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ORIGINAL ARTICLE

A Low Neutrophil to Lymphocyte Ratio Before Preoperative Chemotherapy Predicts Good Outcomes After the Resection of Colorectal Liver Metastases

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Abstract

Background The neutrophil to lymphocyte ratio (NLR) is a marker of inflammation and is associated with poor outcomes. We aimed to evaluate the role of the pretreatment NLR in predicting the outcomes after preoperative chemotherapy in patients with colorectal liver metastases (CRLM).

Methods A retrospective review was performed for 183 patients with CRLM. The NLR was measured before chemotherapy, and a receiver operating characteristic (ROC) curve was used to estimate the cutoff value. Logistic regressions were applied to analyze potential predictors of the pathological response. The Cox proportional hazard method was used to analyze survival.

Results The pre-chemotherapy NLR was 2.4 ± 1.1, whereas the post-chemotherapy NLR was 2.1 ± 1.6 ($p < 0.001$). The pretreatment NLR of 2.3 was a significant predictive marker for the pathological response. The pathological response rates were 67.1% in the patients with an NLR ≤ 2.3 and 48.1% in patients with an NLR > 2.3 ($p = 0.01$). Multivariate analysis revealed that the factors independently associated with pathological responses were a low pretreatment NLR ($p = 0.043$), radiological response to chemotherapy ($p < 0.001$), first-line chemotherapy ($p = 0.001$), and targeted therapy ($p = 0.002$). The median overall survival (OS) and recurrence-free survival (RFS) were worse in the increased NLR cohort than in the low NLR cohort (OS: 31.1 vs. 43.1 months, $p = 0.012$; RFS: 6.5 vs. 9.4 months, $p = 0.06$). According to multivariate analyses, a high pretreatment NLR was a significant predictor for both worse OS (HR = 2.43, 95%CI = 1.49–3.94, $p < 0.001$) and RFS (HR = 1.53, 95%CI = 1.08–2.18, $p = 0.017$).

Conclusions An increased pretreatment NLR was a significant predictor of a poor pathological response and worse prognosis after preoperative chemotherapy. The NLR is a simple biomarker for assessing chemotherapy efficacy.

Keywords Colorectal liver metastases · Neutrophil to lymphocyte ratio · Pathological response

Introduction

More than half of all colorectal cancer (CRC) patients will develop liver metastases during the course of the disease.[1] Liver resection is the treatment of choice for CRLM patients and confers the best prognosis.[2,3] Furthermore, increasing the use of preoperative chemotherapy for both resectable and unresectable CRLM improves survival by treating micro-metastases, down-staging the disease, and increasing the resection rate.[4]

The pathological response is an important prognostic factor in patients with chemotherapy-pretreated CRLM, and it is generally used to assess chemotherapy efficacy. In 2007, Rubbia-Brandt et al.[5] reported an association between histological tumor regression in CRLM and better clinical outcomes, which was confirmed by later studies.[6–9] However, the pathological response was reported in only 45–57% of the patients,[5–9] and preoperative chemotherapy is frequently associated with liver injury, which may increase the risk of post-resection morbidity and mortality.[10] Therefore, the

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ability to predict the chemotherapy response may help select patients for preoperative chemotherapy or resection.

Systemic inflammation in tumors has been proven to be significantly associated with cancer growth, invasion, and metastasis.[11–13] The NLR determined from blood tests is a simple, easily available, and inexpensive marker of systemic inflammation. An elevated NLR before surgery has been associated with an increased risk of recurrence and decreased survival in CRLM.[14–19] Studies have also highlighted the use of the NLR in predicting survival and response to palliative chemotherapy in patients with unresectable mCRC.[20–21] However, data on the use of the pretreatment NLR as a predictive marker for preoperative chemotherapy response is lacking. Moreover, the cut-off values utilized in most reports are somewhat arbitrary and can lead to inaccurate causal inference.

Therefore, we hypothesized that a lower NLR might be related to an increased response to preoperative chemotherapy in CRLM. To address this, we analyzed the NLR before preoperative chemotherapy in our series of CRLM patients.

Materials and Methods

After obtaining Institutional Review Board approval, we identified patients who had undergone liver resection for CRLM at our institution from January 2006 to December 2015, and we evaluated those treated with chemotherapy before surgery. Patients were excluded from the analysis if they had extrahepatic disease detected during preoperative imaging or during surgery; had undergone an incomplete resection (R2); had died within 3 months after surgery; had missing data that made it impossible to calculate the pre-chemotherapy or presurgical NLR; had concomitant infection at the time of the blood tests; or had a history of prior hepatectomy.

As described previously,[22] decisions about the administration of preoperative chemotherapy were reached by consensus of a multidisciplinary team (MDT), including surgeons, oncologists, and radiologists. Generally, preoperative chemotherapy was recommended to patients with initially unresectable liver metastases or to patients with multiple high-risk factors: synchronous metastases; ≥ 4 hepatic lesions; maximal diameter ≥ 5 cm; CEA level ≥ 200 ng/ml; and primary tumor invasion of nearby tissues/organs and mesenteric nodal disease determined by imaging. Chemotherapy comprised mainly a combination of 5-fluorouracil/capecitabine and oxaliplatin/irinotecan with or without bevacizumab and cetuximab. The radiological response was assessed according to the Response Evaluation Criteria In Solid Tumors (RECIST, version 1.1). The responses were then classified as a complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). A clinical response was defined as either CR or PR, and a non-response was defined as either SD or PD. If the clinical effectiveness was judged as PD, second-line chemotherapy was planned, and liver resection was reconsidered if there was a disease response or stabilization in response to the alternative chemotherapy.

Liver resections were performed primarily 4–6 weeks after the completion of chemotherapy. The goal of the surgery was to remove all detectable lesions with a tumor-free margin, with a residual liver volume of at least 30%. During surgery, the peritoneal cavity was inspected for previously undetected extra-hepatic disease. Intraoperative ultrasound was used to rule out occult lesions and confirm the number, size, and location of the liver metastases. Hepatic parenchymal transection was performed primarily with a Cavitron ultrasonic surgical aspirator (CUSA) and a harmonic scalpel or, if not, with the Kelly clamp crushing technique. Intraoperative RFA was used when one hepatic lesion was located deeply or proximal to major vascular structures, especially for lesions less than 3 cm. The pathological response was scored according to the tumor regression grade (TRG) as follows: 1, absence of residual cancer and large amount of fibrosis; 2, few residual cancer cells scattered throughout the fibrosis; 3, more residual tumor cells but fibrosis predominates; 4, residual cancer cells predominate over fibrosis; and 5, no signs of regression.[5] The highest TRG for each patient was used if multiple metastases were present. Metastases with TRG 1–3 were classified as pathological responses. R1 resection was defined as a distance from the metastasis edge to the transection line of less than 1 mm.

After resection, the decision to deliver additional chemotherapy was made based on the number of preoperative chemotherapy cycles, response to preoperative chemotherapy, and margin status. Patients were followed up at regular intervals. The initial post-treatment CT and MRI scans occurred 1 month after surgery. Then, patients were followed up at 3-month intervals for up to 2 years and every 6 months thereafter.

Clinicopathological characteristics, including patient demographics, primary colorectal tumor characteristics, metastatic characteristics, preoperative chemotherapy information, radiological and pathological response, and liver surgery details, were obtained retrospectively from the patient medical records. The NLR was calculated as the neutrophil count divided by the lymphocyte count; these counts were measured within 10 days before chemotherapy and surgery as part of the routine workup.

Statistical Analysis

Continuous and categorical variables were compared using the Mann-Whitney U test and χ^2 test, respectively. The mean NLR values before chemotherapy and before surgery were compared using the Wilcoxon signed-rank test. A ROC curve

was constructed to estimate the optimal cutoff value for the pretreatment NLR. A multivariate logistic regression analysis was performed with the backward elimination method to identify independent factors associated with the pathological response. The OS and RFS were calculated from the date of CRLM resection and compared using the Kaplan-Meier method; comparisons were performed with the log-rank test. Multivariate models were constructed using the Cox proportional hazard method. Variables were included in each multivariate model if they achieved a $p < 0.1$ for significance according to the univariate analysis. $P < 0.05$ was considered to indicate statistical significance. Statistical analyses were performed using SPSS (version 22, Armonk, NY, USA).

Results

Patient and Tumor Characteristics

A total of 183 patients met the inclusion criteria. Most patients (85.2%) developed synchronous liver metastases. Of the patients, 72.7% had more than one metastasis, with a median of 3 lesions. The median diameter of the largest lesion was 2.5 cm, and 45.9% of patients had a lesion larger than 3 cm. Bilobar distribution of metastases was observed in 50% of the patients. The median number of preoperative chemotherapy cycles was 5, with 52 patients (28.4%) receiving more than 6 cycles and 21 patients (11.5%) receiving second-line chemotherapy. Ninety-nine patients (54.1%) achieved a clinical response after chemotherapy. A pathological response was reported in 103 (56.3%) of 183 patients, including a complete response in 2 patients (1.1%) and a partial response (TRG2–3) in 101 patients (55.2%). Forty-eight patients (26.2%) underwent hepatectomy in combination with RFA, and 56 patients (30.6%) had margin invasion at pathological evaluation. The mean pretreatment and preoperative NLRs were 2.4 ± 1.1 and 2.1 ± 1.6, respectively ($p < 0.001$).

Prediction of Chemotherapy Efficacy Based on the NLR

A ROC curve was constructed to estimate the optimal cutoff value of the pretreatment NLR for predicting pathological response. The area under the curve was 0.62, and the optimal cutoff level was 2.3. This value was associated with 0.553 sensitivity and 0.637 specificity. Eighty patients (43.2%) had an NLR ≤ 2.3, and 104 patients (56.8%) had an NLR > 2.3. Baseline clinicopathologic characteristics based on the pretreatment NLR are summarized in Table 1. While the two groups had mostly similar characteristics, patients with an NLR ≤ 2.3 were more likely to achieve a pathological response (67.1 vs. 48.1%, $p = 0.01$). Interestingly, the irinotecan-based regimen was more commonly used in the high NLR cohort (25.2 vs. 12.5%, $p = 0.031$), while patients with a low NLR received oxaliplatin chemotherapy more frequently (78.5 vs. 64.4%, $p = 0.039$).

Predictors of Pathological Response

A comparison between pathological responders and nonresponders was performed. The primary tumor location ($p = 0.023$), clinical response ($p < 0.001$), chemotherapy line ($p = 0.007$), targeted therapy ($p < 0.001$), chemotherapy regimen ($p < 0.001$), and pretreatment NLR ($p = 0.01$) were statistically significant parameters. In a multivariate analysis, a low pretreatment NLR significantly predicted the pathological response compared with the other available factors ($p = 0.015$), as well as clinical response ($p < 0.001$), first-line chemotherapy ($p = 0.001$), and use of targeted therapy ($p = 0.002$) (Table 2).

Survival Outcomes

The median follow-up was 36.3 months. At the time of analysis, 144 (78.7%) patients experienced disease recurrence, and 81 (44.3%) died. The median RFS was 7.4 months (95% CI 6.3–8.5), and the median OS was 38.5 months (95% CI 32.3–44.7). The median RFS was 9.4 months (95% CI 6.8–12) in patients with a pretreatment NLR ≤ 2.3 and 6.5 months (95% CI 4.7–8.3) in those with an NLR > 2.3 ($p = 0.06$). The median OS was 43.1 months (95% CI 35–51.2) in the low NLR group and 31.1 months (95% CI 28.2–34) in those with an NLR > 2.3 ($p = 0.012$) (Fig. 1).

Patients were then categorized into the following groups: both a pretreatment and pre-surgical NLR ≤ 2.3 (50 patients, 27.3%); a pretreatment NLR > 2.3 and a pre-surgical NLR ≤ 2.3, defined as NLR normalization (73 patients, 39.9%); both a pretreatment and pre-surgical NLR > 2.3 (31 patients, 16.9%); and a pretreatment NLR ≤ 2.3 and pre-surgical NLR > 2.3 (29 patients, 15.8%). Normalization of the NLR improved the median OS from 29.6 months (95% CI 23.5–35.7) to 42.9 months (95% CI 35.2–50.6) in patients with an elevated pretreatment NLR ($p = 0.006$). Patients with NLR normalization had an improved RFS of 8.1 months (95% CI 6.3–9.9) compared with patients with a persistently high NLR (4.7 months; 95% CI 3.5–5.9 months), although this did not reach statistical significance ($p = 0.056$). Patients with a normalized NLR showed no difference compared to patients of the low-low group for RFS (10.1 months, 95% CI 5.8–14.4, $p = 0.091$) and OS (42.7 months, 95% CI 32.8–52.6, $p = 0.57$). Patients in the low-high group did not have a median RFS (6.7 months, 95% CI 1.8–11.6, $p = 0.35$) or OS (30.2 months, 95% CI 19.7–40.7, $p = 0.92$) that were significantly different from those of the high-high patients (Fig. 2).

Table 1 Clinicopathologic characteristics of patients who underwent preoperative chemotherapy for CRLM sorted by pre-treatment NLR

	Low NLR group $n = 79$ (%)	High NLR group $n = 104$ (%)	p
Male sex, *n* (%)	55 (65.4%)	68 (69.6)	0.55
Age ≥ 60, *n* (%)	29 (36.7)	38 (36.5)	0.98
CEA (range), ng/ml	7.7 (1.3–528.4)	9.4 (1.1–354.7)	0.87
Primary site, *n* (%)			
Colon	51 (64.6)	53 (51.0)	0.066
Left hemicolon	66 (83.5)	94 (90.4)	0.17
T3–4, *n* (%)	70 (88.6)	96 (92.3)	0.39
Node-positive primary tumor, *n* (%)	53 (67.1)	76 (73.1)	0.38
DFI ≤ 6 months	70 (88.6)	86 (82.7)	0.26
Number (range)	3 (1–9)	3 (1–9)	0.073
Number ≥ 4, *n* (%)	35 (44.3)	38 (36.5)	0.29
Bilobar distribution, *n* (%)	38 (48.1)	54 (51.9)	0.61
Maximum size, (range), cm	2.5 (0.8–14)	2.5 (0.8–10)	0.89
Maximum size ≥ 3 cm, *n* (%)	37 (46.8)	47 (45.2)	0.83
KRAS mutation, *n* (%)[a]	*19 (37.3)*	*33 (46.5)*	*0.31*
Major resection, *n* (%)	22 (27.8)	33 (31.7)	0.57
Concomitant RFA, *n* (%)	24 (27.6)	24 (20.4)	0.22
R0 resection, *n* (%)	51 (64.6)	76 (73.1)	0.22
Preoperative chemotherapy			
Oxaliplatin, *n* (%)	62 (78.5)	67 (64.4)	0.039
Irinotecan, *n* (%)	10 (12.7)	26 (25.0)	0.037
Oxaliplatin + irinotecan, *n* (%)	7 (8.8)	11 (10.6)	0.7
Targeted therapy, *n* (%)	34 (43)	32 (30.8)	0.087
Cycles > 6, *n* (%)	23 (29.1)	29 (27.9)	0.86
Second-line chemotherapy, *n* (%)	11 (13.9)	10 (9.6)	0.36
Pathological response, *n* (%)	53 (67.1)	50 (48.1)	0.01
Clinical response, *n* (%)	46 (58.2)	53 (51.0)	0.33
Postoperative chemotherapy, *n* (%)	62 (78.5)	81 (77.9)	0.92

CRLM colorectal Liver metastases, *NLR* neutrophil to lymphocyte ratio, *RFA* radiofrequency ablation, *CEA* carcino-embryonic antigen, *DFI* disease-free interval. Italics are used for statistical significance

[a] KRAS status was available in 122 patients

Predictors of Survival and Recurrence

Univariate analysis revealed that lymph node metastases, bilobar distribution of lesions, lesion number ≥ 4, R1 resection, > 6 cycles of chemotherapy, second-line chemotherapy, no pathological response, a pretreatment NLR > 2.3, and a persistently elevated NLR after chemotherapy were associated with decreased OS. In a multivariate analysis, a high pretreatment NLR ($p < 0.001$), bilobar distribution ($p = 0.015$), second-line chemotherapy ($p = 0.006$), R1 resection ($p = 0.006$), and lymph node metastases ($p = 0.012$) remained significant for a worse OS.

Regarding RFS, chemotherapy line ($p = 0.008$), lesion number ($p < 0.001$), lymph node metastases ($p = 0.005$), pretreatment NLR ($p = 0.02$), and pathological response ($p = 0.038$) remained significant predictors of RFS after controlling for competing risk factors, such as NLR pattern changes, concomitant RFA, targeted therapy, bilobar distribution, margin status, and clinical response (Table 3).

Table 2 Multivariate analysis of variables for the pathological response in patients who underwent preoperative chemotherapy

	pR rate (%)	OR	95%CI	p
Clinical response	73.7	5.0	2.51–10.01	< 0.001
Left-sided primary tumor	61.2	1.74	0.86–3.52	0.12
Second-line chemotherapy	28.6	0.14	0.04–0.45	0.001
Targeted therapy	74.2	3.40	1.57–7.30	0.002
Oxaliplatin based regimen	62.0	1.09	0.64–1.86	0.74
Pre-treatment NLR ≤ 2.3	67.1	2.40	1.18–4.88	0.015

pR pathological response, *OR* odds ratio, *CI* confidence interval, *NLR* neutrophil to lymphocyte ratio

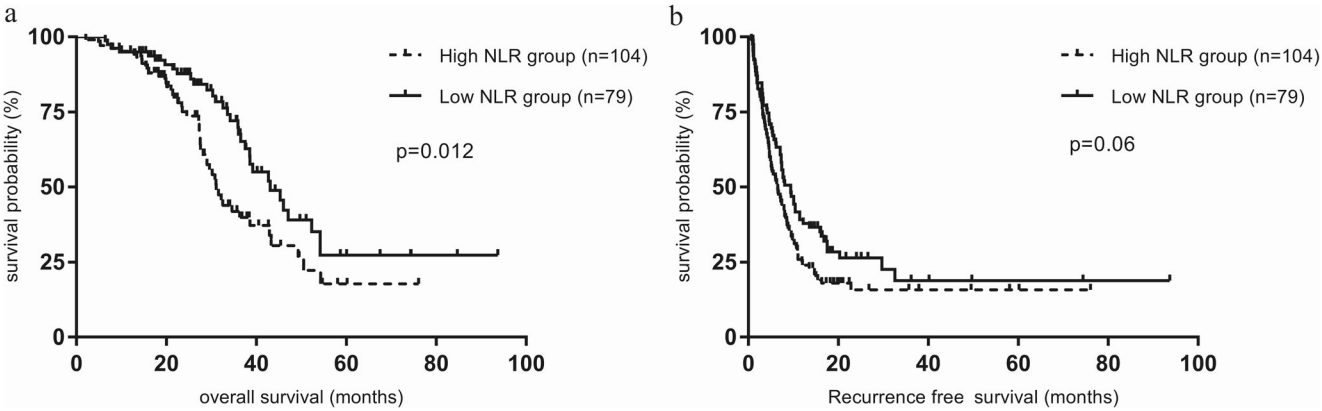

Fig. 1 Overall survival (**a**) and recurrence-free survival (**b**) according to the NLR of patients who underwent preoperative chemotherapy prior to resection

Discussion

To the best of our knowledge, this is the first study to establish a correlation between the outcomes for preoperative chemotherapy and the pretreatment NLR in patients with CRLM. A lower pretreatment NLR was associated with favorable outcomes, which held true for both chemosensitivity and long-term prognosis. These results might aid in selecting patients with CRLM for treatment strategies that include chemotherapy.

Identifying factors with prognostic and predictive ability at the time of diagnosis have clinical utility, as they may provide information about the aggressiveness of a tumor. Previous studies have validated the use of the NLR prior to chemotherapy as a predictor of the pathological response to preoperative therapy in breast cancer,[23,24] advanced esophageal cancer,[25] muscle-invasive bladder cancer,[26] and pancreatic cancer.[27] In the current study, an optimal NLR cut-off of 2.3 can better predict the pathological response in patients with CRLM. However, the sensitivity of the present cut-off level is relatively low (0.553), demonstrating that the inflammatory response is only one aspect of the mechanism underlying chemosensitivity. Consistent with previous studies, the use of molecular target agents in the preoperative setting conferred increased overall response rates.[28,29] In addition, there was a significant correlation between the radiological and pathological tumor responses. The high correlation between these two approaches may be attributed to the fact that MRI was routinely used for therapeutic evaluation at our institution. Indeed, a recent systematic review reported that the apparent diffusion coefficient (ADC) via MRI, compared with PET, PET-CT, and CT, is the most promising parameter for predicting the response to chemotherapy in CRLM.[30] Furthermore, a 28.6% pathological response rate after second-line chemotherapy illustrated the difficulty in achieving a tumor response with second-line chemotherapy.[31] Although the predictive power of the NLR seemed weaker than these factors, the main advantage is that this biomarker can be easily obtained before chemotherapy is started, so clinicians can tailor treatment to individual patients. A combination of risk factors could likely enhance the prediction accuracy.

The results of our study are in accordance with the findings of previous studies that highlighted the association between a decreased NLR and prolonged survival in patients.[14–19] What is unique in our study is that the NLR was assessed at the start

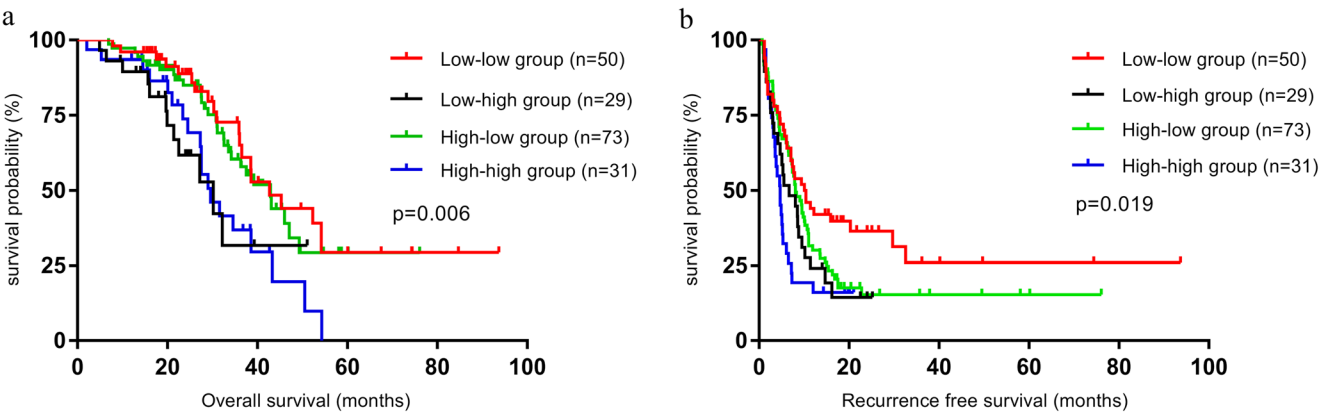

Fig. 2 Overall survival (**a**) and recurrence-free survival (**b**) according to the NLR before and after chemotherapy of the patients who underwent preoperative chemotherapy prior to resection

Table 3 Univariate and multivariate analyses of factors predictive of overall survival (OS) and recurrence free survival (RFS)

	OS			RFS		
	UV (P)	HR [95%CI]	MV (P)	UV (P)	HR [95%CI]	MV (P)
Male sex	0.39			0.83		
Age ≥ 60	0.31			0.33		
CEA > 10 ng/ml	0.54			0.13		
Pre-treatment NLR > 2.3	0.012	*2.43 [1.49–3.94]*	*< 0.001*	0.06	*1.53 [1.08–2.18]*	*0.017*
NLR change	0.006	1.13 [0.91–1.31]	0.11	0.019	1.12 [0.99–1.27]	0.072
Primary site						
Colon	0.55			0.49		
Left hemicolon	0.13			0.69		
T3–4	0.15			0.21		
Node-positive primary tumor	0.027	*2.05 [1.17–3.60]*	*0.012*	0.003	*1.68 [1.34–2.49]*	*0.009*
DFI ≤ 6 months	0.89			0.16		
Number ≥ 4	0.008	1.92 [0.98–3.74]	0.056	< 0.001	*2.28 [1.60–3.24]*	*< 0.001*
Bilobar distribution	0.001	*1.79 [1.12–2.87]*	*0.015*	0.008	0.81 [0.54–1.22]	0.32
Maximum size ≥ 3 cm	0.20			0.84		
Major resection	0.53			0.4		
Concomitant RFA	0.81			0.086	1.19 [0.82–1.73]	0.35
R0 resection	0.008	*0.49 [0.30–0.82]*	*0.006*	0.004	0.80 [0.53–1.20]	0.28
Oxaliplatin-based regimen	0.31			0.28		
Targeted therapy	0.69			0.037	1.11 [0.73–1.68]	0.62
Cycles > 6	0.10	1.17 [0.72–1.92]	0.52	0.27		
Second-line chemotherapy	0.005	*2.46 [1.29–4.68]*	*0.006*	< 0.001	*1.68 [1.16–2.42]*	*0.006*
Pathological response	0.011	1.50 [0.91–2.48]	0.12	0.001	*1.64 [1.17–2.29]*	*0.004*
Clinical response	0.11			0.048	1.17 [0.79–1.73]	0.44
Postoperative chemotherapy	0.80			0.21		

UV univariate analysis, *MV* multivariate analysis, *HR* hazard ratios, *CI* confidence interval, *CEA* carcinoembryonic antigen, *DFI* disease-free interval, *RFA* radiofrequency ablation, *NLR* neutrophil to lymphocyte ratio. Italics are used for statistical significance

of chemotherapy. Even after controlling for competing risk factors, a higher NLR remained associated with an increased risk of recurrence and death. Furthermore, prognosis can be distinguished more accurately by changes in the NLR pattern before and after chemotherapy. Patients with a normalized NLR achieved a survival rate similar to that of patients with a consistently low NLR. In contrast, survival was compromised if the NLR was elevated. This finding implies that a higher pretreatment NLR level is a marker of poor chemosensitivity and indicates inherently worse cancer-related inflammation; chemotherapy may activate the antitumoral immunomodulatory activity in some patients by increasing the lymphocyte levels and/or decreasing the neutrophil levels.[32] Changes in the blood NLR might provide useful prognostic information for clinicians.

The reason for the unfavorable outcome in patients with a higher NLR is largely unknown. One possible mechanism is that the elevated systemic inflammatory response suppresses lymphocyte infiltration within the metastases. Indeed, the blood NLR is negatively associated with intratumoral T cell density,[33] while a higher intratumoral T cell density could significantly increase the pathological and radiological response rates to chemotherapy in CRLM patients.[34] Inflammation-induced cytokine alterations might be another mechanism. Chen et al. recently identified 19 blood cytokines with high expression levels in metastatic CRC patients with a high NLR.[35] Most of these cytokines are functionally involved in angiogenesis, inflammation, and tumor growth promotion and are associated with disease progression, poor survival, and poor treatment outcomes. Therefore, the circulating NLR might be a surrogate biomarker for both local and systemic inflammatory responses, which are determinants of tumor biology.

This study has some limitations. First, it was a retrospective study with a relatively small sample size, and the data were collected from a single institution. Second, chemotherapy was more often irinotecan-based in the high NLR group, while it was predominantly oxaliplatin-based in the low NLR group; this difference could exist because irinotecan is more often used as second-line treatment at our institution, rendering patients in the irinotecan group inherently less chemo-sensitive. In fact, a logistic regression analysis showed that the chemotherapy regimen did not influence the pathological response in this study. Third, the KRAS status, which is an important biomarker for CRLM, was available for only 66.7% of the patients. Last but not least, subgroup analyses according to the combination of regimen and targeted therapy were not performed due to the limited sample size of the subgroups. These limitations make it difficult to draw a definite conclusion, and larger databases are therefore needed to validate the current results.

Conclusions

In conclusion, the pretreatment NLR is a reliable biomarker that helps predict the pathological response to preoperative chemotherapy in patients with CRLM. Our study also confirmed that the pretreatment NLR is an independent prognostic factor. In addition, changes in NLR levels predicted survival. The pre-treatment NLR can be used in CRLM for decision-making, surveillance, and prognosis. Immunotherapy or anti-inflammatory agents could be considered for patients with a high NLR at diagnosis.

Author's Contributions All authors have made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and drafting the work or revising it critically for important intellectual content. All 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. All authors approved the final version to be published.

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Compliance with Ethical Standards

Conflicts of Interest The authors declare that they have no conflict of interest.

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