0.041	0.598 (0.351-1.019)	0.058
T3	0.755 (0.644-0.885)	0.001	0.749 (0.638-0.880)	<0.001
T4	Reference		Reference	
N stage				
N0	0.502 (0.395-0.637)	<0.001	0.476 (0.372-0.610)	<0.001
N1	0.732 (0.623-0.859)	<0.001	0.722 (0.614-0.850)	<0.001
N2	Reference		Reference	
Histology type				
Adenocarcinoma	0.715 (0.551-0.929)	0.012	0.706 (0.543-0.919)	0.010
Others	Reference		Reference	
Chemotherapy				
No	4.187 (3.432-5.109)	<0.001	4.184 (3.414-5.127)	<0.001
Yes	Reference		Reference	
Sex				
Male	1.054 (0.908-1.223)	0.493	1.092 (0.938-1.270)	0.257
Female	Reference		Reference	
Primary Site				
Colon	1.408 (1.167-1.699)	<0.001	1.401 (1.158-1.695)	0.001
Rectum	Reference		Reference	
CEA				
Negative	0.630 (0.520-0.764)	<0.001	0.620 (0.509-0.755)	<0.001
Positive	Reference		Reference	

development set got AUC values of 1-, 3- and 5-year were 0.738 vs 0.694, 0.687 vs 0.669, 0.706 vs 0.688 (**Figure 6A-C**); OS nomogram in validation set got AUC values of 1-, 3- and 5-year were 0.814 vs 0.593, 0.694 vs 0.562, 0.611 vs 0.548 (**Figure 6D-F**). Meanwhile, 1-, 3- and 5-year CSS rates prediction were also got higher AUC values from CSS nomogram compared with that of the TNM stage, in both development set (**Figure 7A-C**) and validation set (**Figure 7D-F**).

To further evaluate the potential clinical application worth, the DCA was used to evaluate clinical decision utility and net benefit of the OS and CSS nomograms. The OS nomogram prediction model (black) showed more area than the TNM stage prediction model (red), in both the development set (**Figure 8A-C**) and validation set (**Figure 8D-F**). These results indicated more clinical net benefit could be gotten from OS nomogram compared to TNM stage. Additionally, in terms of CSS, similar results were also obtained for both the development set (**Figure 9A-C**) and validation set (**Figure 9D-F**).

Discussion

In the present study, we developed nomograms to predict 1- 3- and 5-year OS and CSS of CRSLM patients, who underwent simultaneous surgical treatment of primary and liver metastatic lesions. In addition to applying SEER database for development set, a validation set was used to validate the established nomograms. Results suggested that the nomograms were equipped with favorable discrimination and calibration ability. And compared with TNM stage, the nomogram prediction model displayed more powerful predictive ability and got greater clinical net benefit. Thus, we concluded that our nomograms model are reliable and accurate.

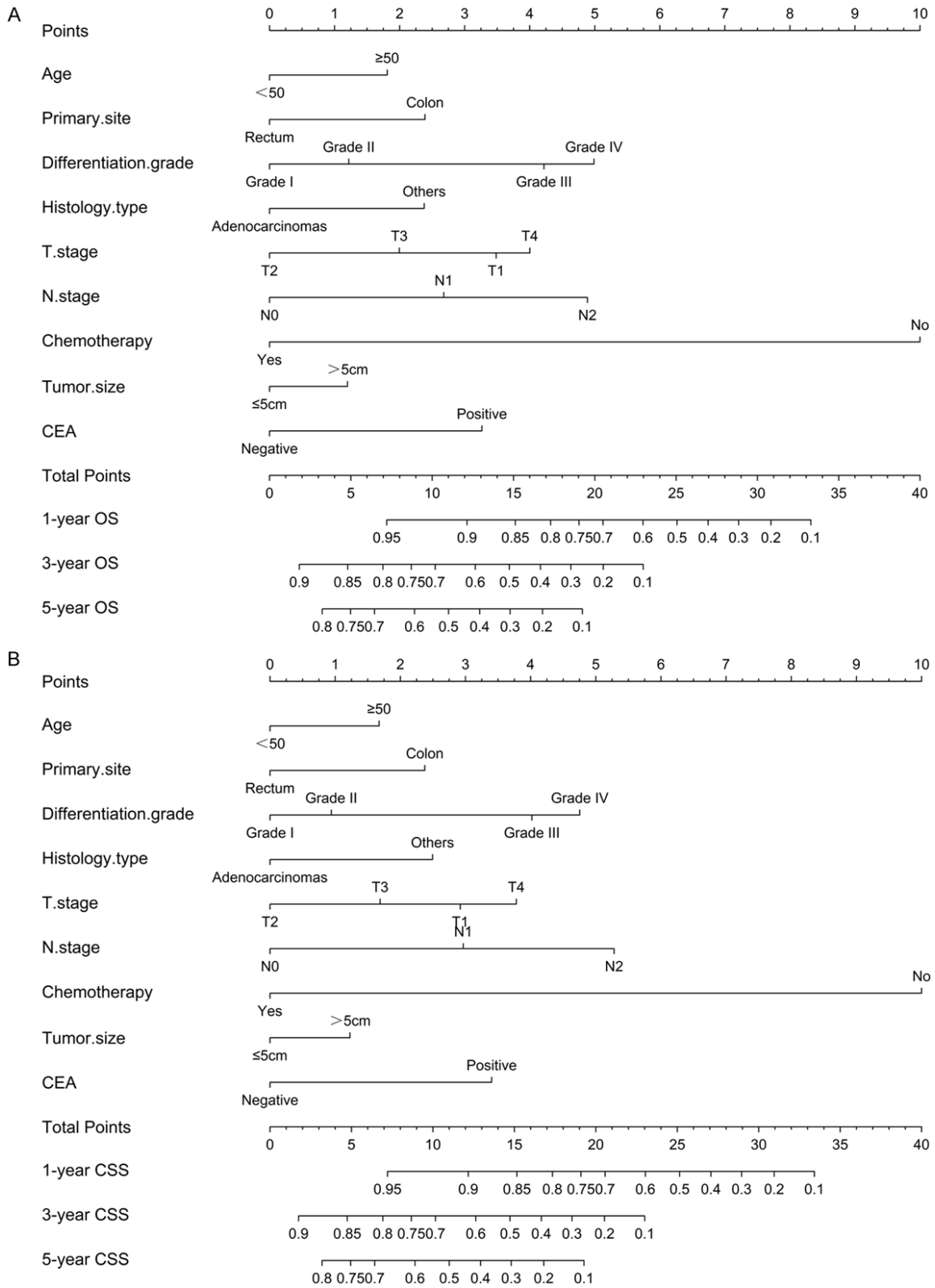

Figure 3. Nomogram for predicting 1-, 3- and 5-year (A) overall survival (OS) and (B) cancer-specific survival (CSS) of patients with CRSLM.

Table 3. C-indexes for the nomograms and TNM stage

Survival		Development set			Validation set		
		C-index	95% CI		C-index	95% CI	
OS	Nomogram	0.701	0.679	0.723	0.670	0.588	0.752
	TNM stage	0.641	0.619	0.663	0.557	0.475	0.639
CSS	Nomogram	0.704	0.682	0.726	0.677	0.596	0.758
	TNM stage	0.649	0.627	0.671	0.569	0.487	0.651

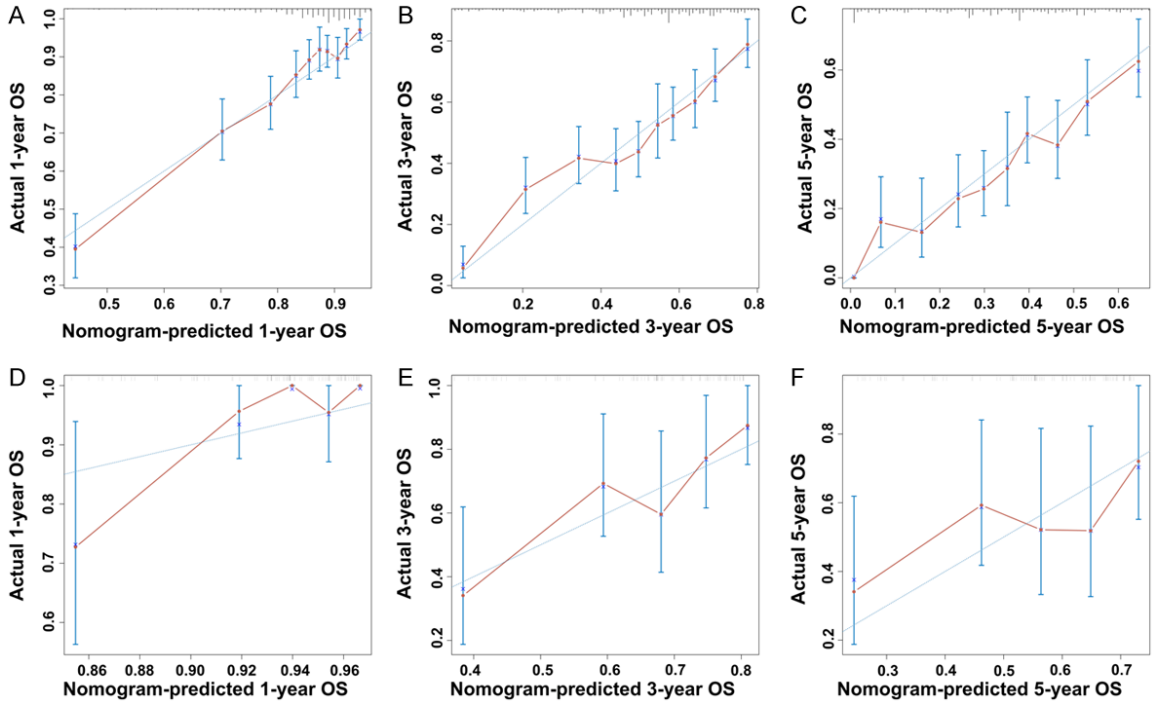

Figure 4. Calibration plots of the nomogram for 1-, 3- and 5-year OS prediction in the development set (A-C) and validation set (D-F).

Compared with other CRLM survival studies, this study had some innovations and advantages. In terms of model validation, previous nomogram studies for CRLM survival have not taken consideration for external set validation [18-23]. To ensure our nomograms would not be over fitted, we enrolled independent validation set from China. Validation set from different research centers not only reflect the prediction accuracy of the nomogram more credibly but also better reflect the clinical applicability of the nomogram. In the statistical method of the model, Time-dependent ROC and DCA were applied to evaluate nomogram, with these method, the nomograms were evaluated deeply for its accuracy and clinical benefit. These methods had not been applied in previous related studies [18-23]. The Time-dependent ROC that changes over time gives a fuller description of prediction models in survival analysis, DCA evaluated the clinical utility of the model and showed the net benefit of the nomogram.

The OS and CSS nomograms in this study consisted of nine identical factors, but these factors got different risk scores (**Table 4**) in the two nomograms respectively. Nomograms shared some identical factors with previous studies on CRLM survival prediction [18-23]. This phenomenon indicated that some of these factors were generally accepted among different studies. The T stage and tumor size were incorporated in our nomograms, for colorectal cancer studies, the T stage represents the depth of tumor invasion, which cannot be rep-

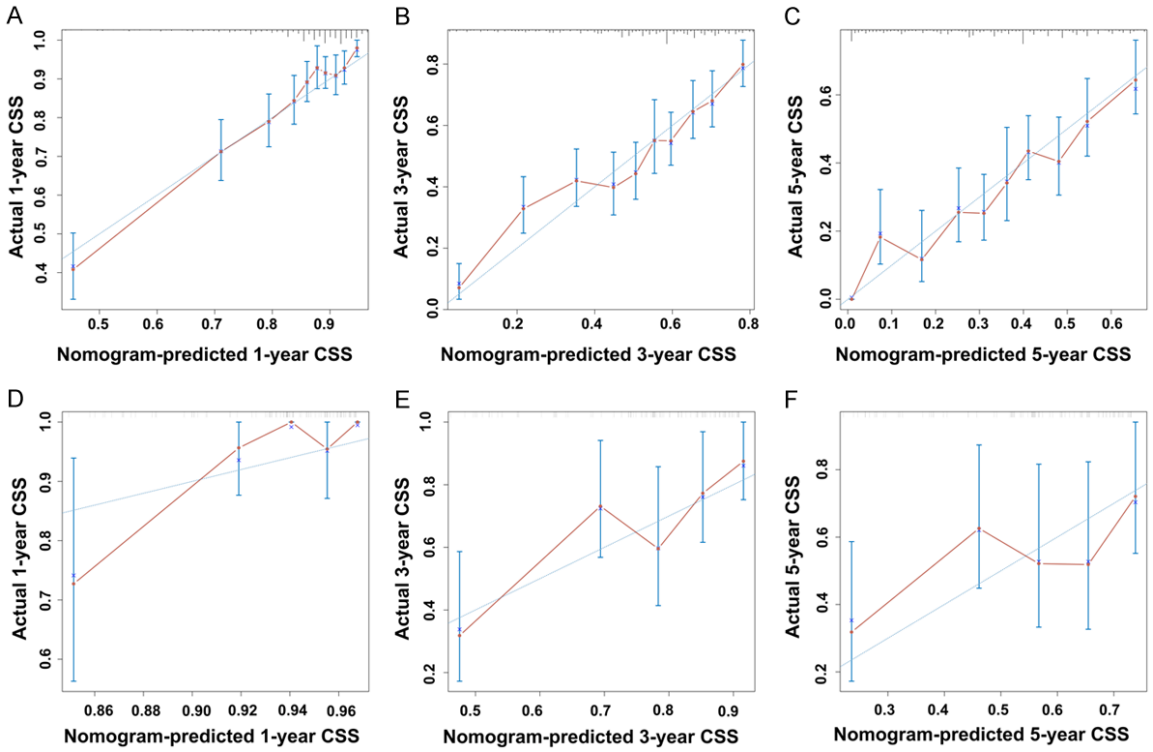

Figure 5. Calibration plots of the nomogram for 1-, 3- and 5-year CSS prediction in the development set (A-C) and validation set (D-F).

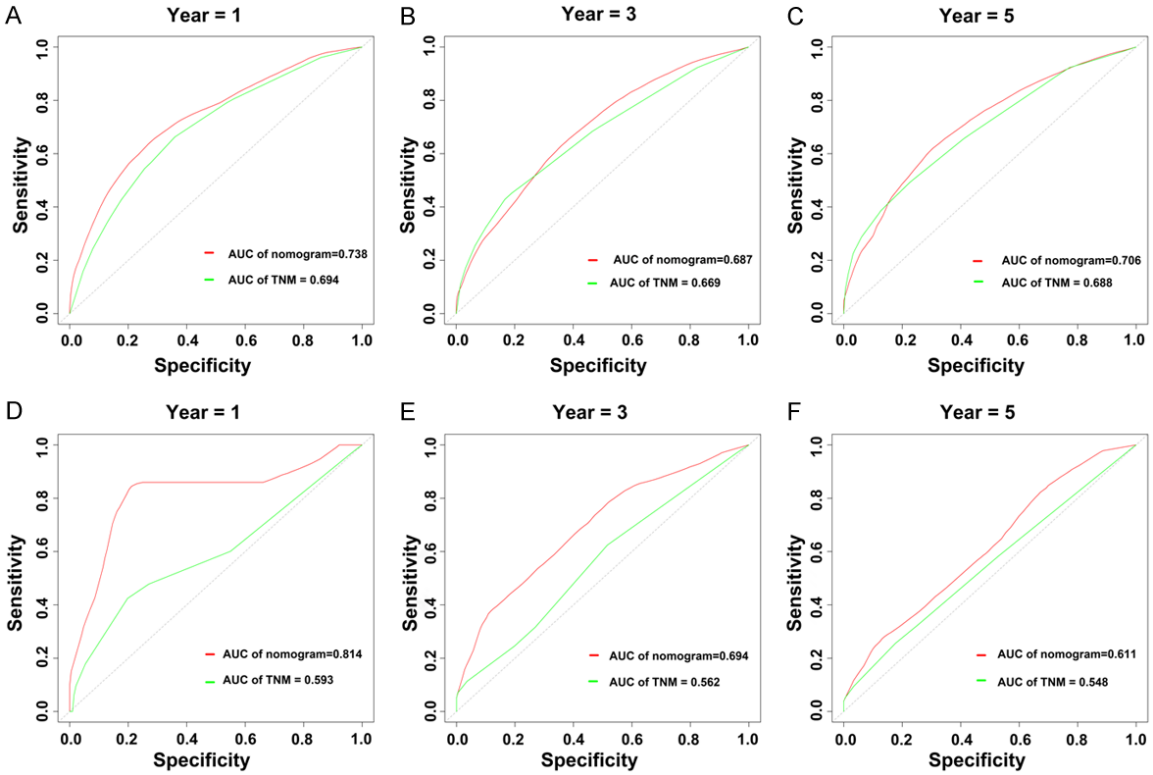

Figure 6. Comparison of the ROC curves of the nomogram and the TNM stage for 1-, 3- and 5-year OS prediction in the development set (A-C) and validation set (D-F).

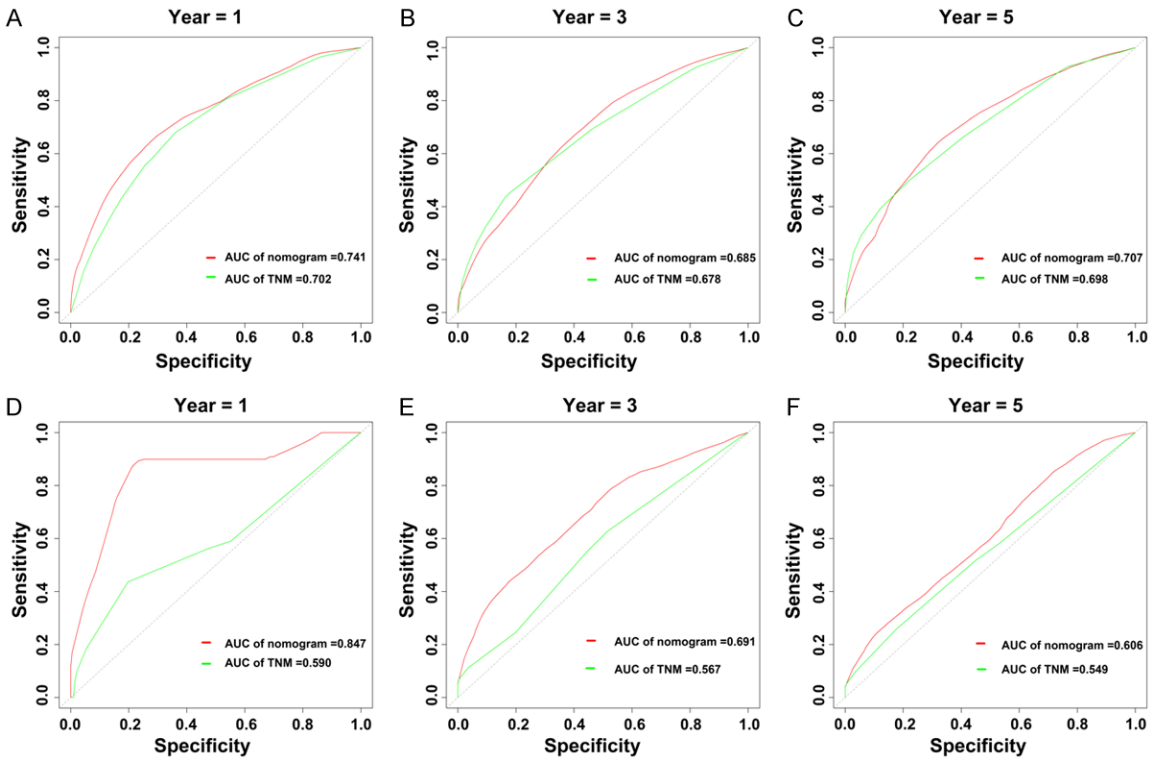

Figure 7. Comparison of the ROC curves of the nomogram and the TNM stage for 1-, 3- and 5-year CSS prediction in the development set (A-C) and validation set (D-F).

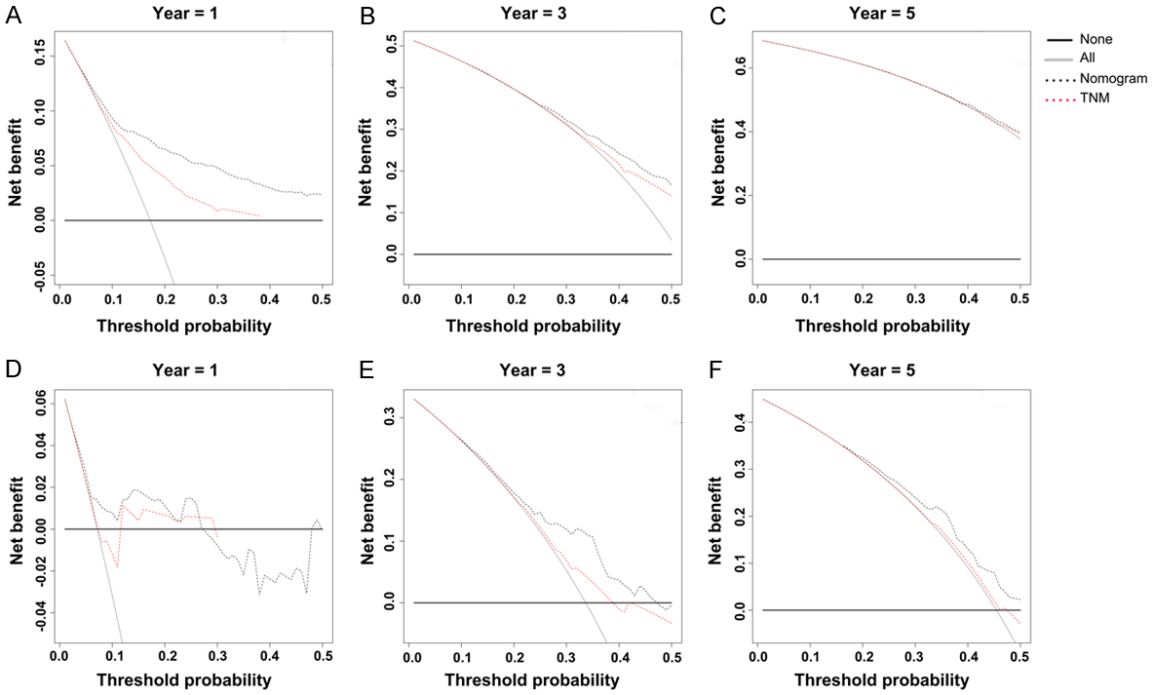

Figure 8. The Decision Curve evaluates the 1-, 3- and 5-year clinical benefit of the OS survival prediction model and compares the clinical benefit of the nomogram prediction model with the clinical benefit of the TNM stage prediction model in the development set (A-C) and validation set (D-F).

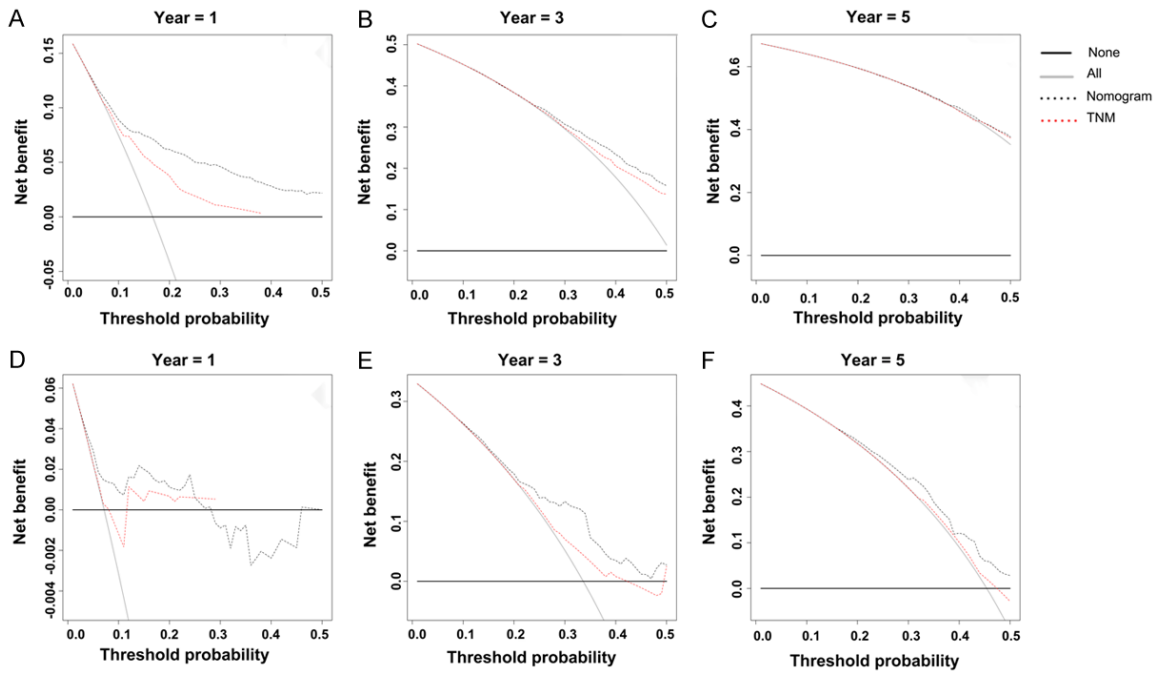

Figure 9. The Decision Curve evaluates the 1-, 3- and 5-year clinical benefit of the CSS survival prediction model and compares the clinical benefit of the nomogram prediction model with the clinical benefit of the TNM stage prediction model in the development set (A-C) and validation set (D-F).

resented by tumor size, so they are independent of each other. T stage, N stage, Chemotherapy, Differentiation grade characterized with a high-risk score in both the OS and the CSS nomograms. We observed an interesting phenomenon the risk score of the T1 stage was higher than that of the T3 and T2 stages in both OS and CSS nomograms, indicated patients with T1 stage tumors had a poorer survival rate. Although this result deviated from common sense, Lupo Wu et al. also found similar manifestations in their research, and they also confirmed that T1 stage tumors had a unique genetic profile, which might attribute to the poor outcomes of these patients [29]. Besides, we found that the lower the degree of differentiation grade of tumor cells, the worse the OS and CSS of patients. Patients with a lower degree of tumor differentiation should be followed-up intensively after discharge. And we found that among T1 patients, there was only one case with Grade III and no patients with Grade IV, which shows that T1 and lower differentiation grade were two independent factors that without correlation with each other. Our study found that CRSLM patients with T1 stage and a lower differentiation grade showed a poor postoperative prognosis when underwent simultaneous surgical treatment. In contrast to synchromesh surgery, stepwise surgery refers to the surgical treatment of liver metastases lesion after radical resection of the primary part of the colon or rectum. Whether these patients could achieve more benefit from stepwise surgery need further validation.

Chemotherapy was a high-rank protective factor in OS and CSS nomograms, implied chemotherapy improved the prognosis of CRSLM patients in our study. This observation was consistent with other [30-33] studies. According to these results, it is reasonable that NCCN Colorectal Cancer Guidelines suggest the chemotherapy should be applied for CRLM patients [9].

Although LASSO regression showed Sex had a certain correlation with OS and CSS. However, the strength of this correlation does not meet the criteria for multiple variable regression by Cox regression, so it was not included in the nomograms. Similarly, some CRLM research also found that there was no correlation between Sex and outcome status [21-23]. But in Michael's research [20], it was found that Sex had a certain effect on the outcome. This devi-

Table 4. Scores of prognostic factors in the OS and CSS nomograms

Variable	OS Score	CSS Score
Age		
<50	0	0
≥50	1.81	1.67
Tumor size		
>5 cm	1.2	1.23
≤5 cm	0	0
Differentiation grade		
Grade I	0	0
Grade II	1.22	0.942
Grade III	4.22	4.019
Grade IV	4.99	4.754
T stage		
T1	3.48	2.92
T2	0	0
T3	1.99	1.69
T4	4	3.78
N stage		
N0	0	0
N1	2.68	2.97
N2	4.89	5.28
Histology type		
Adenocarcinoma	0	0
Others	2.38	2.49
Chemotherapy		
No	10	10
Yes	0	0
Primary Site		
Colon	2.39	2.38
Rectum	0	0
CEA		
Negative	0	0
Positive	3.26	3.4

ation may be related to the difference between the data of different centers.

Perineural invasion is an independent prognostic factor, refers to the degree of tumor invasion to peripheral nerves and is not included in the TNM stage. Our results proved that there was indeed a negative correlation between perineural invasion and OS in LASSO regression analysis. However, when performing multivariate Cox regression, the perineural invasion was not statistically significant for OS. Therefore, we did not include the indicator of perineural invasion in the OS nomogram. The result was same for CSS nomogram. However, perineural invasion is a certain route for cancer cell spread, van Wyk HC and Knijn N all found that perineural invasion was associated with poor prognosis of patients with colorectal cancer [34, 35].

In this study, the SEER database data was used for model development, and our local patients were used for independent external verification of the model. The development set of the model was multi-center data from the United States, and the validation set was created by independent external data from China, by applying these two sets, our study indicated the model has reliable accuracy and applicability. But we also noticed that significant characteristics differences existed between these two cohorts, such as CEA, T stage, N stage, and Chemotherapy, Age, Histologic type (**Table 1**). Compared with the development set, the positive rate of CEA was lower, the majority of patients were ≥50 years old, the proportion of patients who did not receive Chemotherapy was higher in the validation set. Besides, the composition of T stage and N stage was significantly different between the two groups. The reason for these differences may attribute to different countries and regions, genetic, economic conditions, and cultural backgrounds, so there might be differences in tumor biological behaviors, chemotherapy selection criteria, and patient compliance. These differences may be the reason why the C-indexes and AUC values in the validation set are slightly lower than that in the development set, but still good enough.

There were some shortcomings in this study. Firstly, factors such as the number and size of liver metastases, surgical methods of liver resection, the specific method and course of chemotherapy, gene mutations, etc., were not included in this study, because the relevant data cannot be obtained from the SEER data. Although the data extension was not comprehensive enough, the nomograms we constructed showed good predictive capabilities both in the development set and validation set. Secondly, we did not find T1 patients when we collected the validation set, this may be because the sample size of the validation set is relatively small compared to the development set. But the relatively small amount of validation set did not affect the validation effect of

the nomograms; the nomograms have been well verified in the validation set. Finally, because this study was a retrospective analysis, the cases were treated from 2010 to 2015, some surgical plans and adjuvant treatment plans have been changed since then, and the performance of the model for recent cases needs to be verified in a prospective study. In the validation set, we applied a retrospective cohort rather than a prospective cohort. Indeed, for model validation, the data from the prospective cohort is more convincing. However, in this study, almost all characteristics we included are innate characteristics that unique to the patient, such as sex, TNM stage, and tumor size, and we think there should not be a bias between perspective and retrospective cohort.

Conclusion

In summary, the nomograms in this study accurately predict the OS and CSS of CRSLM patients who underwent simultaneous surgical treatment of primary and metastatic lesions. We have screened out distinct patients with poor prognosis, who may obtain better outcomes if they attempt stepwise resection. This study provides a certain reference value for the selection of surgical methods for CRSLM patients.

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Disclosure of conflict of interest

None.

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