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Prognostic analysis of patients with CRLM based on CRS score: a single-center retrospective study

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Abstract

Background To improve prognosis of patients with synchronous colorectal liver metastasis (CRLM), we constructed a nomogram model to improve outcome through risk stratification and decision support.

Methods The 389 CRLM patients (273 training set and 116 validation set at a ratio of 7: 3) receiving systematic chemotherapy and synchronously resection with/without radiofrequency ablation (RFA) were retrospectively investigated. Overall survival (OS) and recurrence free survival (RFS) were mainly endpoint. A normo-gram model was conduct. The receiver operating characteristic (ROC) curve, decision curve analysis (DCA), C-index and calibration curve were performed to assess stablity and efficacy of model. The prognosis was evaluated based on Kaplan-Meier (KM) curve.

Results A total of 389 CRLM patients were included. The median OS and RFS times were 70.20 months (95% CIs: 57.73, 82.68) and 11.70 months (95% CIs: 9.75, 13.65), respectively. These patients were divided into training set and validation set at a ratio of 7: 3. In training set, 1, 3, and 5-year survival rate of OS was 97.38%, 71.18%, and 54.56% as well as RFS was 52.57%, 22.65%, and 21.12%, respectively. Cox model showed that hospital day, R0 resection, RFA, only neoadjuvant chemotherapy and CRS score were independent prognostic factors for CRLM patients. The patients were divided into high-risk group and low-risk group based on cut-off value of score calculated by model. The KM curves were statistically different between two groups ($P < 0.01$). The ROC curve, DCA and calibration curve showed a good prediction efficacy. the C-index of OS and RFS were 0.72 and 0.68, respectively, which were also verified in the validation set (OS, 0.71; RFS, 0.65).

Conclusions A good prediction model was developed and validated to assess the prognoses of CRLM patients. Systematic chemotherapy and R0 resection could benefit patients' survival and improve prognosis.

Keywords Colorectal liver metastasis, Surgery, Chemotherapy, Prognosis

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Introduction

Colorectal cancer (CRC) is one of the most common malignant tumors worldwide, with the third highest incidence rate and the second highest mortality rate [1]. Although the current level of treatment has improved significantly since before, approximately 50% of CRC patients still develop liver metastases annually. Of these, 20–34% of CRC patients have synchronous liver metastases [2, 3]. The median survival for this proportion of patients without treatment was only 6.9 months, with a 5-year survival rate of less than 5% [4, 5]. Therefore, the insidious and the low survival rate of colorectal liver metastases (CRLM) remains a challenge that plagues people.

In the last decade, (neo) adjuvant chemotherapy with FOLFOX and CAPEOX regimens could effectively delay tumor progression and improve patients' prognoses. A meta-analysis of randomized controlled trials (RCTs) also showed that CAPEOX and FOLFOX have similar benefits for metastatic CRC patients [6]. The phase III EORTC 40,983 study evaluated patients with resectable CRLM treated with perioperative FOLFOX (6 cycles preoperatively and 6 cycles postoperatively). There was an absolute improvement for 3-year progression free survival (PFS) in both groups, with increases of 8.1% ($P=0.041$) and 9.2% ($P=0.025$) [7]. However, surgery remains the most effective measure for these patients. Radical surgical resection of CRLM patients significantly improves median overall survival (OS), with 5-year survival rates of 25–50% [8]. Related studies have shown that synchronized surgical resection has a better prognosis than delayed resection, while not increasing the incidence of postoperative complications [9]. Furthermore, radiofrequency ablation (RFA)-based ablation is widely recognized as the standard of care for the treatment of difficult-to-resect small-sized CRLMs (≤3 cm) [10, 11]. Imai et al.'s study found that surgery combined with ablation for CRLM was equivalent to surgical radical resection, with 5-year OS, 57% vs. 61%, $P=0.649$; 5-year RFS, 19% vs. 17%, $P=0.865$ [12]. Even then, recurrence occurs in about 50–75% of patients within two years after resection [8, 13]. Therefore, the whole perioperative period needs to be emphasized for patients with CRLM. There is an urgent to grasp the therapeutic window.

In this study, we retrospectively reported the data of single-center CRLM patients who received systematic chemotherapy combined with surgical resection with or without intraoperative RFA. The treatment characteristiccs of these patients were analyzed in detail, in order to explore the factors affecting patients' prognosis, study the correlation between CRLM and clinical treatment, which informed treatment decisions, risk stratification, patient selection.

Methods

This was a single-center, retrospective cohort study that included CRLM patients who underwent systematic chemotherapy combined with simultaneous surgical resection between December 2009 and December 2020 at the Cancer Hospital of the Chinese Academy of Medical Sciences. All data were divided into training and validation sets at a ratio of 7:3. It could strike a good balance between computational resource consumption and model assessment accuracy, which allows the model to be trained in a reasonable amount of time and provides more accurate performance evaluation results. The study was conducted in accordance with the Declaration of Helsinki (revised 2013), in compliance with the Transparent Reporting of Individual Predictive or Diagnostic Multivariate Predictive Models (TRIPOD) guidelines (supplementary TRIPOD Checklist), and was approved by the Ethics Committee of the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College. Individual written informed consent for this retrospective analysis was waived. All patients' identifying information was removed.

Inclusion and exclusion criteria

Patients were included if they met the following criteria: (1) all patients were diagnosed with CRLM; (2) patients were treated with systematic chemotherapy (3) patients underwent synchronous surgical resection; (4) patients' general status was able to tolerate the surgery [Eastern Cooperative Oncology Group performance status (EOCG-PS) ≤ 1, residual liver function (FLR) > 30% in patients without cirrhosis, FLR > 40% in patients with cirrhosis, Child-Pugh of A-B]. The following criteria will be excluded: (1) patients with non-synchronous CRLM; (2) patients with CRLM who are therapeutically unable to achieve no evidence of disease (NED); (3) Metastases outside the liver; (4) Insufficient data.

Treatment

Treatment for CRLM patients was discussed by a multidisciplinary tumor (MDT) group involving hepatobiliary and/or oncologic surgeons, medical oncologists, radiation oncologists, nuclear medicine physicians, gastroenterologists, and pathologists [14]. Imaging included enhanced computed tomography (CT), enhanced magnetic resonance imaging (MRI), 18 F-fluorodeoxyglucose (18 F-FDG) positron emission tomography (PET)-CT, and colonoscopy with tissue biopsy. Data collection included preoperative baseline indexes, inflammatory indexes, liver function indexes, tumor indexes, and treatment protocols. NLR was defined as neutrophil count (10^9/L)/lymphocyte count (10^9/L). PLR was defined as

platelet count (10^9/L)/lymphocyte count (10^9/L). SII was defined as platelet count (10^9/L) × neutrophil count (10^9/L)/lymphocyte count (10^9/L). The American Society of Anesthesiologists (ASA) refers to the grading of anesthesiologists based on the patient's physical condition and risk of surgery. The clinical risk score (CRS) score is an evaluation for the risk of recurrence in patients with CRLM after surgery [15]. It includes five parameters: (1) primary tumor lymph node status; (2) synchronous liver metastases or disease-free survival time ≤ 12 months; (3) number of liver metastases > 1; (4) preoperative level of carcinoembryonic antigen (CEA) > 200 ng/ml; and (5) maximum diameter of metastatic tumor > 5 cm. Each item is scored out of 1, with 0–2 being a low CRS score and 3–5 being a high CRS score. Higher CRS scores are associated with a greater risk of postoperative recurrence and benefit from perioperative chemotherapy. The details are shown in supplementary Table 1. The specific regimen of systematic chemotherapy is finalized according to the MDT discussion and mainly includes FOLFOX, CAPEOX, FOLFIRI with or without bevacizumab or cetuximab. The indications for neoadjuvant chemotherapy: patients with colorectal cancer liver metastases that can achieve NED status without bleeding, obstruction, or perforation of the primary focus; patients with liver metastases that are technically difficult to resect; patients with poor prognostic factors [e.g., clinical risk score (CRS) ≥ 3]; patients with large size of liver metastases; patients with large number of metastatic foci; patients with suspected metastasis in lymph nodes of the primary foci. Patients who have not received chemotherapy after resection of the primary site or who have completed chemotherapy 12 months before detection of liver metastases; patients without chemotherapy after primary resection; patients with liver metastases that have been treated with chemotherapy 12 months prior to discovery of liver metastases. Indications for adjuvant chemotherapy: patients with resected liver metastases, especially those who have not undergone preoperative chemotherapy; patients with CRLM who are unable to achieve NED status. Neoadjuvant chemotherapy is administered 2–3 months before surgery and adjuvant chemotherapy is followed for 2–3 months after surgery. For small tumors (less than 3 cm) in deeper locations that are difficult to resect by surgical R0, intraoperative RFA with ultrasound localization was performed. Although this subset of patients could not be clearly defined by R0 resection, we considered them to have achieved NED status, which also applies to the CRS score. The RITA 1500 system (USA) was used to produce local destruction of the tumor and surrounding liver tissue by heating. The ablation power was gradually started to increase from 60 W to 180 W. The electrode needle was selected as XL anchor needle. The microwave instrument was a KY-2000 microwave ablator. The duration of ablation depends on the size of the target lesion and the ablation cycle effect. R0 resection implies that the tumor was completely removed during surgery and the resection margins were negative when viewed under a microscope. All patients achieved NED status after treatment, i.e., no evidence of tumor presence by current investigations (pathology, imaging, molecular biology, etc.).

Follow up

All patients were followed up until 04, 2023. OS was defined as the time interval from the date of the patient's surgery to the date of the patient's death or the cutoff date for follow-up. RFS was defined as the time interval from the date of the patient's surgery to the date of the patient's development of a new lesion.

Statistical analysis

The dichotomous variables were recorded as number plus percentage. The continuous variables were described as median and interquartile range (IQR) or 95% confident intervals (CIs). X^2 test, independent samples t-test, Pearson correlation analysis, Cox regression, Kaplan-Meier (KM) survival curves and Log-rank analysis were used in this study. Factors with p-values < 0.10 in univariate Cox regression were included in multivariate regression. Multivariate Cox was analyzed using stepwise regression. Stepwise regression is able to take into account the effects of multiple factors on the timing of events while not being constrained by the assumption of temporal proportionality, which makes it more applicable to data from real-world studies. P-value of < 0.05 was regarded as significant. R packages include survivalROC, survival, survminer, ggplot2, ggDCA, nomogramFormula, caret, rms, MASS, pROC. all analyses were performed using IBM SPSS Statistics 25 and R version 4.3.2.

Results

Baseline and characteristics of patients

A total of 389 CRLM patients were included, 273 in the training set and 116 in the validation set (Fig. 1). As shown in Table 1, there was no difference between the two datasets at baseline. Univariate Cox analysis showed that hospital day, R0 resection, RFA, white blood cell count, neutrophil count, lymphocyte, hemoglobin, platelets, D-Dimer, NLR, only neoadjuvant chemotherapy, only adjuvant chemotherapy, and CRS scores may be the factors affecting patients' prognosis. Multivariate Cox analysis suggested that hospital day, R0 resection, RFA, neoadjuvant chemotherapy, and CRS score were independent risk factors for OS. R0 resection, RFA, and CRS score were independent risk factors for RFS (Table 2).

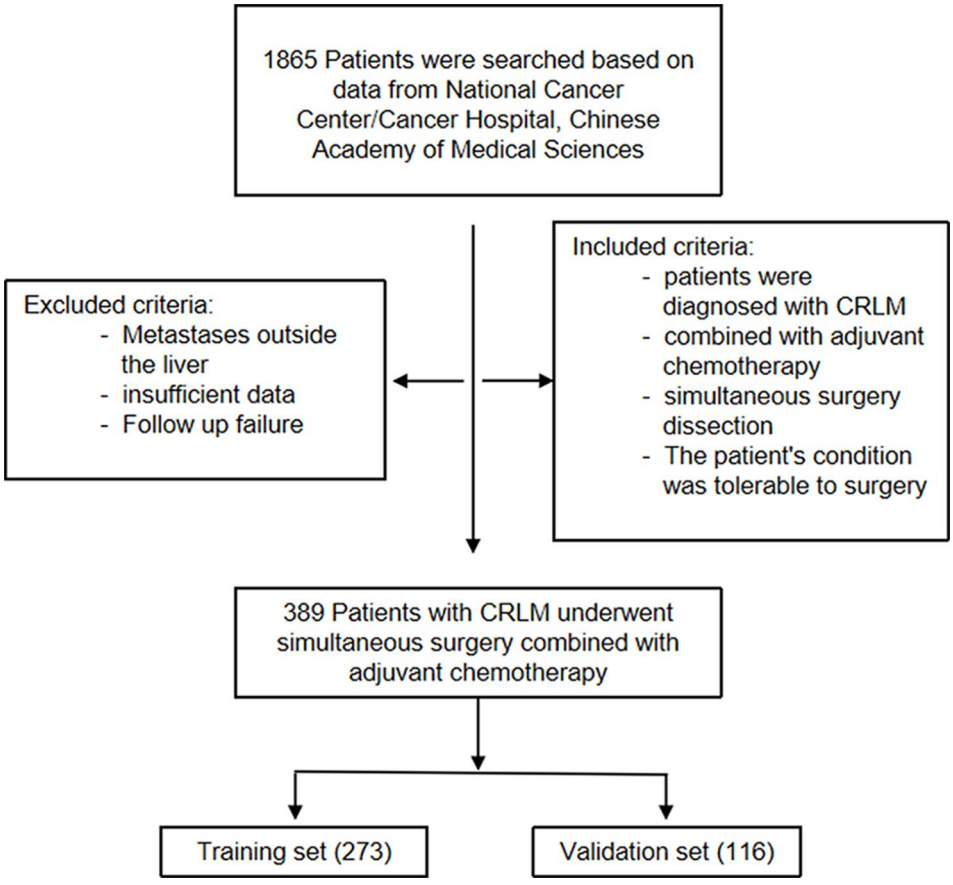

Fig. 1 The flow chart of eligible CRLM patients

The prognosis analysis for OS

Factors that predicted OS meaningfully were displayed in Fig. 2A. These factors were used to construct the normogram model of OS (Fig. 2B). According to the model, the areas under receiver operating characteristic (ROC) curves of 1, 3, and 5 years were 0.795, 0.759, and 0.771, respectively (Fig. 2C). The calibration curves showed that the predicted survival curves at 1, 3, and 5 years were similar to the actual survival curves and not significantly different (supplementary Fig. 1A, 1 C, and 1E). Decision curve analysis (DCA) was used to validate the stability of the model. As shown in Fig. 2E, the DCA of 1, 3, and 5 years were all above the two reference lines, indicating good predictive efficacy of the model [C-index: 0.72 (0.66, 0.77)]. Similarly, the validation set was used for model valuation. As shown in Fig. 2D, the ROC curves of 1, 3, and 5 years are 0.881, 0.739, and 0.745, respectively. The calibration curves of 1, 3, and 5 years are at the diagonal level in supplementary Fig. 1B, 1D, and 1 F. The DCA of 1, 3, and 5 years are displayed in Fig. 2F, and the results similarly show that the model has a good stability and a superior prediction effect in the validation set [C-index: 0.71 (0.63, 0.79)].

The prognosis analysis for RFS

Factors that predicted RFS meaningfully were displayed in Fig. 3A, and these factors were used to construct the normo-gram model of RFS (Fig. 3B). According to the model, the areas under ROC curves of 1, 3, and 5 years were 0.725, 0.746, and 0.736, respectively (Fig. 3C). The calibration curves showed that the predicted survival curves at 1, 3, and 5 years were similar to the actual survival curves and not significantly different (supplementary Fig. 2A, 2 C, and 2E). The DCA were used to assess the stability of the model. As shown in Fig. 3E, the DCA of 1, 3, and 5 years were all above the two reference lines, indicating good predictive efficacy of the model [C-index: 0.68 (0.62, 0.73)]. Similarly, the evaluation was performed using the validation set. As shown in Fig. 3D, the ROC curves of 1, 3, and 5 years were 0.711, 0.691, and 0.824, respectively. The calibration curves of 1, 3, and 5 years were displayed in supplementary Fig. 2B, 2D, and 2 F. The DCA was displayed in Fig. 3F, and the results similarly showed the model's good predictive efficacy in the validation set [C-index: 0.65 (0.59, 0.70)].

Table 1 The baseline characteristics of CRLM patients

Factors	Train Set (*n* = 273)	Validation Set (*n* = 116)	*P*-values
Gender (Female: Male)	177: 96	73:43	0.720
Age, years (median, IQR)	58.00 (51.00, 65.00)	59.00 (52.25, 63.75)	0.828
BMI, Kg/m^2 (median, IQR)	23.83 (22.05, 26.01)	23.63 (21.89, 26.22)	0.906
Hospital day, day (median, IQR)	10.00 (9.00, 14.00)	10.00 (9.00, 13.00)	0.608
R0 resection, (%)	205 (75.1%)	93 (80.2%)	0.279
RFA, (%)	27 (9.9%)	10 (8.6%)	0.696
CA19-9, U/ml (median, IQR)	19.11 (8.78, 45.00)	19.73 (9.45, 43.87)	0.478
CEA, ng/L (median, IQR)	8.89 (3.90, 31.46)	9.17 (3.82, 32.31)	0.538
WBC, 10^9/L (median, IQR)	5.83 (4.76, 7.20)	6.09 (5.08, 7.56)	0.536
NEUT, 10^9/L (median, IQR)	3.45 (2.69, 4.50)	3.61 (2.84, 4.96)	0.212
LYMPH, 10^9/L (median, IQR)	1.76 (1.40, 2.17)	1.69 (1.33, 2.00)	0.116
HGB, g/L (median, IQR)	133.00 (119.00, 145.00)	134.50 (119.25, 146.00)	0.608
PLT, 10^9/L (median, IQR)	225.00 (179.50, 276.00)	220.50 (170.00, 278.00)	0.823
ALT, U/L (median, IQR)	19.00 (13.00, 29.50)	18.50 (13.00, 26.75)	0.840
AST, U/L (median, IQR)	22.00 (17.00, 28.00)	22.00 (17.00, 29.75)	0.804
TBIL, μmol/L (median, IQR)	9.30 (7.00, 12.20)	9.35 (6.70, 12.40)	0.968
DBIL, μmol/L (median, IQR)	3.50 (2.80, 4.55)	3.60 (2.70, 4.68)	0.883
ALB, μmol/L (median, IQR)	42.20 (39.60, 44.50)	42.95 (40.23, 45.00)	0.381
D-Dimer, mg/L (median, IQR)	0.39 (0.24, 0.75)	0.44 (0.27, 0.79)	0.558
NLR	1.94 (1.45, 2.82)	2.07 (1.67, 3.08)	0.473
PLR	125.33 (96.90, 158.22)	128.83 (95.61, 175.46)	0.555
SII	411.46 (285.78, 664.90)	452.96 (317.60, 724.90)	0.993
Chemotherapy, (%)			
Full-course	117 (42.9%)	49 (42.2%)	0.911
Only neoadjuvant	64 (23.4%)	26 (22.4%)	0.826
Only adjuvant	92 (33.7%)	41 (35.3%)	0.754
ASA Score, (%)			0.629
1	9 (3.3%)	4 (3.4%)	
2	226 (82.8%)	100 (86.2%)	
3	38 (13.9%)	12 (10.3%)	
CRS Score, (%)			0.146
1	27 (9.9%)	17 (14.7%)	
2	105 (38.5%)	39 (33.6%)	
3	122 (44.7%)	48 (41.4%)	
4	15 (5.5%)	12 (10.3%)	
5	4 (1.5%)	0 (0%)	
RFS, months (median, IQR)	10.67 (4.14, 23.34)	9.90 (4.27, 19.78)	0.760
Recurrence, (%)	191 (70.0%)	87 (75.0%)	0.314
OS, months (median, IQR)	34.60 (24.54, 51,19)	34.72 (23.70, 49.03)	0.949
Death, (%)	99 (36.3%)	43 (37.1%)	0.880

Abbreviation: BMI, Body mass index; RFA, Radiofrequency ablation; CEA, Carcinoembryonic antigen; WBC, White blood cell; NEUT, Neutrophil; LYMPH, Lymphocyte; HGB, Hemoglobin; PLT, platelet; ALT, Alanine aminotransaminase; AST, aspartate aminotransferase; TBIL, Total bilirubin; DBIL, Direct bilirubin; ALB, Albumin; NLR, Neutrophil to lymphocyte ratio; PLR, Platelet to lymphocyte ratio; SII, Systemic immune inflammatory index; ASA, American society of anesthesiologists; CRS, Clinical risk score; CRLM, Colorectal liver metastasis; RFS, Recurrence free survival; OS, Overall survival; IQR, Interquartile range

Follow-up and outcome

All patients were followed up until 04, 2023. A total of 142 patients experienced death and median OS was 70.20 months (95% CIs: 57.73, 82.68). 278 patients experienced recurrence and median RFS was 11.70 months (95% CIs: 9.75, 13.65). In training set, 1, 3, and 5-year survival rate of OS was 97.38%, 71.18%, and 54.56% as well as RFS was 52.57%, 22.65%, and 21.12%, respectively (Table 3). In addition, as shown in Fig. 4A, adjuvant chemotherapy and full-course chemotherapy had significant superiority over neoadjuvant chemotherapy for OS ($P < 0.001$). Although there was no significant difference among the three chemotherapies for RFS, the risk of recurrence was reduced with adjuvant chemotherapy and full-course chemotherapy compared with neoadjuvant chemotherapy (Fig. 4B). Details of surgery and postoperative complications were recorded in supplementary Table 2. Of these, 84 (44.2%) patients were resected by

Table 2 The univariable and multivariable Cox-regression analysis of OS and RFS for CRLM patients

Factors	OS				RFS			
	Univariable Cox-regression analysis, HR (95% CI)	*P*- values	Multivariable Cox-regression analysis, HR (95% CI)	*P*- values	Univariable Cox-regression analysis, HR (95% CI)	*P*- values	Multivariable Cox-regression analysis, HR (95% CI)	*P*- values
Gender (F: M)	0.980 (0.654, 1.471)	0.924	-	-	1.240 (0.917, 1.675)		-	-
Age	0.999 (0.979, 1.021)	0.962	-	-	0.993 (0.978, 1.008)	0.381	-	-
BMI	1.032 (0.963, 1.106)	0.368	-	-	1.010 (0.961, 1.062)	0.687	-	-
Hospital day	1.054 (1.023, 1.085)	**0.001**	1.050 (1.018, 1.084)	0.002	1.029 (1.006, 1.051)	**0.012**	-	0.054
R0 resection	0.454 (0.302, 0.683)	**<0.001**	0.620 (0.406, 0.948)	0.027	0.531 (0.388, 0.727)	**<0.001**	0.667 (0.481, 0.926)	0.016
RFA	3.215 (1.962, 5.269)	**<0.001**	2.326 (1.386, 3.905)	0.001	2.496 (1.631, 3.819)	**<0.001**	2.160 (1.399, 3.337)	0.001
CA19-9	1.000 (1.000, 1.001)	0.852	-	-	1.000 (1.000, 1.000)	0.541	-	-
CEA	1.001 (0.999, 1.002)	0.336	-	-	1.000 (0.999, 1.001)	0.500	-	-
WBC	1.114 (1.024, 1.212)	**0.012**	-	0.077	0.980 (0.909, 1.057)	0.600	-	-
NEUT	1.116 (1.028, 1.211)	**0.009**	-	0.069	1.008 (0.928, 1.094)	0.851	-	-
LYMPH	0.999 (0.772, 1.293)	0.996	-	-	0.790 (0.632, 0.988)	**0.038**	-	0.056
HGB	1.011 (1.000, 1.022)	**0.043**	-	0.305	1.009 (1.002, 1.017)	**0.013**	-	0.112
PLT	1.000 (0.997, 1.002)	0.723	-	-	0.998 (0.996, 1.000)	**0.055**	-	0.285
ALT	0.994 (0.983, 1.006)	0.325	-	-	1.004 (0.999, 1.010)	0.113	-	-
AST	0.995 (0.981, 1.009)	0.488	-	-	1.004 (0.995, 1.013)	0.445	-	-
TBIL	0.997 (0.965, 1.031)	0.868	-	-	1.007 (0.988, 1.026)	0.495	-	-
DBIL	0.983 (0.885, 1.093)	0.755	-	-	1.034 (0.967, 1.107)	0.327	-	-
ALB	1.002 (0.949, 1.058)	0.945	-	-	1.001 (0.963, 1.040)	0.974	-	-
D-Dimer	1.064 (0.859, 1.319)	0.570	-	-	1.117 (0.980, 1.275)	**0.098**	-	0.098
NLR	1.031 (0.996, 1.068)	**0.087**	-	0.229	1.014 (0.982, 1.047)	0.390	-	-
PLR	1.001 (0.999, 1.002)	0.529	-	-	1.000 (0.999, 1.002)	0.687	-	-
SII	1.000 (1.000, 1.000)	0.162	-	-	1.000 (1.000, 1.000)	0.707	-	-
Chemotherapy								
Full-course	0.744 (0.494, 1.121)	0.157	-	-	0.969 (0.726, 1.294)	0.832	-	-
Only neoadjuvant	3.153 (2.093, 4.751)	**<0.001**	2.790 (1.828, 4.257)	<0.001	1.494 (1.083, 2.061)	**0.014**	-	0.103
Only adjuvant	0.496 (0.313, 0.787)	**0.003**	-	0.953	0.757 (0.559, 1.027)	**0.073**	-	0.709
ASA Score	0.873 (0.530, 1.440)	0.595	-	-	1.068 (0.752, 1.519)	0.712	-	-
CRS Score	1.515 (1.209, 1.898)	**<0.001**	1.424 (1.117, 1.815)	0.004	1.498 (1.282, 1.750)	**<0.001**	1.444 (1.228, 1.698)	<0.001

Abbreviation: BMI, Body mass index; RFA, Radiofrequency ablation; CEA, Carcinoembryonic antigen; WBC, White blood cell; NEUT, Neutrophil; LYMPH, Lymphocyte; HGB, Hemoglobin; PLT, platelet; ALT, Alanine aminotransaminase; AST, aspartate aminotransferase; TBIL, Total bilirubin; DBIL, Direct bilirubin; ALB, Albumin; NLR, Neutrophil to lymphocyte ratio; PLR, Platelet to lymphocyte ratio; SII, Systemic immune inflammatory index; ASA, American society of anesthesiologists; CRS, Clinical risk score; CRLM, Colorectal liver metastasis; RFS, Recurrence free survival; OS, Overall survival; HR, Hazard ratio; CI, Confidence interval

laparoscopic surgery. The number of patients with primary lesions originating from colon and rectum were 223 and 166, respectively. Postoperatively, anastomotic leakage occurred in 6 patients, hemorrhage in 21, and pleural and abdominal fluid in 33. Except for the location of liver metastases and the intraoperative blood transfusion, other factors were significantly correlated with hospital day but weakly ($P<0.05$, supplementary Table 3). Based on molecular level, supplementary Table 4 shows 221 patients with Kras mutations. The results analyzed by KM suggested that patients with Kras mutations had a poorer prognosis compared with those without mutations ($P<0.05$, supplementary Fig. 5). As shown in supplementary Figs. 3 and 4, the optimal cut-off values were 66 and 51, respectively, and the population was divided into high-risk and low-risk groups based on the cut-off values. The KM curves showed that OS was significantly higher in the low-risk group compared with the high-risk group (Fig. 4C, $P<0.0001$; Fig. 4E, $P=0.00063$). Similarly, there was a significant difference in RFS between the two groups (Fig. 4D, $P<0.0001$; Fig. 4F, $P=0.00017$).

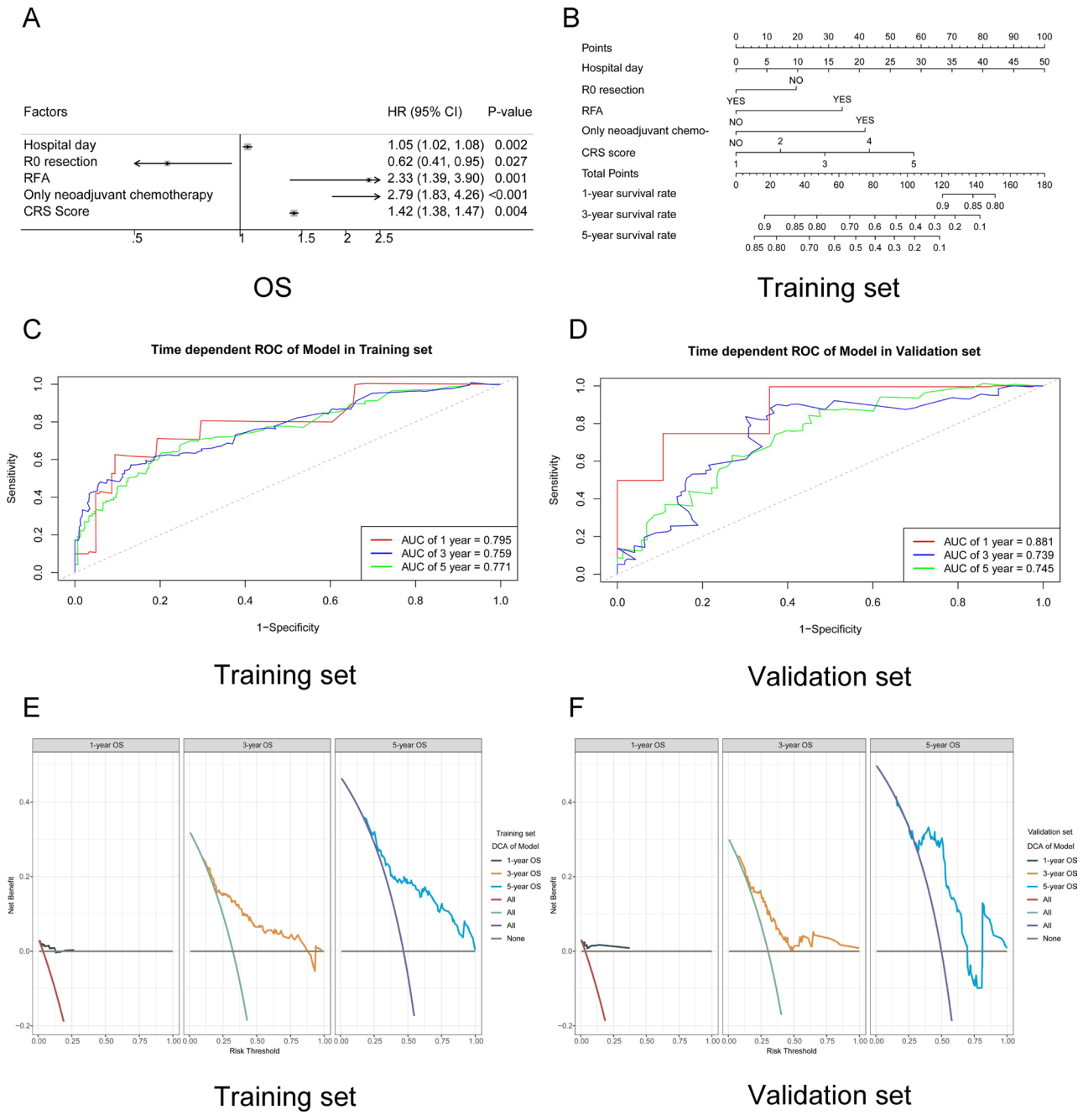

Fig. 2 The construction of model for OS between training and validation set. (**A**), The forest plot of OS based on multivariable Cox regression analysis. (**B**), The normo-gram of OS in training set. The ROC curve of OS between training (**C**) and validation set (**D**). The DCA curve of OS between training (**E**) and validation set (**F**)

Discussion

This is a single-center, retrospective cohort study. The results showed independent risk factors that could effectively predict the prognosis of patients with CRLM. Based on these factors, a clinical prognostic model was constructed. Compared with the high-risk group, both OS and RFS were significantly longer in the low-risk group ($P < 0.001$). The stability and good predictive ability of the model were assessed by ROC curve, calibration curve and DCA. By the time of follow-up, a total of 142 patients suffered death and 278 patients experienced recurrence. The median OS and RFS were 70.20 months and 11.70 months, respectively. In addition, adjuvant chemotherapy and full-course chemotherapy have obvious advantages compared with single neoadjuvant chemotherapy, which significantly improved the prognosis and prolonged the survival of CRLM patients ($P < 0.001$). The model is based on the CRS score and combined with fewer factors (e.g.,

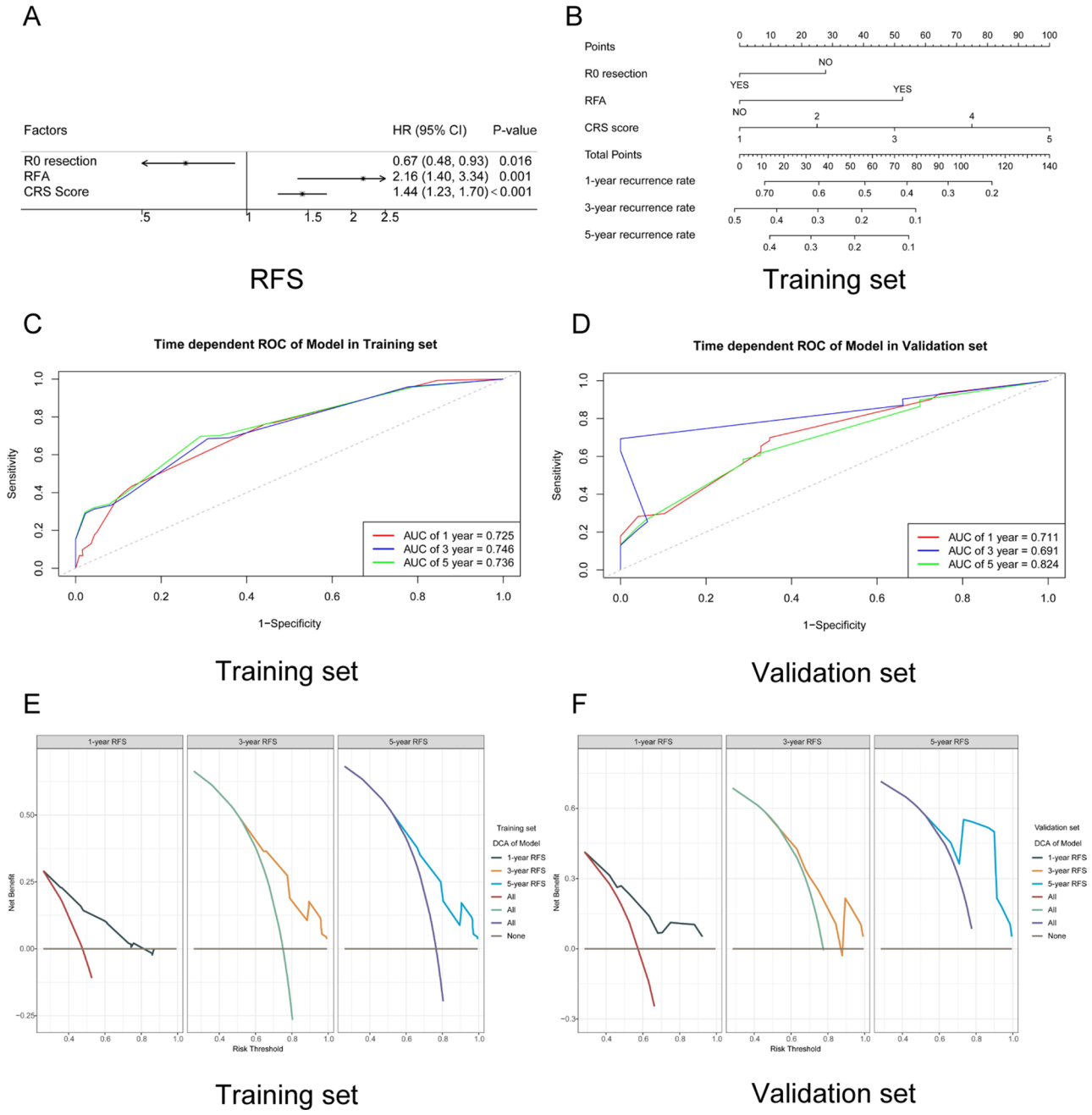

Fig. 3 The construction of model for RFS between training and validation set. (**A**), The forest plot of RFS based on multivariable Cox regression analysis. (**B**), The normo-gram of RFS in training set. The ROC curve of RFS between training (**C**) and validation set (**D**). The DCA curve of RFS between training (**E**) and validation set (**F**)

hospitalization days, R0 resection, RFA, chemotherapy), which is simple, practical, and easy to apply clinically, and can be accepted by most clinicians. At the same time, the model's excellent predictive efficacy can guide clinical work and bring benefits to patients.

Along with the rising incidence of CRLM, related studies have been increasingly conducted both at home and abroad to explore potential pathogenesis and good treatment. Mechanistically, CRLM is thought to be the result of some CRC cells gaining the ability to evade through genetic and molecular alterations as well as dysregulation of signaling pathways, which leads to tumorigenesis, progression, and invasion by altering morphology and invading into neighboring tissues, endocytosis, surviving in the circulation, exocytosis, and finally colonizing the liver [16–18]. The high degree of inter- and intratumor variability highlights the complex molecular biology of tumors, which in turn affects the patient's survival

Table 3 The characteristics of prognosis for CRLM patients

Factors	1-year rate	3-year rate	5-year rate
OS (Training set), %	97.38%	71.18%	54.56%
OS (Validation set), %	97.52%	72.93%	51.56%
RFS (Training set), %	52.57%	22.65%	21.12%
RFS (Validation set), %	42.78%	20.96%	18.26%
Median OS time, months (95% CIs)	70.20 (57.73, 82.68)		
Median RFS time, months (95% CIs)	11.70 (9.75, 13.65)		

Abbreviation: CRLM, Colorectal liver metastasis; RFS, Recurrence free survival; OS, Overall survival; IQR, Interquartile range

in response to therapy. Even in the presence of identified and druggable genetic alterations, the antitumor activity of the corresponding matched-target therapy remains unpredictable [19, 20]. The complexity and genotypic heterogeneity of CRLM means that we need to implement more effective and individualized treatments for each patient.

In this study, a prognostic model was constructed through the results of multivariate analysis to comprehensively and multidimensionally predict the prognosis of CRLM patients [15]. First, CRS score was considered as a predictor of recurrence after CRLM, which contained tumor status, level of CEA, and survival. In addition, systemic chemotherapy plays a pivotal role in patients with CRLM. Data from studies in recent decades have shown that patients with metastatic CRC treated with systemic chemotherapy have extended OS duration to nearly 20 months [21, 22]. Mitry et al. conducted a meta-analysis of 278 patients from the ENG trial and FFCD-ACHBTH-ARUC trial. The results found that chemotherapy was an independent prognostic risk factor for patients compared to surgery along (PFS, $P=0.036$; OS, $P=0.046$) [23]. In this study, neoadjuvant chemotherapy alone for patients with CRLM has a significantly worse prognosis compared to patients treated with full-course chemotherapy and adjuvant chemotherapy. The EORTC 40,983 study (EPOC study) showed that patients who received preoperative and postoperative FOLFOX chemotherapy had an improved 3-year PFS rate compared to patients who received surgery only [24]. On the one hand, neoadjuvant chemotherapy can control microscopic metastatic lesions at an early stage, assess tumor response to chemotherapy, and provide patients with a "tumor biology waiting window". However, early studies have shown that although patients with CRLM undergoing neoadjuvant chemotherapy achieved complete imaging remission on CT, most liver metastases were still found to have viable tumor cells on pathology [25]. Furthermore, approximately 25% of patients progressed during the period between neoadjuvant chemotherapy discontinuation and waiting for surgery. One study reported that the median postoperative survival of patients who progressed at ≤ 8 weeks of preoperative discontinuation was no more than 2 years [26]. In this study, patients had a poorer prognosis for patients who underwent preoperative neoadjuvant chemotherapy only for the presence of postoperative high-risk factors for recurrence (positive lymph nodes, more number of liver metastases, a larger diameter of the tumor, and a higher preoperative level of CEA) without the targeted adoption of adjuvant chemotherapy postoperatively. On the other hand, postoperative adjuvant chemotherapy can help eliminate residual microscopic metastases and reduce the risk of recurrence. Several studies have shown that patients who received postoperative adjuvant chemotherapy had significantly improved 5-year survival compared with those who did not receive adjuvant chemotherapy. Therefore, full-course chemotherapy or adjuvant chemotherapy is necessary for synchronous CRLM. However, the neurotoxicity of oxaliplatin should also be cautioned to avoid unnecessary damage to patients due to excessive treatment. Secondly, gene mutant status should also be taken into account [27]. Kras mutations had a poorer prognosis compared with those without mutations in the study ($P<0.05$). Finally, surgery is an extremely important part of the treatment for patients with CRLM. After MDT discussion, patients with CRLM should be aggressively treated with surgical resection if there is an operable opportunity. RFA is desirable for patients who cannot achieve R0 resection. However, in this study, we found that intraoperative RFA was an independent risk factor affecting patients' prognosis, and patients with CRLM without intraoperative ablation had significantly increased OS and RFS compared with those with ablation. The reason may be that patients without RFA have had resectable disease, thus inherently leading to better OS and RFS. RFA is a remedy for CRLM patients who cannot achieve R0 resection. Even though it is possible to achieve NED status with RFA guided by intraoperative ultrasound, it still has a worse prognosis than surgical R0 resection, which may overlook key confounding factors, such as tumor burden and resectability. In a meta-analysis of 20 high-quality studies, Martino et al. found that surgical resection significantly reduced the rate of tumor progression and improved patient OS and PFS compared to local ablative therapy [28]. RFA has been reported in several studies to be inferior to hepatic resection in terms of both local control and patient survival rates in the treatment of CRLM [29–31]. Higher rates of local control failure (up to 20–40%) have also been a major concern for RFA [32]. Patients undergoing hepatic resection combined with ablation are more likely to experience recurrence [11, 12]. The reason may be that intraoperative RFA may cause tumor hyper-progression as well as the release of tumor cells into the bloodstream or surrounding tissues during ablation, resulting in the formation of micro-metastases or microsatellite lesions. Finally, the

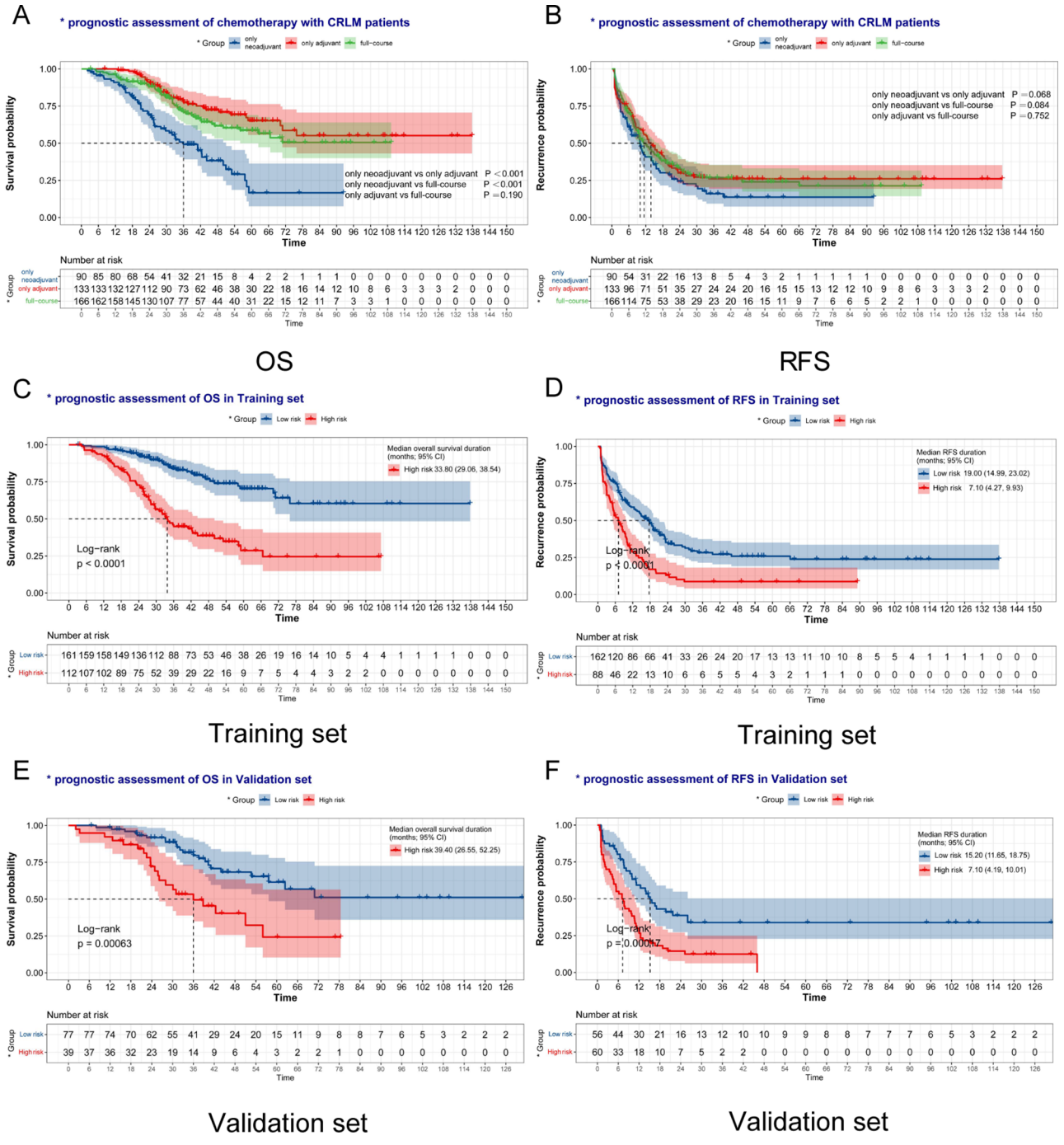

Fig. 4 The prognostic assessment for CRLM patients. (**A**), The KM curve of OS for CRLM patients based on chemotherapy. (**B**), The KM curve of RFS for CRLM patients based on chemotherapy. (**C**), The KM curve of OS in training set. (**D**), The KM curve of RFS in training set. (**E**), The KM curve of OS in validation set. (**F**), The KM curve of RFS in validation set

hospitalization was also associated with OS in patients with CRLM. In this study, the length of hospitalization was significantly correlated with the patients' surgery and postoperative complications although the correlation was weak. The length of hospitalization could be empirically understood to be related to the patient's fundamentals and the incidence of postoperative complications. The results of the study suggest that patients with a longer hospitalization have a poorer prognosis compared to a shorter one. Therefore, it is significant to prevent and minimize the incidence of postoperative complications through intraoperative meticulous operation and postoperative strengthening of recovery management.

The following limitations should also be noted in this study. Firstly, this was a single-center observable study. Secondly, the detailed type of chemotherapy and treatment regimens for the patients are lacking. Systematic chemotherapy was not restricted to a specific regimen and dose of medication, which may favor the applicability of the conclusions, but accurate dosing is more conducive to the stability of the conclusions. Thirdly, the study includes various blood routine and biochemical indicators, which likely have limited impact on prognosis. Including a high number of such variables, especially given the relatively small sample size, may reduce the statistical power of the analysis. Additionally, the study lacks essential indicators of genetic status (e.g., braf and MMR statuses) as well as primary tumor sites, which are crucial for accurately assessing patient prognosis and should also be considered to improve the model's relevance and accuracy. Finally, characteristics of tumors are variable, and CRS scores were used to minimize discrepancy. We provide single-center, retrospective data aimed at improving progress in the field from the perspective of current treatments.

Conclusion

In this study, we concluded that hospital days, R0 resection, intraoperative RFA, only neoadjuvant chemotherapy, and CRS score were independent prognostic factors for OS in patients with CRLM. R0 resection, intraoperative RFA, and CRS score were independent prognostic factors for RFS in patients with CRLM. A prediction model was constructed and able to predict the prognosis of CRLM patients well. Preoperative neoadjuvant chemotherapy, surgical resection with or without intraoperative ablation therapy under ultrasound localization, and postoperative adjuvant chemotherapy as well as postoperative strengthening of rehabilitation management to prevent and reduce the occurrence of postoperative complications could significantly improve the prognosis of CRLM patients. It is hopeful that this study can provide some experience for clinical practice. Together with the trend of colorectal liver metastases, the complexity of tumor treatment modalities and the diversity of drugs also need to be more attention. More prospective studies are warranted to advance this field in the future.

Abbreviations

CRC	Colorectal cancer
CRLM	Colorectal liver metastases
RCTs	Randomized controlled trials
PFS	Progression free survival
RFS	Recurrence-free survival
OS	Overall survival
RFA	Radiofrequency ablation
TRIPOD	Transparent reporting of individual predictive or diagnostic multivariate predictive models
EOCG-PS	Eastern cooperative oncology group performance status
FLR	Residual liver function
NED	No evidence of disease
MDT	Multidisciplinary tumor
CT	Computed tomography
MRI	Magnetic resonance imaging
18F-FDG	18 F-fluorodeoxyglucose
PET	Positron emission tomography
NLR	Ratio of neutrophil count /lymphocyte count
PLR	Ratio of platelet count /lymphocyte count
SII	Ratio of platelet count × neutrophil count /lymphocyte count
ASA	American Society of Anesthesiologists
CEA	Carcinoembryonic antigen
IQR	Interquartile range
KM	Kaplan-Meier

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Author contributions

JSX and JQC were responsible for designing the study. JSX, Maimaitiming N, BLZ, BWX, XY, ZH, XC and HZ primarily performed the quality assessment as well as supervision. JSX analyzed, interpreted the data, and drafted the manuscript. JQC revised the manuscript. All data and methods were included in this article. All authors have read and approved the final version of the manuscript.

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Data availability

The original data presented in this study are included in the article or supplement materials, additional information can be obtained from the corresponding authors.

Declarations

Ethics approval and consent to participate

The study protocol, including treatment protocol and data collection, was in accordance with the Declaration of the Helsinki Association of World Medical Ethics Guidelines. Approved by the Research Ethics Committee of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College and individual written informed consent for this retrospective analysis was waived.

Competing interests

The authors declare no competing interests.

Conflict of interest

There are no conflicts of interest to declare.

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