Original Article

Preoperative nomogram to predict survival following colorectal cancer liver metastasis simultaneous resection

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Background: Simultaneous resection for patients with synchronous colorectal cancer liver metastases (CRLM) remains an optimal option for the sake of curability. However, few studies so far focus on outcome of this subgroup of patients (who receive simultaneous resection for CRLM). Substantial heterogeneity exists among such patients and more precise categorization is needed preoperatively to identify those who may benefit more from surgery. In this study, we formulated this internally validated scoring system as an option.

Methods: Clinicopathological and follow-up data of 234 eligible CRLM patients undergoing simultaneous resection from January 2010 to March 2019 in our center were included for analysis. Patients were randomized to either a training or validation cohort. We performed multivariable Cox regression analysis to determine preoperative factors with prognostic significance using data in training cohort, and a nomogram scoring system was thus established. Time-dependent receiver operating characteristic (ROC) curve and calibration plot were adopted to evaluate the predictive power of our risk model.

Results: In the multivariable Cox regression analysis, five factors including presence of node-positive primary defined by enhanced CT/MR, preoperative CEA level, primary tumor location, tumor grade and number of liver metastases were identified as independent prognostic indicators of overall survival (OS) and adopted to formulate the nomogram. In the training cohort, calibration plot graphically showed good fitness between estimated and actual 1- and 3-year OS. Time-dependent ROC curve by Kaplan-Meier method showed that our nomogram model was superior to widely used *Fong's* score in prediction of 1- and 3-year OS (AUC 0.702 *vs.* 0.591 and 0.848 *vs.* 0.801 for 1- and 3-year prediction in validation cohort, respectively). Kaplan-Meier curves for patients stratified by the assessment of nomogram showed great discriminability ($P<0.001$).

Conclusions: In this retrospective analysis we identified several preoperative factors affecting survival of synchronous CRLM patients undergoing simultaneous resection. We also constructed and validated a risk model which showed high accuracy in predicting 1- and 3-year survival after surgery. Our risk model is expected to serve as a predictive tool for CRLM patients receiving simultaneous resection and assist physicians to make treatment decision.

Keywords: Colorectal cancer (CRC); liver metastasis; nomogram; survival; preoperative prediction

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Introduction

Colorectal cancer (CRC) is the fourth most prevalent malignancy and the fifth leading cause of cancer death worldwide (1). Liver is the most common site of metastases from CRC and approximately 15% of colorectal cancer liver metastases (CRLM) present liver lesion at the initial diagnosis (synchronous metastasis) (2,3). Despite advances in systemic therapy, surgery is still an irreplaceable part of modern therapy approach for CRLM. The median survival of CRLM without treatment is 9.6 months, while the 5-year overall survival (OS) of resected CRLM approaches 50 months (4). In recent years, surgical strategies of synchronous CRLM have changed dramatically. Although several studies revealed the surgical outcome or survival advantage among classical colorectum-first, liver-first, and synchronous surgery is similar for CRLM, synchronous resection has gradually been accepted and popularized with advantages of safety, minimal damage, and less cost (5-8). However, few studies so far have focused on outcome of this subgroup of patients who receive simultaneous resection for CRLM. The survival of CRLM patients undergoing simultaneous resection remains highly variable and more precise categorization is needed preoperatively to identify those who may benefit more from surgery. Fong's score (9) is a well-accepted prognostic system initially formulated for metachronous CRLM, and GAME score (10), put forward by Margonis, is a preoperative model based on American cohort requiring genetic status of KRAS, which is not specifically designed for simultaneous CRLM resection. Therefore, we provided this scoring system merely requiring clinicopathological data as an option for CRLM patients undergoing simultaneous resection for preoperative risk stratification.

The present study assessed the preoperative prognostic factors in CRLM patients undergoing synchronous resection. A nomogram was established and validated to quantify the impact of every variable. We present this article in accordance with the TRIPOD reporting checklist (11) (available at http://dx.doi.org/10.21037/jgo-20-329).

Methods

Patients and data sources

Clinicopathological information of 415 consecutive patients with CRLM who underwent combined liver and colon/rectum resection with or without chemoradiotherapy from January 2010 to March 2019 in Changhai Hospital was retrospectively collected for analysis. Telephone follow-up was completed by May 2020. Inclusion criteria were as follows: (I) verified diagnosis of CRC by colonoscope and biopsy; (II) synchronous liver metastasis demonstrated by enhanced computed tomography (CT) scan of abdomen or enhanced liver magnetic resonance (MR); (III) R0 resection of primary lesion and liver metastasis; (IV) definite diagnosis of CRC with liver metastasis by postoperative biopsy; (V) treated with postoperative systemic chemotherapy (5-FU-based) ± targeted therapy. Exclusion criteria were as follows: (I) presence of extrahepatic metastasis; (II) 30-day mortality from operative complications; (III) loss to follow-up or absence of clinicopathological information. A total of 234 cases meeting the eligibility criteria above were included in this study.

Preoperative assessment consisted of gender, age, primary tumor location, preoperative serum CEA and CA-199, number and diameter of liver metastases, presence of node-positive primary defined by enhanced CT/MR, tumor grade obtained via endoscopic biopsy, and neoadjuvant therapy, all transformed as categorical or hierarchical variables. Postoperative pathological characteristics including primary tumor location, tumor grade, pT stage, pN stage, tumor deposit (TD, focal aggregates of cancer cells in the pericolic and mesenteric adipose tissue around primary tumor). perineural invasion (PNI), lymphovascular invasion (LVI), status of KRAS (exon 2, 3 and 4), NRAS (exon 2, 3 and 4) and BRAF (V600E), number and maximal diameter of liver metastases was obtained. All the auxiliary examination findings were interpreted by experienced specialists unaware of patients' clinical condition. The American Joint Committee on Cancer (AJCC) 7th edition was adopted in most cases and pathologists were consulted to ensure consistency of criteria (12). Simultaneous hepatectomy was performed by experienced hepatologic surgeons who assessed imaging finding to determine surgical procedure. Major liver resection was defined as resection of three or more segments. Survival information was obtained via telephone follow-up survey by May 2020.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of Changhai Hospital, Secondary Military Medical University, Shanghai, China (No. CHEC2015-146). Because of the retrospective nature of the study, the requirement for informed consent was waived.

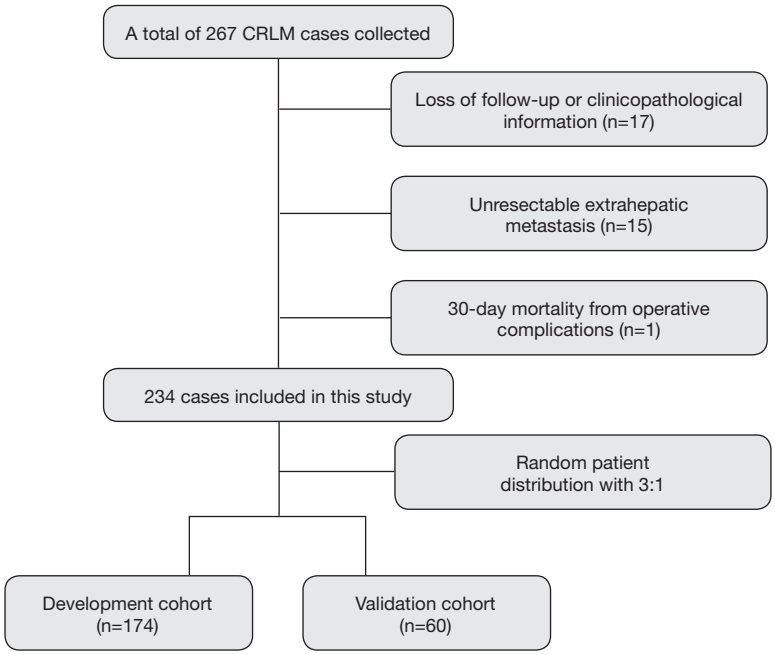

Figure 1 Flowchart of case selection and distribution in this study.

Statistical analysis

Categorical variables were analyzed with non-parametric test and continuous data with Student *t*-test or Log-rank test. Univariable and multivariable Cox regression analyses were employed to assess prognostic factors. Survival analyses were performed with Kaplan-Meier method, and compared by log-rank test.

The 234 patients were grouped into training cohort and validation cohort by a ratio of 3 to 1 (174:60) with random number (*Figure 1*). Univariable and multivariable Cox regression analyses to identify predictors of survival were performed using data in training cohort. For the sake of comprehensive inspection of relevant factors, variables with P<0.15 in univariable analysis were entered into multivariable analysis. Hazard ratio (HR) and 95% confidence interval were reported and variables with P less than 0.05 in multivariable analysis were considered statistically significant. Based on the results of multivariable Cox regression analysis, a nomogram was generated to predict 1- and 3-year OS of CRLM patients undergoing synchronous resection. The predictive accuracy and discriminative ability were evaluated by calibration plot and survival curve, respectively. We adopted time-dependent receiver operating characteristic (ROC) curve to compare the accuracy of the nomogram with Fong's clinical risk score (CRS) system (9).

The demographical comparison was completed with SPSS 22.0 (SPSS, Inc., Chicago, IL, USA), and Cox proportional hazard model, nomogram, time-dependent ROC, calibration plot and Kaplan-Meier curve with R 3.6.2.

Results

Clinicopathological characteristics of the patients

Among these 234 patients, 174 patients were included in the training cohort while 60 in the validation cohort. The 3-year OS in this study was 30.3% and median follow-up time was 26 months. Preoperative clinicopathological characteristics comparison in the two groups showed no statistical differences (P≥0.05, *Table 1*). Also, survival analysis comparing OS between patients receiving surgery in different periods showed stable procedure outcome through the follow-up (Figure S1, P=0.47).

Preoperative prognostic factors of OS in the training cohort

In training cohort, the hazard ratio (HR) and P value with 95% confidence interval of every candidate predictor generated by Cox regression analysis are shown in *Table 2*. Presence of positive-node primary defined by enhanced

Table 1 Demographic characteristics in the training and validation cohorts

Variables	All, No. (%)	Training, No. (%)	Validation, No. (%)	P
Subjects, n	234	174	60	
Gender				0.058
Male	126 (53.85)	100 (57.47)	26 (43.33)	
Female	108 (46.15)	74 (42.53)	34 (56.67)	
Age				0.947
<65 years old	164 (70.09)	122 (70.11)	42 (70.00)	
≥65 years old	70 (29.91)	52 (29.89)	18 (30.00)	
Primary tumor location				0.768
Left-sided	148 (63.25)	111 (63.79)	37 (61.67)	
Right-sided	86 (36.75)	63 (36.21)	23 (38.33)	
Preoperative CEA, ng/mL				0.541
≤100	205 (87.61)	150 (86.21)	55 (91.67)	
>100 and ≤200	17 (7.26)	14 (8.05)	3 (5.00)	
>200	12 (5.13)	10 (5.75)	2 (3.33)	
Preoperative CA-199				0.617
≤200	194 (82.91)	143 (82.18)	51 (85.00)	
>200	40 (17.09)	31 (17.82)	9 (15.00)	
No. of metastases				0.651
1	119 (50.85)	90 (51.72)	29 (48.33)	
>1	115 (49.15)	84 (48.28)	31 (51.67)	
Diameter of metastasis				1.000
<5	195 (83.33)	145 (83.33)	50 (83.33)	
≥5	39 (16.67)	29 (16.67)	10 (16.67)	
Histologic type				0.514
Highly/moderately differentiated	205 (87.61)	151 (86.78)	54 (90.00)	
Poorly differentiated/mucinous	29 (12.39)	23 (13.22)	6 (10.00)	
Nodal positivity by imaging				0.691
Negative	79 (33.76)	60 (34.48)	19 (31.67)	
Positive	155 (66.24)	114 (65.52)	41 (68.33)	
Neoadjuvant therapy				0.240
Negative	166 (70.94)	127 (72.99)	39 (65.00)	
Positive	68 (29.06)	47 (27.01)	21 (35.00)	
Procedure of hepatic resection				0.271
Major resection	88	69	19	
Minor resection	146	105	41	
Transfusion				0.360
Yes	109	78	31	
No	125	96	29	

CA-199, carbohydrate antigen-199; CEA, carcino-embryonic antigen.

Table 2 Univariable and multivariable analysis in the training cohort

Variables	Univariable		Multivariable	
	HR (95% CI)	P	HR (95% CI)	P
Gender		0.568		
Male	1			
Female	0.869 (0.538–1.406)			
Age, years old		0.474		
<65	1			
≥65	0.821 (0.479–1.409)			
Primary tumor location		0.007		0.024*
Left-sided	1		1	
Right-sided	1.928 (1.201–3.095)		1.769 (1.077–2.904)	
Preoperative CEA, ng/mL				
<100	1		1	
100–200	2.103 (1.029–4.300)	0.042	1.896 (0.919–3.912)	0.084
≥200	2.203 (1.000–4.857)	0.050	2.287 (1.020–5.129)	0.045*
Preoperative CA-199, ng/mL		0.655		
<200	1			
≥200	0.863 (0.452–1.646)			
No. of metastases		0.058		0.007*
1	1		1	
>1	1.588 (0.985–2.560)		1.991 (1.207–3.283)	
Diameter of Metastasis, cm		0.240		
<5	1			
≥5	1.387 (0.804–2.393)			
Tumor grade		0.111		0.046*
Highly/moderately differentiated	1		1	
Poorly differentiated/mucinous	1.698 (0.886–3.254)		2.009 (1.011–3.992)	
Positive lymph node by imaging		0.002		0.001*
Negative	1		1	
Positive	2.434 (1.370–4.327)		2.598 (1.442–4.681)	
Neoadjuvant therapy		0.194		
Negative	1			
Positive	0.660 (0.352–1.236)			

The symbol "*" denotes P less than 0.05 in multivariable analysis. CA-199, carbohydrate antigen-199; CEA, carcino-embryonic antigen.

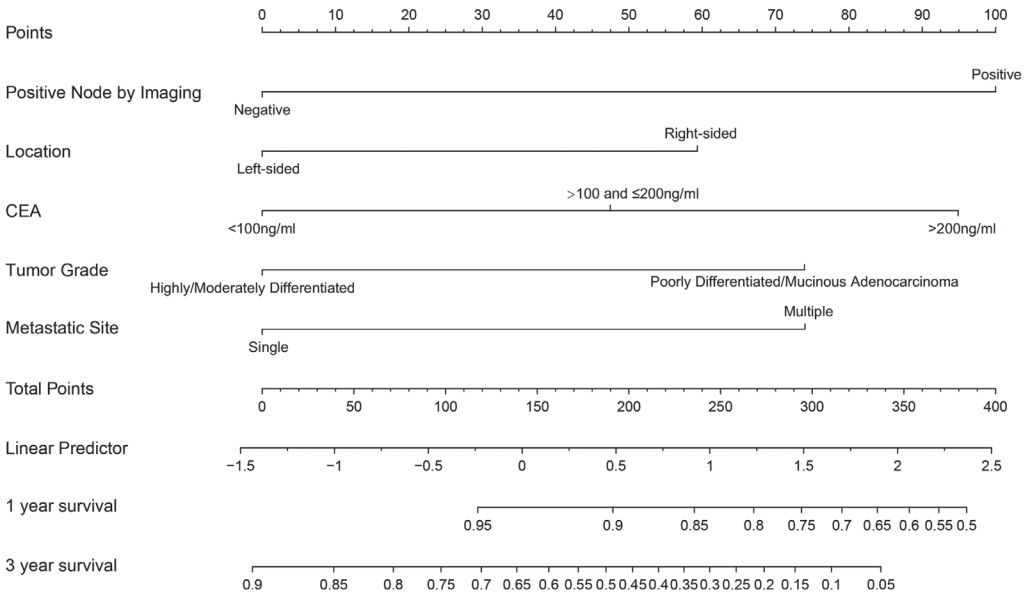

Figure 2 Nomogram based on Cox proportional hazard model to quantify risk of death using five indicators, also shown here are relationship between total points and probabilities of 1- and 3-year survival. CEA, carcino-embryonic antigen.

CT/MR, preoperative CEA level and primary tumor site are statistically associated with OS in univariable analysis. These three factors combined with tumor grade (P=0.111) and number of liver metastases (P=0.058) were included in further multivariable analysis and all these five variables were demonstrated to be independent risk factors associated with OS of patients receiving simultaneous resection for CRLM. Patients with higher preoperative CEA level, right-sided primary location, poor tumor grade, positive lymph node and multiple liver metastasis tend to have less opportunity of long-term postoperative survival according to above results.

Generation and validation of predictive nomogram for OS

A nomogram was formulated based on five independent risk factors selected by multivariable analysis of Cox proportional hazard model to visualize and quantify the weight of every factor (*Figure 2*). We applied the nomogram to all cases in both training and validation cohorts and calculated the total score and predicted probability of 1- and 3-year survival of every patient. Calibration plot graphically showed good fitness between estimated and actual 1- and 3-year survival in both cohorts (*Figure 3*).

Evaluation of the preoperative prognostic nomogram model

Time-dependent ROC curve by Kaplan-Meier method was adopted to assess the predictive power. To estimate the predictive validity of our scoring system, we applied modified Fong's scoring system: (I) dissected lymph node biopsy replaced with MR finding, and (II) disease-free interval uniformly deemed as less than 12 months. The result showed that our nomogram scoring system can better predict 1-year survival [area under curve (AUC) 0.788 *vs.* 0.652 and 0.702 *vs.* 0.591 in training and validation cohort respectively]. As for 3-year prediction, modified Fong's score retained high accuracy, with AUC 0.712 and 0.801 in training and validation cohorts respectively, while slightly lower than those of our nomogram (0.752 and 0.848, *Figure 4*). However, in predicting 5-year OS, both Fong's score and our model showed low power of test, partially reflecting the heterogeneity among long-surviving CRLM patients.

For convenience of clinical use, we stratified patients with maxstat, an algorithm in R used to decide on cut-point to yield the most significant difference. Based on the result, a total mark of 135 was identified as the cut-point and patients were divided into low- and high-risk groups. Survival analysis was performed by Kaplan-Meier

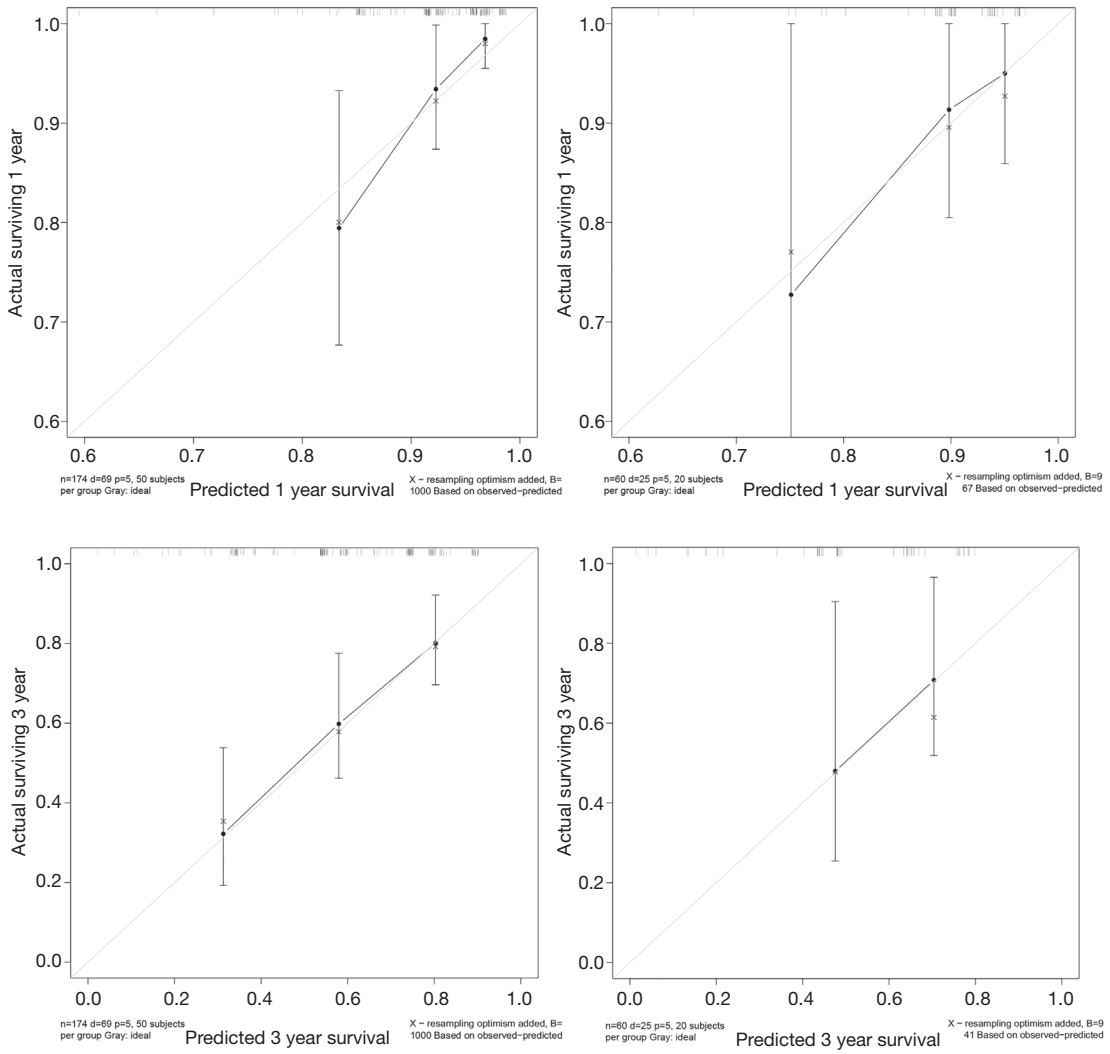

Figure 3 Calibration curve showing fitness between predicted and actual survival (the left-sided two plots for training cohort and right-sided for validation cohort).

method with log-rank test and graphically displayed in *Figure 5*, showing good discriminability of this stratification solution (P<0.001). Among three groups, there were statistical differences in several postoperative pathological characteristics including primary location, tumor grade, pT stage, pN stage, peripheral nervous invasion, and number of liver metastases (P<0.05, *Table 3*).

Discussion

Combined primary tumor and liver resection is the most preferred curative treatment for synchronous CRLM and should be taken into consideration when R0 resection is possible (13). To date, simultaneous surgery has been accepted widely for its perioperative safety, good long-term effects and improved economic efficiency (14,15). However, when CRLM patients decide to receive synchronous surgery for complete R0 resection, the individual oncological benefit is still difficult to predict. Therefore, optimal preoperative prognostic models for patient selection are required.

The present study demonstrated that preoperative factors including primary tumor location, preoperative CEA level, number of liver metastases, tumor grade and positive lymph node by imaging were independent indicators to predict survival benefit from surgery, which was in line with findings of certain reports (16-18). Notably, there

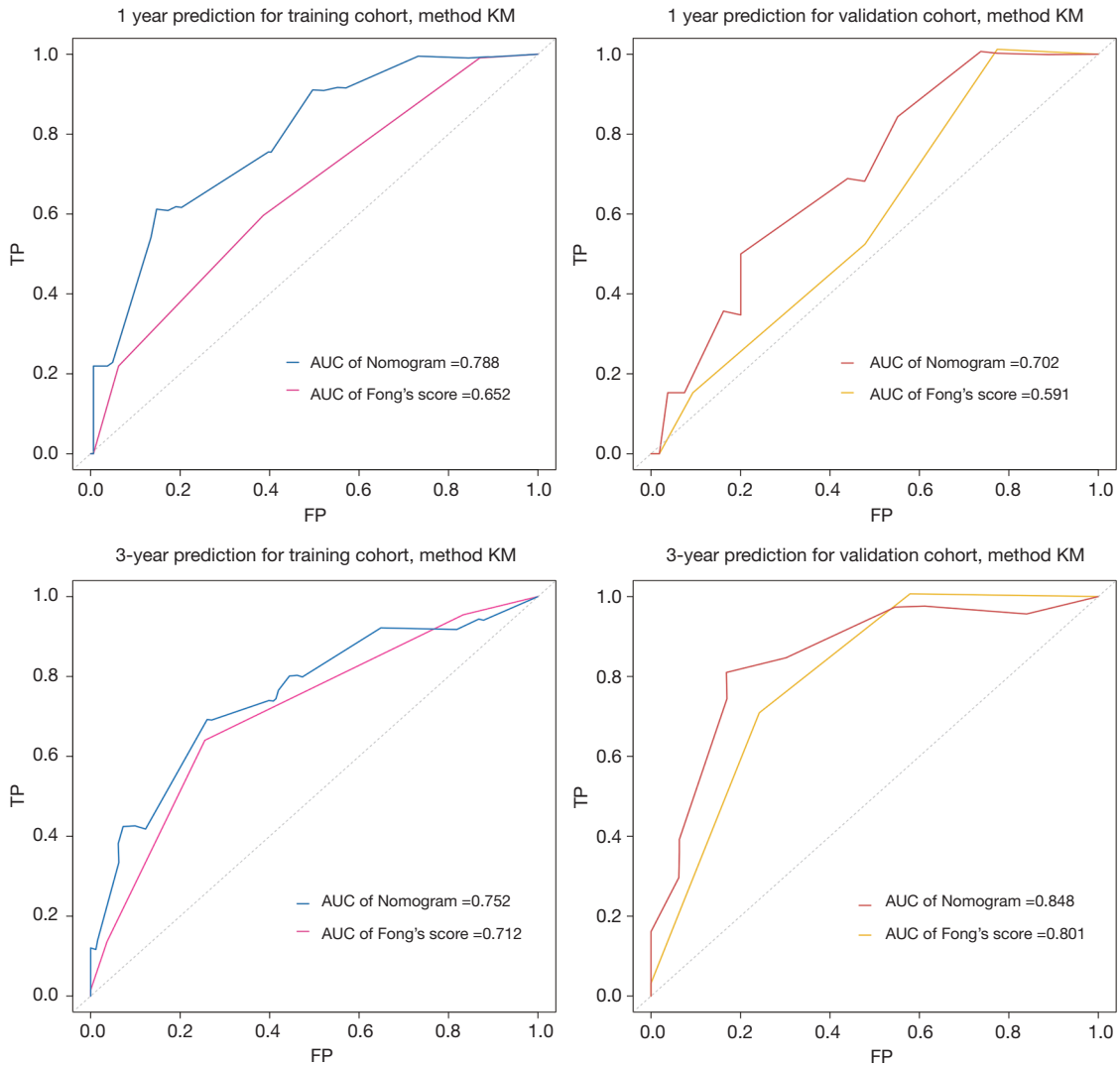

Figure 4 Time-dependent receiver operating curve comparing power of test between Fong's and our scoring system. AUC, area under curve; CRS, clinical risk score; FP, false positivity; KM, Kaplan-Meier; TP, true positivity.

was no significant difference in OS between the patients receiving neoadjuvant chemoradiotherapy (nCRT) or not. Despite that the National Comprehensive Cancer Network (NCCN) recommends 6 months of perioperative chemotherapy, standard treatment strategy is poorly defined (19). Neoadjuvant therapy has been proposed to be an essential part of comprehensive treatment, and individual response to nCRT reflects tumor biologic characteristic and prognosis (20,21), while redundant chemoradiotherapy has been reported to cause liver damage and poor short-term outcome (22). Our data suggested that neoadjuvant therapy was not essential when patients with resectable CRLM treated with postoperative chemotherapy ± targeted therapy.

Nomograms have been considered a reliable tool to quantify risk factors of prognosis (23,24). In our study, a nomogram based on five prognostic indicators was generated to predict 1- and 3-year OS of synchronous CRLM patients undergoing combined resection. The predictive accuracy and the discriminative ability of the nomogram were internally and externally validated, and the results showed good fitness between estimated and actual 1- and 3-year OS. At present, Basingstoke score system, Nordlinger scoring system, Iwatsuki scoring system and Fong's CRS scoring system, which requires postoperative

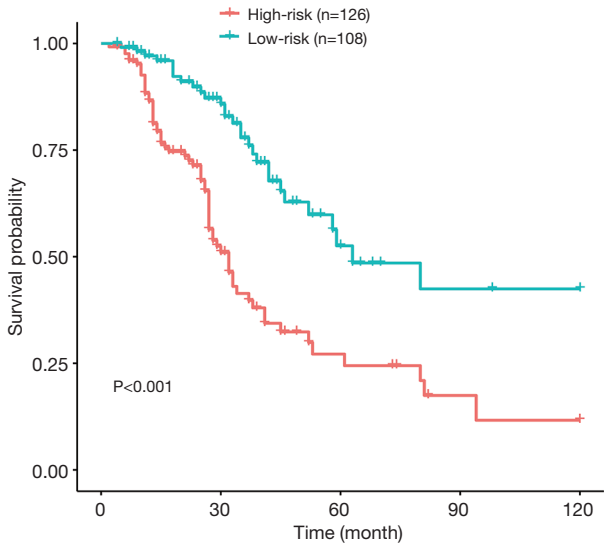

Figure 5 Survival analysis comparing overall survival of patients stratified by nomogram score, using Kaplan-Meier method and Log-rank test.

Table 3 Clinicopathologic comparison among different risk groups defined by nomogram score

Variables	Low-risk, n=108	High-risk, n=126	P
Primary location			
Left-sided or rectum	84	64	<0.001*
Right-sided	24	62	
Tumor grade			
Highly/moderately differentiated	104	101	<0.001*
Poorly differentiated/ mucinous	4	25	
pT stage			
1	1	0	0.008*
2	7	3	
3	92	102	
4	8	21	
pN stage			
0	60	18	<0.001*
1	31	67	
2	17	41	

Table 3 (*continued*)

Table 3 (*continued*)

Variables	Low-risk, n=108	High-risk, n=126	P
Tumor deposit			
Negative	79	78	0.068
Positive	29	48	
PNI			
Negative	88	87	0.029*
Positive	20	39	
LVI			
Negative	87	96	0.420
Positive	21	30	
KRAS			
Wild type	53	51	0.094
Mutant type	37	39	
Information absent	18	36	
NRAS			
Wild type	24	28	0.537
Mutant type	0	1	
Information absent	84	97	
BRAF			
Wild type	88	87	0.086
Mutant type	1	3	
Information absent	19	36	
Metastatic site			
1	80	39	<0.001*
>1	28	87	
Diameter of metastasis, cm			
<5	94	101	0.159
≥5	14	25	

The symbol "*" denotes P less than 0.05 in statistical comparison. LVI, lymphovascular invasion; PNI, perineural invasion.

biopsy of primary tumor, are widely used for the prognosis evaluation of CRLM patients undergoing staged resection, but might not be appropriate for simultaneous resection (9,25-27).

According to the nomogram-based stratification, patients in low-risk group have a highly favorable outcome, and simultaneous resection is a rational option for such patients. Patients in high-risk group have a relatively poor outcome, therefore, further studies of the better surgical and therapeutic strategies for such patients are needed. There was a statistically significant difference in primary location, tumor grade, pT and pN stage, neural invasion, and metastatic site among the three groups. However, despite genetic predictors having been used with increasing frequency for patients with CRLM, the status of KRAS, NRAS, and BRAF did not differ obviously among risk groups (28,29).

The present study has several noteworthy limitations. First, our preoperative prognostic nomogram model was based on the retrospective data from a single clinical center, which may have biased the selection. Second, this model was internally validated with part of cases in our dataset but not externally validated. Third, incomplete genetic testing results and neoadjuvant therapy schemes might limit the accuracy of our conclusions. We do hope with the popularization of more accessible genetic testing method, molecular pathology will serve a prior part in future scoring systems. Further exploration is urgently needed to provide more precise risk assessment for CRLM patients.

Conclusions

This study formulated and validated a practicable preoperative prognostic nomogram model for surgeons and CRLM patients to predict individualized mortal risk after combined resection. We also designated cut-off to stratify patients at different level of risk to provide better assessment of postoperative survival. The CRLM patients ranked high-risk by the scoring system should consider comprehensive and more individualized treatment.

In conclusion, we identified five survival-associated preoperative factors of synchronous CRLM and established a prognostic model which can assess survival of CRLM patients undergoing simultaneous resection and exhibits high predictive power.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at http://dx.doi.org/10.21037/jgo-20-329

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jgo-20-329). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board at Changhai Hospital prior to the collection of data (No. CHEC2015-146). Because of the retrospective nature of the study, the requirement for informed consent was waived.

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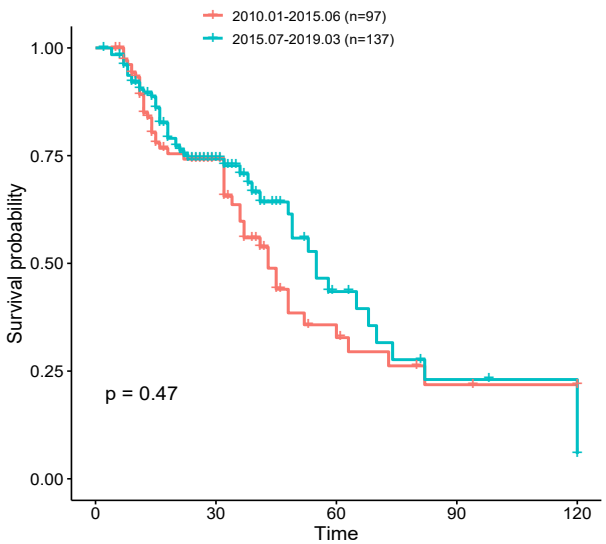

Figure S1 Kaplan-Meier curve showing stable procedure outcome through follow-up period.

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