Original Article

Pre-therapeutic Neutrophil-to-lymphocyte Ratio (NLR) for Prediction of Efficacy in Metastatic Colorectal Cancer (mCRC) Patients with Bevacizumab Plus FOLFIRI as First-line Treatment: A Single Institutional Data

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Key Words
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Efficacy

Purpose. The prognosis of metastatic colorectal cancer (mCRC) is hard to predict. Nowadays, there are several indexes for prognostic evaluation. In this paper, we focus on pre-therapeutic neutrophil-to-lymphocyte ratio (NLR) for prediction on mCRC patients treated with bevacizumab plus FOLFIRI as first-line therapy.
Methods. We collected mCRC patients who received bevacizumab plus FOLFIRI as first-line therapy from August 2014 to February 2020. Based on receiver operating characteristic (ROC) of disease control rate (DCR), we selected the cut-off value of pre-therapeutic NLR, then analyzed the correlation between pre-therapeutic NLR and progress-free survival (PFS) and overall survival (OS). The ORR and DCR were also determined with clinicopathologic characteristics of those patients.
Results. Finally, 130 mCRC were enrolled from August 2014 to February 2020. The cut-off value of pre-therapeutic NLR was 2.3 based on ROC results of DCR. They revealed significant effects on ORR including primary site of mCRC, pre-therapeutic NLR and type of mCRC (p value = 0.03, 0.009, and 0.031 respectively). On the other hand, only pre-therapeutic NLR had significant effect on DCR (p value = 0.003). The overall survival rates of the patients with pre-therapeutic NLR < 2.3 were better (p value = 0.005), but no statistically significant differences on progress-free survival rates (p value = 0.246) were found.
Conclusions. Pre-therapeutic NLR might be a predictor of ORR, DCR and OS of mCRC patients treated with bevacizumab plus FOLFIRI, although a prospective study is required to confirm this result.

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The incidence of colorectal cancer (CRC) is increasing in Asian countries and is currently the fourth most common cause of cancer-related deaths after cancers of the lung, liver, and stomach.[1] Moreover, between 20% to 30% of patients present with synchronous metastatic disease, and more than 50%

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of patients ultimately develop metastatic diseases, with most being unresectable.[2] Despite recent advances in medicine, the management of patients with metastatic colorectal cancer (mCRC) remains challenging due to considerable inter-individual differences in therapeutic responses. In recent years, pharmacogenomics has been adopted for the personalization of mCRC treatment.[3] Typically, the majority of patients with mCRC receiving first-line treatment might require later lines of therapy, so first-line treatment is the most critical phase of therapy, and its effects on patient outcomes might be more prominent than those of any subsequent line. For example, absolute improvements in median overall survival (OS) even with intensive second-line regimens tend to be relatively minimal.[4-6]

Despite the importance of molecular and biological features in defining the prognosis of cancer patients, many studies have suggested the impact of the host-driven inflammatory response to tumor behavior and treatment outcomes.[7,8] Several interactions between tumoral and stromal factors, including blood vessels, inflammatory cells and the immunity system result in tumor growth and metastatic spread.[9,10] The role of inflammation markers in predicting prognosis of colorectal cancer (CRC) patients has been clearly evidenced in radically resected patients[11] and more recently suggested also in advanced settings.[12]

Pre-therapeutic neutrophil-to-lymphocyte ratio (NLR), defined as the absolute neutrophilic count divided by the absolute lymphocytic count,[13] has been reported as a poor prognostic factor in several cancers such as breast cancer,[14] gastric cancer,[15] pancreatic cancer[16] and hepatocellular carcinoma.[17] Kishi et al. demonstrated that high NLR seems to predict worse outcome in colorectal liver metastases (CRLM) patients undergoing radical resection of metastasis following neoadjuvant therapy.[18]

The aim of this analysis was to evaluate the prognostic and predictive role of pre-therapeutic NLR in mCRC patients treated with first-line FOLFIRI plus bevacizumab, while further investigating the potential of pretreatment inflammation-based scores for mCRC patients to predict the efficacy of FOLFIRI plus bevacizumab.

Materials and Methods

Patient and study design

In this retrospective observational study, mCRC patients with histologically proven synchronous or metachronous adenocarcinoma were screened. Among them, mCRC patients receiving bevacizumab plus FOLFIRI as first line therapy were enrolled. The clinicopathological characteristics included age, sex, Eastern Cooperative Oncology Group (ECOG), primary tumor site, type of mCRC, numbers of metastases and pre-treatment NLR. The treatment regimen comprised bevacizumab (5 mg/kg) as a 120-min intravenous (IV) infusion on day 1, followed by irinotecan (180 mg/m^2) plus normal saline 500 mL as 4-h IV infusion and leucovorin (200 mg/m^2) plus 5-FU (2800 mg/m^2) plus 500 mL of IV normal saline for 42-48 h; this regimen was repeated once every two weeks.

Written informed consent was obtained from each participant. The study was conducted in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki. The protocol was approved by the Institutional Review Board of Kaohsiung Medical University Hospital [KMUHIRB-E(I)-20200036].

Blood sample analysis

Pre-therapeutic NLR was calculated by percentage of neutrophil to lymphocyte on blood test. All blood tests were drawn before the first treatment of FOLFIRI plus bevacizumab.

Efficacy and safety outcome measures

Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 was used for assessment of tumor responses after six cycles of treatment. In each cycle, AEs were recorded according to the National Cancer Institute–Common Terminology Criteria for Adverse Events (NCT-CTCAE) Version 4.3.

The first recorded time of progression was defined as progression-free survival (PFS). Overall survival (OS) was the time from the date of diagnosis till death or the last date of follow-up. Object response rate

(ORR) included complete responses and partial responses; whereas disease control rate (DCR) included complete responses, partial responses and stable disease, with both of the above being documented as best response during follow-up time. We also analyzed the resection rates of primary lesion between the two groups.

Statistical analysis

Pre-therapeutic NLR cut-off value was calculated by receiver operating characteristic (ROC) curve based on DCR. The Youden index was used to determine the cut-off value of pre-therapeutic NLR. We divided them into two groups according to the cut-off value of pre-therapeutic NLR. Pearson's chi-square test was used for the significance of the correlation between pre-therapeutic NLR and clinicopathological characteristics, while the logistic analysis was used as multivariate analysis to predict the independent factors related to ORR and DCR. The cumulative progress-free survival (PFS) and overall survival (OS) were calculated by the Kaplan-Meier method, and differences in the survival rates between the two groups were analyzed using the log-rank test. All statistical analyses were performed using the Statistical Package for Social Sciences, version 21.0 (SPSS, Inc., Chicago, IL, USA). A p value of < 0.05 was considered statistically significant.

Results

Patients' characteristics

From August 2014 to February 2020, 130 mCRC patients undergoing bevacizumab plus FOLFIRI as first-line regimen were enrolled. Eleven mCRC patients including 7 patients who had less than 6 cycles of treatment, 3 patients lost to follow-up over 6 months and 1 patient with double cancers were all excluded; finally, 119 mCRC patients were analyzed.

Among them, 74 (62.2%) were male and 45 (37.8) were female with mean age of all patients being 57 years. Thirty-one (26.1%) were allocated in the right-sided mCRC and eighty-eight (73.9%) were left-sided mCRC; seventy-nine (66.4%) were synchronous mCRC, and forty (33.6%) were metachronous; while ninety-two mCRC patients (77.3%) had only one metastatic lesion but 27 (22.7%) had more than two sites. Among them, the wild type of *RAS* gene accounted for 75 mCRC patients (63.0%) and the mutant type for 44 (37.0%) (Table 1). Median follow-up time was 23 months, with interquartile range (IQR) being 20.0 months (range, 14.0-34.0 months).

Table 1. The clinicopathologic characteristics of 119 patients with metastatic colorectal cancer (mCRC) under bevacizumab plus FOLFIRI as first-line treatment

Variables	Number (%)
Gender	
Male	74 (62.2)
Female	45 (37.8)
Age (y/o)	
≥ 65	34 (28.6)
< 65	85 (71.4)
Primary site of mCRC	
R't-sided[a]	31 (26.1)
L't-sided[b]	88 (73.9)
ECOG[c]	
≥ 2	1 (0.8)
< 2	118 (99.2)
Type of mCRC	
Synchronous	79 (66.4)
Metachronous	40 (33.6)
Numbers of metastasis sites	
Only 1	92 (77.3)
≥ 2	27 (22.7)
RAS type	
Wild type	75 (63.0)
Mutant type	44 (37.0)
NLR[d]	
< 2.3	65 (54.6)
≥ 2.3	54 (45.4)
Response	
Complete response (CR)	1 (0.8)
Partial response (PR)	66 (55.5)
Stable disease (SD)	37 (31.1)
Progressive disease (PD)	15 (12.6)
Severe adverse events (SAEs)[e]	
No	95 (79.8)
Yes	24 (20.2)

[a] Right-sided mCRC: cecum + ascending colon + transverse colon. [b] Left-sided mCRC: descending colon + sigmoid colon + rectum.
[c] ECOG: eastern cooperative oncology group. [d] NLR: neutrophil-to-lymphocyte ratio.
[e] Severe adverse events: adverse events ≥ grade 3.

Cut-off value of neutrophil-to-lymphocyte ratio (NLR)

The value of AUC was 0.753 and the optimal cut-off point of pre-therapeutic NLR was observed at 2.3, with a sensitivity of 86.7% and specificity of 60.7% by DCR (Fig. 1). The 119 mCRC patients were divided into two groups according to the pre-treatment value of NLR at 2.3 (< 2.3 vs. ≥ 2.3). The clinicopathological characteristics of the two groups are summarized in Table 2; significantly, NLR ratio showed only factors related to the numbers of metastatic sites among clinicopathological characteristics. The resection rates of the primary lesion were 64.6% and 51.9% respectively (NLR < 2.3 vs. NLR ≥ 2.3) without significant difference ($p = 0.16$).

Efficacy

For ORR, the gender, age, Eastern Cooperative Oncology Group (ECOG), number of metastatic sites and *RAS* gene were not significant by using univariate and multivariate analysis (all $p > 0.05$). The sidedness of mCRC and the NLR (cut-off value at 2.3) were independent factors in ORR ($p = 0.031$ and 0.009 respectively in Table 3). For DCR, it was the only independent factor where NLR (cut-off value at 2.3) was significant via univariate and multivariate analysis ($p = 0.001$ and 0.004 respectively in Table 4).

Comparison of the median PFS and median OS for the two groups (NLR < 2.3 vs. NLR ≥ 2.3). The

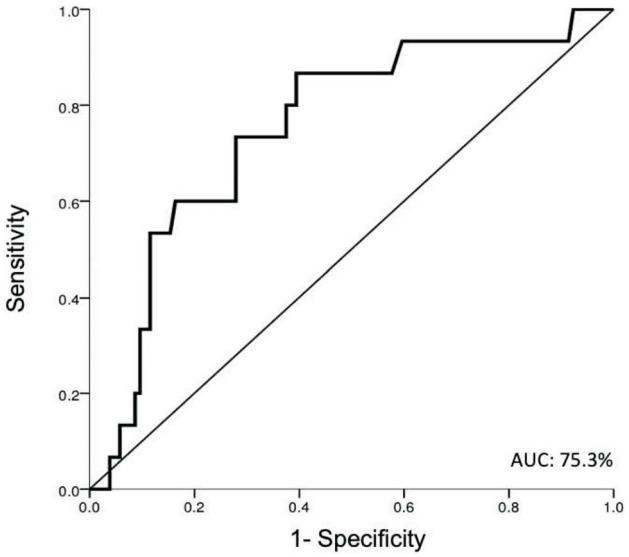

Fig 1. ROC curve of the disease-control rates (DCR) and pre-therapeutic neutrophil-to-lymphocyte ratio (NLR). The area under the curve (AUC) was 0.753 with a sensitivity of 86.7 % and specificity of 60.7%.

Table 2. Univariate analysis correlations of neutrophil-to-lymphocyte ratio (NLR) among 119 metastatic colorectal cancer (mCRC) patients

Variables	NLR < 2.3 (n = 65) (%)	NLR ≥ 2.3 (n = 54) (%)	*p*-value
Gender			
Male/Female	41 (63.1)/24 (36.9)	33 (61.1)/21 (38.9)	0.826
Age (y/o)			
≥ 65/< 65	20 (30.8)/45 (69.2)	40 (74.1)/14 (25.9)	0.560
Primary site of mCRC			
R't-sided[a]/L't-sided[b]	17 (26.2)/48 (73.8)	14 (25.9)/40 (74.1)	0.978
ECOG[c]			
≥ 2/< 2	1 (1.5)/64 (98.5)	0 (0)/54 (100)	0.360
Type of mCRC			
Synchronous/Metachronous	43 (66.2)/22 (33.8)	36 (66.7)/18 (33.3)	0.953
Numbers of metastasis sites			
Only 1/≥ 2	55 (84.6)/10 (15.4)	37 (68.5)/17 (31.5)	0.037*
RAS type			
Wild/Mutant	40 (61.5)/25 (38.5)	35 (64.8)/19 (35.2)	0.712
Resection of primary lesion			
Yes/No	42 (64.6)/23 (35.4)	28 (51.9)/26 (48.1)	0.16

[a] Right-sided mCRC: cecum + ascending colon + transverse colon. [b] Left-sided mCRC: descending colon + sigmoid colon + rectum.
[c] ECOG: eastern cooperative oncology group.

Table 3. Univariate analysis and multivariate logistic regression analysis correlations of objective response rates (ORR)[a] among 119 metastatic colorectal cancer (mCRC) patients

Variables	CR + PR (n = 67) (%)	SD + PD (n = 52) (%)	Univariate analysis[b]	Logistic analysis	
			p-value	OR[c] (95% CI[d])	*p*-value
Gender					
Male/Female	40 (59.7)/27 (40.3)	34 (65.4)/18 (34.6)	0.526	1.058 (0.630-3.660)	0.351
Age (y/o)					
≥ 65 /< 65	19 (28.4)/48 (71.6)	15 (28.8)/37 (71.2)	0.953	1.058 (0.430-2.602)	0.902
Primary site of mCRC					
R't-sided[e]/L't-sided[f]	12 (17.9)/55 (82.1)	19 (36.5)/33 (63.5)	0.022*	2.862 (1.110-7.378)	0.030*
ECOG[g]					
≥ 2 / < 2	1 (1.5)/66 (98.5)	0 (0)/52 (100)	0.376	*	1.000
Type of mCRC					
Synchronous/Metachronous	49 (73.1)/18 (26.9)	30 (57.7)/22 (42.3)	0.077	0.367 (0.148-0.911)	0.031*
Numbers of metastasis sites					
Only 1/≥ 2	56 (83.6)/11 (16.4)	36 (69.2)/16 (30.8)	0.064	2.122 (0.772-5.829)	0.145
RAS type					
Wild/Mutant	47 (70.1)/20 (29.9)	28 (53.8)/24 (46.2)	0.068	0.457 (0.194-1.078)	0.074
NLR[h]					
< 2.3/≥ 2.3	44 (65.6)/23 (34.3)	21 (40.4)/31 (59.6)	0.006*	3.050 (1.315-7.077)	0.009*

[a] ORR: objective response rates including complete response (CR) + partial response (PR).
[b] Univariate analysis: Chi-square test (two-sided).
[c] OR: odds ratio. [d] CI: confidence interval.
[e] Right-sided mCRC: cecum + ascending colon + transverse colon. [f] Left-sided mCRC: descending colon + sigmoid colon + rectum.
[g] ECOG: Eastern Cooperative Oncology Group. [h] NLR: neutrophil-to-lymphocyte ratio.

Table 4. Univariate analysis and multivariate logistic regression analysis correlations of disease-control rates (DCR)[a] among 119 metastatic colorectal cancer (mCRC) patients

Variables	CR + PR + SD (n = 104) (%)	PD (n = 15) (%)	Univariate analysis[b]	Logistic analysis	
			p-value	OR[c] (95% CI[d])	*p*-value
Gender					
Male/Female	66 (63.5)/38 (36.5)	8 (53.3)/7 (46.7)	0.450	0.671 (0.198-2.279)	0.523
Age (y/o)					
≥ 65/< 65	28 (26.9)/76 (73.1)	6 (40.0)/9 (60.0)	0.295	2.554 (0.708-9.214)	0.152
Primary site of mCRC					
R't-sided[e]/L't-sided[f]	28 (26.9)/76 (73.1)	3 (20.0)/12 (80.0)	0.568	0.572 (0.130-2.526)	0.461
ECOG[g]					
≥ 2/< 2	1 (1.0)/103 (99.0)	0 (0)/15 (100.0)	0.703	*	1
Type of mCRC					
Synchronous/Metachronous	70 (67.3)/34 (32.7)	9 (60.0)/6 (40.0)	0.575	0.654 (0.183-2.337)	0.513
Numbers of metastasis sites					
Only 1/ ≥ 2	82 (78.8)/22 (21.2)	10 (66.7)/5 (33.3)	0.292	1.495 (0.383-5.836)	0.563
RAS type					
Wild/Mutant	65 (62.5)/39 (37.5)	10 (66.7)/5 (33.3)	0.755	1.168 (0.332-4.112)	0.809
NLR[h]					
< 2.3/≥ 2.3	63 (60.6)/41 (39.4)	2 (13.3)/13 (86.7)	0.001*	11.799 (2.273-61.256)	0.003*

[a] DCR: disease-control rates including complete response (CR) + partial response (PR) + stable disease (SD).
[b] Univariate analysis: Chi-square test (two-sided).
[c] OR: odds ratio. [d] CI: confidence interval.
[e] Right-sided mCRC: cecum + ascending colon + transverse colon. [f] Left-sided mCRC: descending colon + sigmoid colon + rectum.
[g] ECOG: Eastern Cooperative Oncology Group. [h] NLR: neutrophil-to-lymphocyte ratio.

median PFS of NLR < 2.3 group was 15.5 months and 12.2 months in NLR ≥ 2.3 group [hazard ratio (HR), 0.8; 95% confidence interval (CI), 0.542-1.182; p = 0.246, Fig. 2]. However, the median OS of NLR < 2.3 group was 40.7 months and 20.8 months in NLR ≥ 2.3 group (HR, 0.518; 95% CI, 0.323-0.830; p = 0.005, Fig. 3). There was a significant difference of median OS between the two groups.

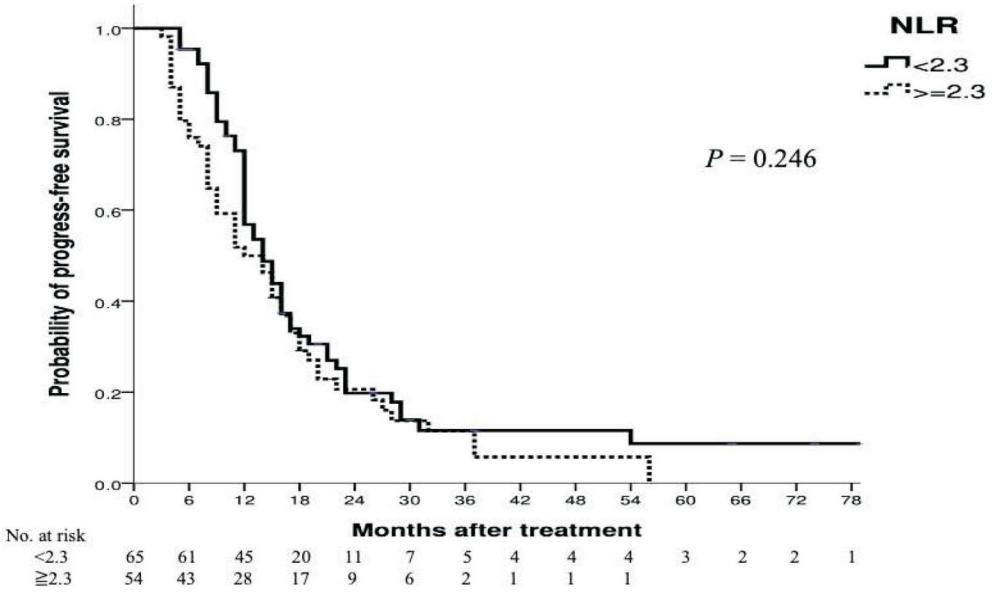

Fig. 2. The cumulative progress-free survival (PFS) rates of the 119 mCRC patients. The differences in PFS were analyzed by the log-rank test. The median PFS between the two groups (NLR < 2.3 vs. NLR ≥ 2.3) was not significant [15.5 months vs. 12.6 months; hazard ratio (HR), 0.800; 95% confidence interval (CI), 0.542-1.182; p = 0.246].

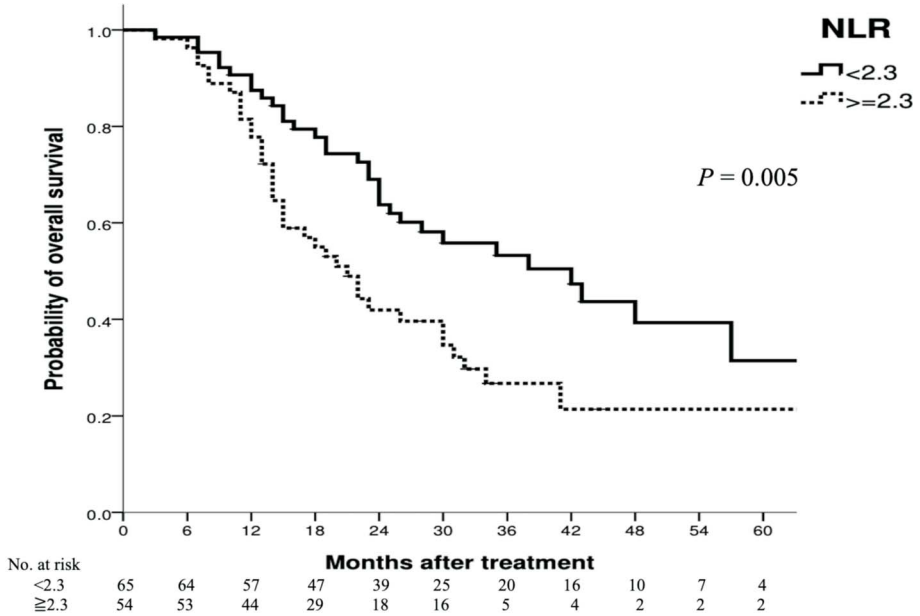

Fig. 3. The cumulative overall survival (OS) rates of the 119 mCRC patients. The differences in OS were analyzed by the log-rank test. The median OS between the two groups (NLR < 2.3 vs. NLR ≥ 2.3) was significant (40.7 months vs. 20.8 months; HR, 0.518; 95% CI, 0.323-0.830; p = 0.005).

Discussion

NLR has been suggested for prediction in prognosis of different kinds of cancer.[19-21] The proportion of neutrophil and lymphocyte in the blood stream demonstrates the severity of systemic inflammation, playing an important role in different stages of tumorigenesis. Genetic mutation, instability and modification are keys to tumor initiation. The tissue-repair activation by inflammation response induces premalignant cells, and during the process, this leads to apoptosis and DNA damage, ultimately promoting metastatic spread.[10] The value of high NLR represents raised neutrophilic and depleted lymphocytic levels.

In our current study, we selected the cut-off value of NLR as 2.3 based on ROC of DCR and ORR, with the results demonstrating that the mCRC patients with the pre-therapeutic NLR value < 2.3 were significantly superior to those patients with the pre-therapeutic NLR value ≥ 2.3 in overall survival (OS) rates.

Expert clinicians are currently seeking a simple index that can be obtained by a convenient method pre-therapeutically to assess the efficacy of mCRC patients after treatment, with the inflammatory response catching great attention on tumor development with paradoxical issues. The marker, NLR, has become one of the powerful indices that has been reported.[22] Several studies have shown the efficacy of NLR to predict prognosis in mCRC;[22-25] however, different stages, different regimens of chemotherapy, and target therapies are all reported as reflecting differing cut-off values of NLR. A meta-analysis reported by Malietzis et al. showed that cut-off value of NLR at 3.0 could be used to predict the efficacy of mCRC.[26] In previous studies, the NLR was used to predict the response of systematic chemotherapy when the cut-off value was set at 5.0;[18,27,28] however, Kubo et al. demonstrated that it had higher specificity and accuracy but lower sensitivity when the cut-off value of NLR was ≥ 5 while also suggesting that a higher cut-off point might be used to predict a prognosis in early stage cancer.[29] In our study, we found that the cut-off value of NLR at 2.3 was correlated to the numbers of metastases, ORR and DCR. On the other hand, the OS was also significantly different between the two groups (NLR < 2.3 versus NLR ≥ 2.3). Argiles et al. reported NLR was shown to be an independent prognostic factor in mCRC populations;[30] similarly, we had the same result of OS in our current study. On the other hand, NLR seemed that no significant in PFS[31] and DFS.[32] In this present study, it reported similar outcome.

The limitations of the current study were as follows: (1) it was a retrospective, observational study; (2) some patients were excluded due to noncompletion of six cycles (7 patients), loss to follow-up over 6 months (3 patients), and one patient with double cancers; (3) it was based on single-institutional research; and (4) there are several diseases conditions known to affect NLR values including acute coronary syndromes, essential hypertension, renal and liver disease, and medication use with antibiotics, antidiabetics and antihypertension drugs.[33-35] These are biases due to diversities of clinicopathological character not recorded in detail in our study. A further prospective, large case-number study is warranted to validate our observational results in the future.

In summary, the current results of this present study suggest that pre-therapeutic NLR is a simple and useful tool for predicting the efficacy of mCRC patients with bevacizumab plus FOLFIRI as first-line treatment. This index might help to determine the strategy for mCRC treatment additional to TNM staging in cancer patients.

Conclusions

In summary, we conclude that pre-therapeutic NLR could be an available predictive value on OS, ORR and DCR for mCRC patients with FOLFIRI plus bevacizumab as first-line treatment.

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Authors' Contributions

All authors contributed equally to the writing of the manuscript. All authors also reviewed any revisions that were made and provided their final approval of the manuscript.

Consent for Publication

Written informed consent was obtained for the treatment from the patients. In addition, written informed consent was obtained from the patients' family for publication of this case report and any accompanying images.

Competing Interests

The authors declare that they have no competing interests.

Sources of Financial Support

Nil.

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原　著

嗜中性球-淋巴細胞比值在以 Bevacizumab 加上 FOLFIRI 為第一線治療的轉移性結直腸癌患者效益預測上的臨床意義 – 單一機構研究

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目的　轉移性結直腸癌患者的預後是難以預測。目前，有一些預後評估的索引。本研究專注在藉由化療前血液中嗜中性球-淋巴細胞比值，來預測轉移性結直腸癌患者在以 Bevacizumab 加上 FOLFIRI 為第一線治療的效益預測的臨床意義。

方法　我們收集了 2014 年 8 月至 2020 年 2 月期間接受癌思停合併 FOLFIRI 作為一線治療的轉移性結直腸癌患者。根據疾病控制率 (DCR) 的接受者操作特徵曲線 (ROC)，我們選擇了嗜中性球-淋巴細胞比的臨界值。之後，我們分析了嗜中性球-淋巴細胞比值與無疾病進展存活率 (PFS) 和整體生存率 (OS) 之間的相關性。還根據這些患者的臨床病理特徵對反應率 (ORR) 和疾病控制率 (DCR) 進行了分類。

結果　最終，在 2014 年 8 月至 2020 年 2 月共有納入 130 位轉移性結直腸癌。根據疾病控制率 (DCR) 的接受者操作特徵曲線 (ROC) 的結果，嗜中性球-淋巴細胞比的臨界值為 2.3。對反應率 (ORR) 有顯著影響包括轉移性結直腸癌原發部位、嗜中性球-淋巴細胞比值和轉移性結直腸癌類型 (p 值分別為 0.03、0.009 和 0.031)。另一方面，只有嗜中性球-淋巴細胞比對疾病控制率 (DCR) 有顯著影響 (p 值 = 0.003)。嗜中性球-淋巴細胞比值 < 2.3 的患者整體存活率較好 (p 值= 0.005)，但無疾病進展存活率的差異則無統計學意義 (p 值= 0.246)。

結論　嗜中性球-淋巴細胞比值可以作為轉移性結直腸癌以 FOLFIRI 加上癌思停治療的反應率 (ORR)、疾病控制率 (DCR) 及整體存活率的預測因子。此外，這還是需要前瞻性的研究來證實這個結論。

關鍵詞　嗜中性球-淋巴細胞比值、轉移性大腸直腸癌、癌思停、FOLFIRI、效益。