



Dynamics of neutrophil-to-lymphocyte ratio predict outcomes of metastatic colorectal carcinoma patients treated by FOLFOX

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Background: Peripheral blood cell count is the most common clinical laboratory test. Neutrophil-to-lymphocyte ratio (NLR) as an economic marker has been reported in various cancer types. It is believed that NLR is associated with the prognosis and treatment outcomes of some cancers. Low baseline NLR has been reported as associated with better overall survival (OS) in advanced cancer patients. In this study, we aimed to determine whether the changes of NLR may predict the outcome of metastatic colorectal carcinoma (mCRC) patients treated with folinic acid, fluorouracil, and oxaliplatin (FOLFOX) combined with bevacizumab/cetuximab.

Methods: The clinical data obtained from 128 mCRC patients between January 2014 and December 2018 were retrospectively analyzed. The NLR values of patients were calculated after 4 cycles of treatments. Kaplan-Meier analysis and Cox regression modeling were performed to assess the impact of NLR dynamics on OS and progression-free survival (PFS).

Results: Among the 128 participants, the optimum pre-treatment NLR cutoff value was 3. A total of 70 (54.7%) participants had a pre-treatment of NLR lower than 3. The median of PFS was 9.1 months for NLR <3 compared with 6.1 months for pre-treatment NLR >3. A lower pre-treatment NLR was significantly associated with better PFS ($P < 0.001$), but not associated with OS ($P = 0.064$). A total of 94 (73.4%) participants had a post-treatment NLR <3, which was associated with better PFS and OS ($P = 0.007$). However, changes in NLR significantly affected PFS and OS. Decrease in post-treatment NLR was associated with longer PFS and OS. Patients with changes from low pre-treatment NLR to high post-treatment NLR had worse OS and PFS than that of NLR changes from high to low.

Conclusions: It is not the NLR but the changes of NLR that may predict the efficacy of FOLFOX treatment in mCRC patients.

Keywords: Metastatic colorectal carcinoma (mCRC); neutrophil-to-lymphocyte ratio (NLR); Folinic acid, fluorouracil, and oxaliplatin (FOLFOX); bevacizumab/cetuximab

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Introduction

The incidence of colorectal cancer (CRC) is increasing worldwide. In 2018, CRC ranked third in terms of incidence, and second in terms of mortality globally (1). Although great improvements in therapeutic strategies including chemotherapy and surgical treatments have been made, the mortality of CRC has remained high (2).

In the past decades, some novel treatments have been reported. Folinic acid, fluorouracil, and oxaliplatin (FOLFOX) combined with bevacizumab/cetuximab as the first-line chemotherapy has played an important role in metastatic colorectal carcinoma (mCRC) patients. However, FOLFOX might exert severe toxicity and side-effects to some mCRC patients due to patient heterogeneity. Therefore, predictive markers for the effect of FOLFOX on mCRC patients are needed before individualized treatment may progress.

Peripheral blood cell count is the most common clinical laboratory test. The count of neutrophils, lymphocytes, and monocytes are special markers for host immunity, and may reflect the condition of cytokine activation and some diseases. It is neutrophils not monocytes or macrophages were essential to deter tumor-infiltrating bacteria and dampen CRC promoting inflammation. Neutrophils represent an important component of the tumor microenvironment (3). Neutrophil specific IL-1R signaling controlled bacterial invasion and tumor elicited inflammation (4). It is believed that neutrophil-to-lymphocyte ratio (NLR) (5-8), Monocyte-to-lymphocyte ratio (MLR) and Plate-to-lymphocyte ratio (PLR) (9-11) are associated with the prognosis and treatment outcomes of some cancers, include CRC. Previous studies have indicated that an elevated NLR before surgery or chemotherapy is associated with poor outcome in CRC patients (12,13). NLR yielded a significant difference in five-year progression-free survival (PFS) (14). in lung metastasectomy for CRC patients. It shows that NLR is a strong predictor of outcome in mCRC patients undergoing pulmonary metastasectomy (11,15). However the role of PLR in the prognosis of CRC patients is still controversial. Yang *et al.* (16) indicated that elevated PLR was significantly associated with poor PFS but not with OS. However, Jiang *et al.* (17) hold that PLR was not significantly associated with either PFS or OS. Many studies agreed that NLR was an independent prognostic factor not only for PFS but also for OS in mCRC patients treated by FOLFOX. But most researches evaluated the pre-treatment NLR.

Post-treatment NLR was rarely studied. Therefore, we evaluate pre-treatment NLR and post-treatment NLR simultaneously. We believe changes in the NLR may be a useful predictor for CRC patients' outcomes. In this study, we retrospectively investigated the relationship between the outcomes of FOLFOX treatment in mCRC patients and the change of NLR. This study might be helpful for developing a predictive marker regarding the efficacy of FOLFOX chemotherapy in mCRC patients. We present the following article in accordance with the STARD reporting checklist (available at <https://dx.doi.org/10.21037/jgo-21-716>).

Methods

Patients and data collection

In this study, we retrospectively enrolled all mCRC patients treated with FOLFOX at our hospital from January 2014 to December 2018. The inclusion criteria were as follows: stage IV CRC patients without previous chemotherapy history. Patients were excluded from the analysis if they had active infectious disease, anemia, hematological disorder, a treatment history of hypertension, cardiac failure, autoimmune disease, or a history of other malignancies.

The clinical data collected from electrical medical records included age, gender, date of diagnosis, initial stage, localization of the tumor, histological data, site of metastasis, and all subsequent treatments.

The complete blood count (CBC) was detected using a hematology analyzer ADVIA 2120i (Siemens Corporation, Munich, Germany). The laboratory data collected from CBC included white blood cell count, absolute neutrophil count, and absolute lymphocyte count. The NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count. Baseline NLR (within 3 days of the first chemotherapy) was defined as NLR1, and NLR measured after 8 weeks (4 cycles) of treatments was defined as NLR2.

Treatment assessment

Tumor response was assessed according to the response evaluation criteria in solid tumors (RECIST 1.1) regarding complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The primary endpoint was PFS, which was defined as the period time from the start date of chemotherapy to the first documentation of progression. Overall survival (OS) was

Table 1 Clinicopathological features and NLR

Characteristics	N (%), (n=128)	High NLR1 (n=70)	Low NLR1 (n=58)	P-value	High NLR2 (n=34)	Low NLR2 (n=94)	P-value
Gender							
Female	30 (23.4)	14	16		4	26	
Male	98 (76.6)	56	42		30	68	
Tumor location							
Left colon	40 (31.2)	18	22		8	32	
Right colon	28 (21.9)	16	12		10	18	
Rectum	60 (46.9)	36	24		16	44	
Metastatic sites							
Lung metastatic	26 (20.3)	14	12		6	20	
Liver metastatic	48 (37.5)	26	22		14	34	
Lung and liver metastatic	14 (10.9)	6	8		2	12	
Other	40 (31.3)	24	16		12	28	
Number of metastatic sites							
0–2	88 (68.7)	46	42		22	66	
>2	40 (31.3)	24	16		12	28	
ORR		40%	68.90%	<0.001	23.50%	63.80%	<0.001

NLR, neutrophil-to-lymphocyte ratio; ORR, objective response rate.

the secondary endpoint, and it was defined as the time from the date of first chemotherapy to death from any cause. The end of the follow-up period was December 2019. The objective response (OR) was defined as either CR or PR, and a non-response was defined as either SD or PD. Participants were also evaluated for adverse events according to the National Cancer Institute (NCI) Common Toxicity Criteria, version 3.0 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae3.pdf). The study protocol was approved by the Ethics Committees of Changzhou Cancer Hospital. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). Individual consent for this retrospective analysis was waived.

Statistical analysis

The software SPSS version 22 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Continuous and categorical variables were compared using the Mann-Whitney U test and χ^2 test, respectively. Receiver operating

characteristic (ROC) curve analysis was used to determine the cutoff values for the NLR, and Youden index (YI) was used to identify the optimal cutoff values for the NLR. All cases were divided into high and low NLR groups according to the cutoff value. Comparison between groups was evaluated using one-way analysis of variance (ANOVA) or unpaired Student's *t*-tests. Multiple comparison between the groups was performed using Student-Newman-Keuls method. Logistic regression analysis was conducted to evaluate the clinicopathological factors. Kaplan-Meier analysis was used to calculate the survival probability. Significant indicators for survival determined in univariate analysis were assessed via multivariate analysis using Cox's proportional hazards model. A P-value <0.05 was considered statistically significant.

Results

Baseline participant characteristics

Baseline participant characteristics are presented in the *Table 1*. The median age was 59 years (range, 21 to 76 years). There were 30 (23.4%) female and 98 (76.6%) male

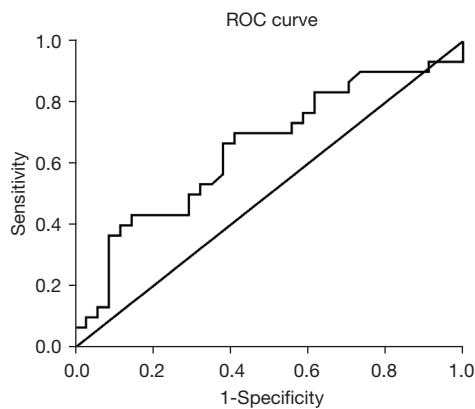


Figure 1 ROC curves analysis for NLR in mCRC patients. The AUC was 0.649 ($P=0.004$, 95% CI: 0.552 to 0.749). ROC, receiver operating characteristic; NLR, neutrophil-to-lymphocyte ratio; mCRC, metastatic colorectal carcinoma; AUC, area under the curve; CI, confidence interval.

participants. A total of 40 (31.2%) tumors were located in the left colon, 28 (21.9%) were in the right colon, and 60 (46.9%) were in the rectum. There were 26 (20.3%) participants with only lung metastases, 48 (37.5%) with only liver metastases, and 14 (10.9%) participants had both lung and liver metastases. There were 40 (31.3%) participants with more than 2 metastases.

Prediction of chemotherapy efficacy based on the NLR

The pre-treatment median NLR value of all participants was 3.15 and the median NLR of participants after 8 weeks (4 cycles) of treatment was 3.04. An ROC curve was constructed to estimate the optimal cutoff value of the pre-treatment NLR for predicting clinical response (*Figure 1*). The area under the curve (AUC) was 0.649, and the optimal cutoff value was 3.0. Participants were then divided into 2 groups according to the pre-treatment NLR: low NLR1 (pre-treatment NLR <3.0 , $n=70$, 54.7%) and high NLR1 (pre-treatment NLR >3.0 , $n=58$, 45.3%). While the 2 groups had similar characteristics (*Table 1*), the low NLR1 group demonstrated a better overall response rate (ORR) (68.9% *vs.* 40%; $P<0.001$). Participants were then categorized into the following groups: Low NLR2 group (those with NLR2 <3.0 , $n=94$, 73.4%) and High NLR2 group (those with NLR2 >3.0 , $n=34$, 26.6%). Participants with an NLR1 <3.0 had an ORR of 68.9%. Participants with an NLR2 <3.0 after 8 weeks (4 cycles) of treatments were more likely to achieve an ORR (63.8% *vs.* 23.5%;

$P<0.001$; *Table 1*).

Survival analysis of prognostic factors

The median OS of all 128 participants was 25.1 months, and the median PFS was 8.5 months. The median PFS was 9.1 months (95% CI) in the low NLR1 group and 6.1 months in the high NLR1 group ($P<0.001$). The median OS was 28.7 months (95% CI) in the low NLR1 group and 21.9 months in the high NLR1 group ($P=0.064$; *Figure 2*). After 8 weeks of treatment, participants with low NLR (low NLR2 group) had PFS of 8 months and OS of 23.9 month, compared to high NLR2 group for PFS of 4.2 months ($P<0.001$) and OS of 18.6 months ($P=0.007$; *Figure 3*). Therefore, the baseline NLR was significantly associated with PFS, but not associated with OS.

To investigate the relationship between NLR variation trend and prognosis of patients, we divided all participants into 4 groups: low-low group (NLR1 <3.0 and NLR2 <3.0 : 40 participants, 31.2%), low-high group (NLR1 <3.0 and NLR2 >3.0 : 18 participants, 14.1%), high-low group (NLR1 >3.0 and NLR2 <3.0 : 48 participants, 37.5%), and high-high group (NLR1 <3.0 and NLR2 <3.0 : 22 participants, 17.2%). Patients with a persistently low NLR had the best PFS across the 4 groups. Patients with high NLR1 but low NLR2 had an improved PFS of 7 months (95% CI), and those with a persistently high NLR had a PFS of 4 months (*Figure 4*). Although low baseline NLR could benefit more from the chemotherapy, NLR after 4 cycles was also important for PFS and OS.

Univariate analysis revealed that gender, age, tumor location, metastatic sites, and number of metastatic sites were not significantly associated with survival rate.

Discussion

The prognosis of tumor patients is closely related to their systemic immune status. Neutrophils can promote tumor invasion and metastasis by releasing elastase and cathepsin, which can hydrolyze antitumor factors (18). Neutrophil-derived leukotrienes can selectively amplify the subpopulations of cancer cells with high tumorigenic potential to help distant tissues to colonize. Lymphocyte is the main effector cell of immunity, and NLR may reflect the balance between pro-tumor inflammatory response and antitumor immune response (12,19). Baseline NLR has been described as a prognostic indicator in various cancers (20,21). In this study, we investigated whether NLR can

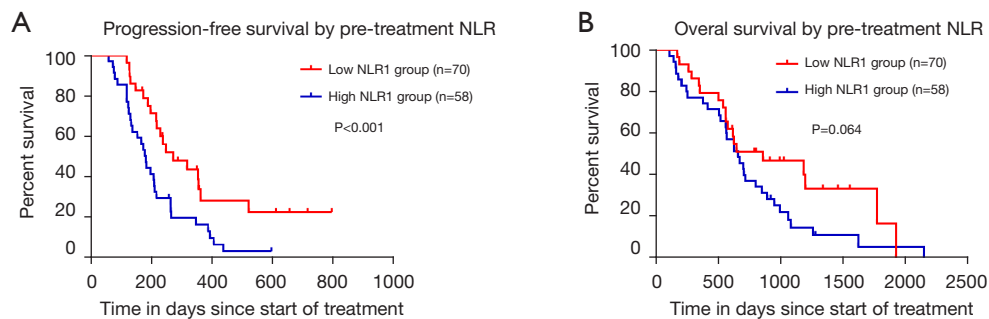


Figure 2 Kaplan–Meier curves of 128 mCRC patients determined by pre-treatment NLR. (A) PFS of 128 mCRC patients determined by pre-treatment NLR; (B) OS of 128 mCRC patients determined by pre-treatment NLR. PFS, progression-free survival; OS, overall survival; mCRC, metastatic colorectal cancer; NLR, neutrophil-to-lymphocyte ratio.

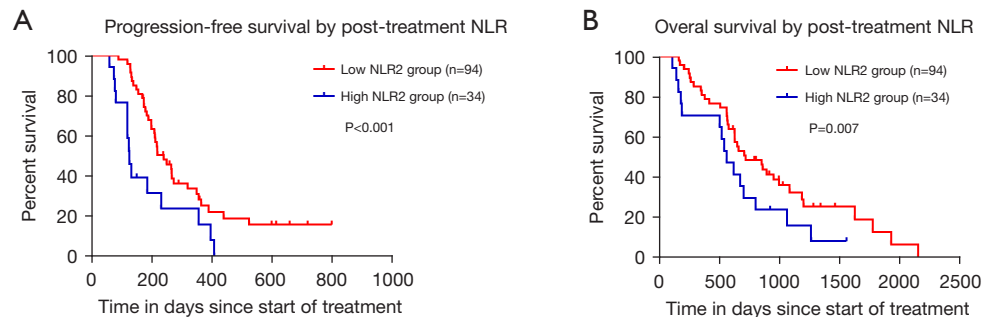


Figure 3 Kaplan–Meier curves of 128 mCRC patients determined by post-treatment NLR. (A) PFS of 128 mCRC patients determined by post-treatment NLR; (B) OS of 128 mCRC patients determined by post-treatment NLR. progression-free survival; OS, overall survival; mCRC, metastatic colorectal cancer; NLR, neutrophil-to-lymphocyte ratio.

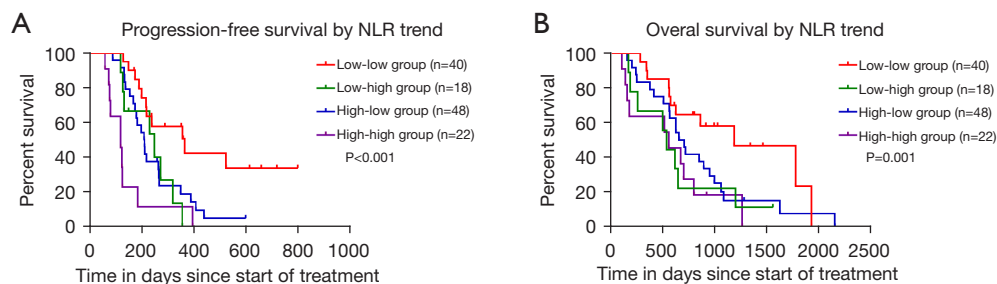


Figure 4 Kaplan–Meier curves for PFS of 128 mCRC patients according to the NLR trends before and after 4 cycles chemotherapy. (A) PFS of 128 mCRC patients according to the NLR trends before and after 4 cycles chemotherapy; (B) OS of 128 mCRC patients according to the NLR trends before and after 4 cycles chemotherapy. PFS, progression-free survival; OS, overall survival; mCRC, metastatic colorectal cancer; NLR, neutrophil-to-lymphocyte ratio.

predict the therapeutic effect of FOLFOX in 128 mCRC patients.

In this study, the cutoff value for baseline NLR was determined to be 3.0 according to the ROC curve.

This cutoff can effectively distinguish the efficacy of chemotherapy. The cutoff of NLR ranged from 2 to 5 in different diseases, race, and ages. Therefore, it is necessary to establish the NLR cutoff in different population

demographics according to disease species and race with a large sample size in the future.

Baseline NLR has been reported to be associated with survival in cancer patients treated with both conventional chemotherapy and targeted treatments (22,23). Baseline NLR was found to be correlated with OS in advanced cancer treated with programmed cell death protein 1/programmed death ligand 1 (PD-1/PD-L1) inhibitors (24). However, our study showed that an elevated baseline NLR greater than the cutoff of 3 was associated with worse PFS, and that baseline NLR was not correlated with OS. This result may be explained by the limited sample size and specific metastatic CRC.

We then analyzed the NLR changes in mCRC patients from pre-treatment to 4 cycles of treatment with FOLFOX, to evaluate the significance of NLR as an independent biomarker in predicting clinical benefit in terms of PFS and OS. The Kaplan-Meier cumulative survival rates for OS and PFS demonstrated that decrease in NLR after 4 cycles of treatment with FOLFOX was associated with longer PFS and OS. Therefore, mCRC patients with reduced NLR after 4 cycles FOLFOX chemotherapy can benefit more from chemotherapy, regardless of their baseline NLR level. Interestingly, patients with changes in NLR from low baseline NLR to high post-treatment NLR had worse OS and PFS than those with NLR changes from high baseline to low post-treatment. According to the results mentioned above, it is not the post-treatment NLR but the changes in temporal profiles of NLR that are important.

Compared to a baseline NLR, a post-treatment NLR more objectively reflects the dynamic change in inflammatory responses of the body after FOLFOX treatment. Thus, NLR variation may directly predict the outcomes in mCRC patients undergoing FOLFOX chemotherapy. The fact that mCRC patients with an increased post-treatment NLR had higher progression rates suggests that FOLFOX treatment may have aggravated the inflammatory response which contributed to the tumor progression in these patients.

The NLR can be obtained from peripheral blood and act as an easy and cost-effective biomarker for survival in patients with FOLFOX chemotherapy. In CRC patients, whose life expectancy is relatively short, the efficacy of FOLFOX chemotherapy must be assessed early. Patients can benefit more from replacement of the treatment package early if FOLFOX chemotherapy is predicted as valid.

The small-sized, retrospective study design may be the most obvious limitation of this study. We selected mCRC

patients treated with FOLFOX primarily. Patients who had previously undergone surgery or other chemotherapy were excluded. A large sample and Multicenter study should be added for verification later. However, the economic endowment of patients may affect their treatment choice, and thus influence the OS.

Conclusions

The NLR is a valuable predictor for the clinical efficacy of FOLFOX chemotherapy for mCRC patients. Identification of patients with elevated pre-chemotherapy or increased post chemotherapy NLRs will predict early recurrence and allow for timely interventions. The efficacy of chemotherapy can be also predicted by the variation trend of NLR after chemotherapy. Further studies conducted with larger prospective patient cohorts are needed to confirm the predictive role of NLR in FOLFOX chemotherapy.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at <https://dx.doi.org/10.21037/jgo-21-716>

Data Sharing Statement: Available at <https://dx.doi.org/10.21037/jgo-21-716>

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