

Retrospective Study

Prognostic significance of the lymphocyte-to-monocyte ratio in patients with metastatic colorectal cancer

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Abstract

AIM: To evaluate the prognostic significance of the lymphocyte to monocyte ratio (LMR) in patients with unresectable metastatic colorectal cancer who received palliative chemotherapy.

METHODS: A total of 104 patients with unresectable metastatic colorectal cancer who underwent palliative chemotherapy were enrolled. The LMR was calculated from blood samples by dividing the absolute lymphocyte count by the absolute monocyte count. Pre-treatment LMR values were measured within one week before the initiation of chemotherapy, while post-treatment LMR values were measured eight weeks after the initiation of chemotherapy.

RESULTS: The median pre-treatment LMR was 4.16 (range: 0.58-14.06). We set 3.38 as the cut-off level based on the receiver operating characteristic curve. Based on the cut-off level of 3.38, 66 patients were classified into the high pre-treatment LMR group and 38 patients were classified into the low pre-treatment LMR group. The low pre-treatment LMR group had a significantly worse overall survival rate ($P = 0.0011$). Moreover, patients who demonstrated low pre-treatment LMR and normalization after treatment

exhibited a better overall survival rate than the patients with low pre-treatment and post-treatment LMR values.

CONCLUSION: The lymphocyte to monocyte ratio is a useful prognostic marker in patients with unresectable metastatic colorectal cancer who receive palliative chemotherapy.

Key words: Colorectal cancer; Prognosis; Unresectable; Chemotherapy; Lymphocyte to monocyte ratio

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Core tip: We retrospectively analyzed 104 patients who had unresectable metastatic colorectal cancer. This study indicated that patients with a low pre-treatment lymphocyte to monocyte ratio (LMR) had a significantly worse overall survival rate. Moreover, patients who demonstrated low pre-treatment LMR and normalization after chemotherapy exhibited a better overall survival rate than patients with low pre-treatment and post-treatment LMR values.

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INTRODUCTION

Colorectal cancer (CRC) is the third leading cause of cancer-related death worldwide^[1]. Patients with unresectable metastatic CRC have a particularly poor prognosis. Despite the recent major advances in new cytotoxic and molecular targeted therapies for unresectable CRC that have been developed within the last 10 years^[2-5], the median survival time of patients with unresectable metastatic CRC is approximately only 30 mo^[6,7]. According to the guidelines of the European Society for Medical Oncology (ESMO), it is recommended to individualize the treatment of patients with metastatic CRC based on their tumor- and disease-related characteristics^[8]. Therefore, it is necessary to detect biomarkers for predicting survival.

It is well known that the systemic inflammatory response plays an important role in cancer progression^[9]. Markers based on systemic inflammation, such as the neutrophil to lymphocyte ratio (NLR) and Glasgow prognostic score, have been reported to be useful for predicting the prognosis in patients with various types of cancer^[10-14]. Recently, the lymphocyte to monocyte ratio (LMR), which also reflects the

degree of systemic inflammation, has been reported to correlate with survival in various types of malignancies. However, the prognostic value of the LMR has been investigated mainly in patients with hematological malignancies and there have been only a few reports focusing on patients with solid tumors, such as colon, bladder, and lung cancers^[15-22]. Moreover, to the best of our knowledge, no studies regarding the prognostic significance of the LMR in patients with unresectable metastatic CRC are available. The aim of this retrospective study was to evaluate the prognostic significance of the LMR in patients with unresectable metastatic CRC.

MATERIALS AND METHODS

Patients

We retrospectively reviewed a database of 104 patients who underwent palliative combination chemotherapy for unresectable metastatic colorectal cancer at the Department of Surgical Oncology of Osaka City University between 2005 and 2010.

The patient characteristics are listed in Table 1. The patient population consisted of 59 males and 45 females, with a median age of 64 years (range: 27-86). According to the definition of the Eastern Cooperative Oncology Group performance status (PS), 96 patients were classified as having a PS of 0, 6 patients were classified as having a PS of 1, and 2 patients was classified as having a PS of 2. Sixty patients had primary tumors located in the colon and 44 had primary tumors located in the rectum. A total of 42 patients had metachronous unresectable cancer, and 62 patients had synchronous unresectable cancer. Fifty-eight patients had only one organ affected by metastasis and 46 patients had more than one organ affected by metastasis. Among the 104 patients, 88 underwent resection of a primary tumor. All patients underwent combination chemotherapy with oxaliplatin or irinotecan plus 5-fluorouracil/leucovorin or a prodrug of 5-fluorouracil as first-line chemotherapy. There was no initiation of palliative chemotherapy for recurrence while undergoing adjuvant chemotherapy. 64 patients received 5-fluorouracil + leucovorin + oxaliplatin (FOLFOX), 26 patients received capecitabine + oxaliplatin (CapeOX), nine patients received 5-fluorouracil + leucovorin + irinotecan (FOLFIRI), and five patients received S-1 + oxaliplatin (SOX). Seventy-six patients underwent chemotherapy combined with molecular targeted therapy. The median follow-up period in the survivors was 22.4 mo (range: 2.6-69.5). During the follow-up period, a total of 67 patients died.

Evaluation

Response evaluations were performed every eight weeks. A variation of approximately one week was regarded as an allowable error. All patients were

Table 1 Patient characteristics

Age (yr)	
Median (range)	64 (27-86)
Gender	
Male	59
Female	45
Performance status	
0	96
1	6
2	2
Location of primary tumor	
Colon	60
Rectum	44
Histological type	
Well, moderately	81
Poorly, mucinous	14
KRAS	
Wild type	25
Mutant type	25
Unknown	54
Detection of unresectable tumor	
Synchronous	62
Metachronous	42
Number of organs affected by metastasis	
One organ	58
More than one organ	46
Resection of primary tumor	
No	16
Yes	88
Regimen of first-line chemotherapy	
FOLFOX	64
CapeOX	26
FOLFIRI	9
SOX	5
Molecular targeted therapy	
No	28
Yes	76
Pre-treatment LMR (mean ± SD)	4.548 ± 2.314
Pre-treatment NLR (mean ± SD)	3.204 ± 2.284

FOLFOX: 5-fluorouracil + leucovorin + oxaliplatin; CapeOX: Capecitabine + oxaliplatin; FOLFIRI: 5-fluorouracil + leucovorin + irinotecan; SOX: S-1 + oxaliplatin; LMR: Lymphocyte to monocyte ratio; NLR: Neutrophil to lymphocyte ratio.

followed up with a physical examination, blood tests, and tumor marker level measurements [*i.e.*, carcinoembryonic antigen (CEA), computed tomography, and ultrasonography].

We adopted the response evaluation criteria in solid tumors (RESIST)^[23] to classify the treatment response of each patient as one of the following: complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). An objective response was defined as either CR or PR, while disease control was defined as CR, PR, or SD.

Pre-treatment blood samples were obtained within one week before the initiation of chemotherapy and post-treatment blood samples were obtained eight weeks after the initiation of chemotherapy. The differential white blood cell count was analyzed using an XE-5000 hematology analyzer (Sysmex, Kobe, Japan) based on the manufacturer's protocol. In each case, the LMR was calculated from a blood sample by

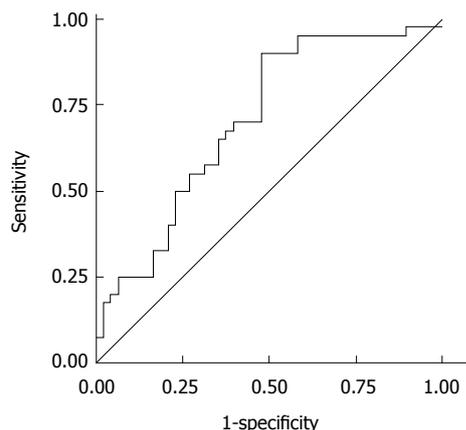


Figure 1 Receiver operating characteristic curve analysis of the lymphocyte to monocyte ratio in patients with unresectable metastatic colorectal cancer. Area under the curve = 0.703, 95%CI: 0.594-0.812, *P* = 0.001, positive predictive value = 80.65%, negative predictive value = 59.65%.

dividing the absolute lymphocyte count by the absolute monocyte count. The neutrophil to lymphocyte ratio (NLR) was calculated from a blood sample by dividing the absolute neutrophil count by the absolute lymphocyte count.

Statistical analysis

The significance of correlations between the pre-treatment LMR and the clinicopathological characteristics were analyzed using the χ^2 test, *t*-test, and Mann-Whitney *U*-test. The duration of survival was calculated according to the Kaplan-Meier method. Differences in the survival curves were assessed using the log-rank test. A multivariate analysis was performed according to the Cox proportional hazards model. All statistical analyses were conducted using the SPSS software package for Windows (SPSS Japan, Tokyo, Japan). Statistical significance was set at a value of *P* < 0.05.

Ethical consideration

This research conformed to the provisions of the Declaration of Helsinki established in 1995. All patients were informed of the investigational nature of the study and provided their written informed consent. This retrospective study was approved by the ethics committee of Osaka City University.

RESULTS

Classification according to pre-treatment LMR/NLR

We used the LMR, a continuous variable, as the test variable and the 24.8-mo survival (median survival time: 24.8 mo) as the state variable. When we investigated the cut-off value for the LMR using the receiver operating characteristic (ROC) curve, we found that the appropriate cut-off value for the LMR was 3.38 (sensitivity: 90.0%; specificity: 52.1%) (Figure 1). We therefore set 3.38 as the cut-off value and the patients

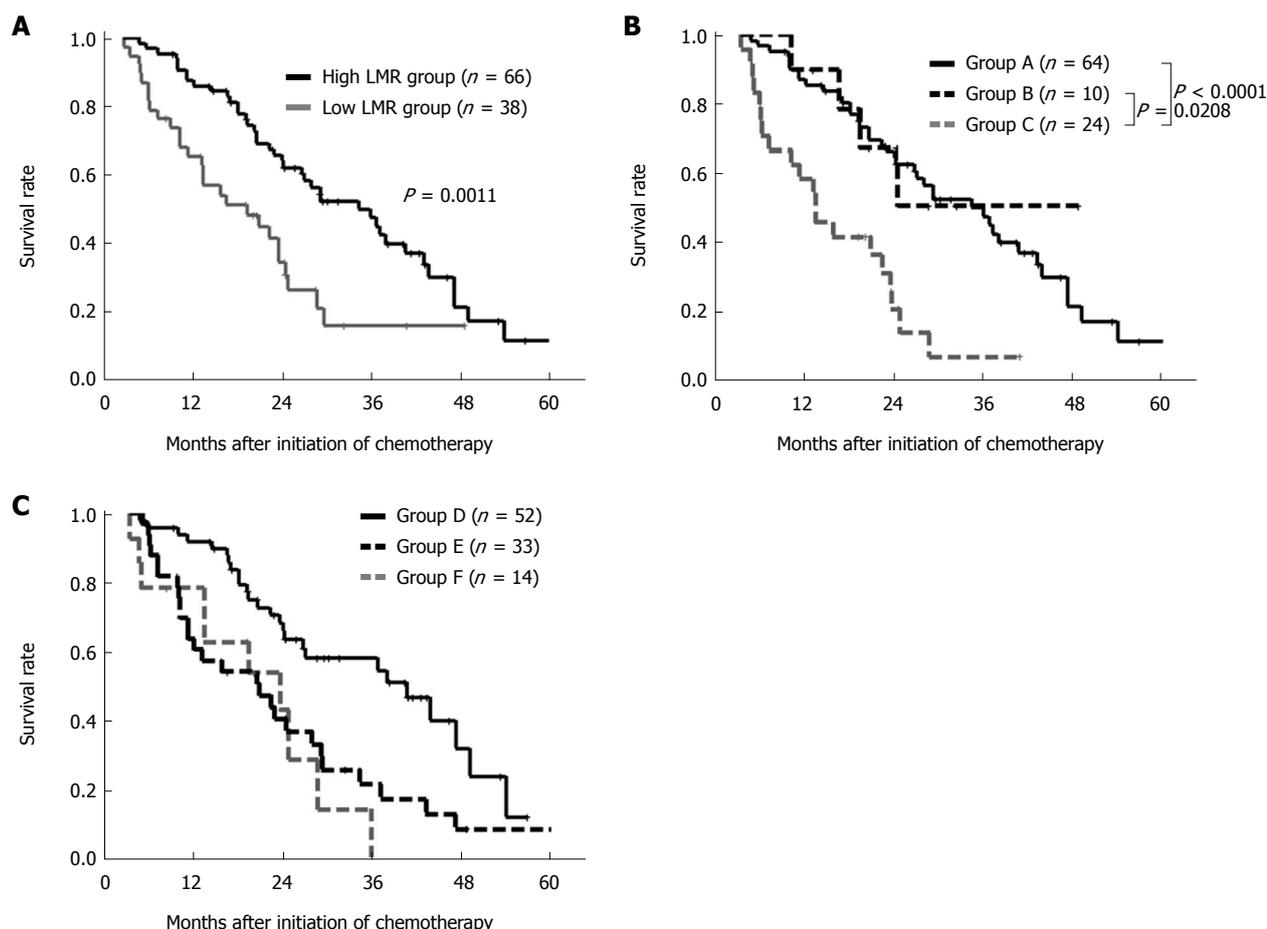


Figure 2 Overall survival. A: According to the pre-treatment LMR. The overall survival rate was significantly worse in the low pre-treatment LMR group than in the high pre-treatment LMR group ($P = 0.0011$); B: According to the combination of the pre-treatment and post-treatment LMR values. The patients in group C exhibited a worse prognosis than those in groups A and B; C: According to the combination of the pre-treatment and post-treatment neutrophil to lymphocyte ratio values. There was no significant difference between groups E and F. LMR: Lymphocyte to monocyte ratio.

were classified into high-LMR ($n = 66$) and low-LMR ($n = 38$) groups. We also set the cut-off value for the NLR at 2.8 in accordance with the findings of a previous report^[10].

Survival analysis according to pre-treatment LMR

The overall survival rate was significantly worse in the low pre-treatment LMR group than in the high pre-treatment LMR group ($P = 0.0011$) (Figure 2A).

Correlation between pre-treatment LMR and clinicopathological factors

Correlations between the pre-treatment LMR and clinicopathological factors are shown in Table 2. The pre-treatment LMR had no significant relationship with any of the clinicopathological factors, with the exception of the pre-treatment NLR.

Chemotherapeutic response

The distribution of the chemotherapeutic response after the administration of first-line chemotherapy with reference to the LMR/NLR subgroup is shown in Table 3. The objective response rate did not differ according

to the LMR (34.4% vs 28.9%, $P = 0.664$). However, the disease control rate of the high-LMR group was significantly higher than in that of the low-LMR group (82.8% vs 63.2%, $P = 0.033$). On the other hand, there was no significant relationship between the NLR and the chemotherapeutic response.

Prognostic factors influencing long-term survival

The correlations between overall survival and the various clinicopathological factors are shown in Table 4. According to the results of a univariate analysis, overall survival exhibited significant relationships with performance status ($P < 0.001$), number of organs affected by metastasis ($P = 0.045$), response to molecular targeted therapy ($P = 0.011$), response to chemotherapy ($P = 0.006$), pre-treatment LMR ($P = 0.002$), and pre-treatment NLR ($P < 0.001$). A multivariate analysis indicated that performance status (HR = 3.345, 95%CI: 1.558-7.182, $P = 0.002$), response to molecular targeted therapy (HR = 0.462, 95%CI: 0.263-0.813, $P = 0.007$), and response to chemotherapy (HR = 0.432, 95%CI: 0.244-0.765, $P = 0.004$) were independent prognostic factors for

Table 2 Correlations between the pre-treatment lymphocyte to monocyte ratio and clinicopathological factors

	Pre-treatment LMR		
	High	Low	<i>P</i> value
Performance status			
0	62	34	
1, 2	4	4	0.459
Location of primary tumor			
Colon	39	21	
Rectum	27	17	0.837
Detection of unresectable tumor			
Synchronous	39	23	
Metachronous	27	15	1.000
Resection of primary tumor			
No	8	8	
Yes	58	30	0.264
Histological type			
Well, moderately	51	30	
Poorly, mucinous	10	4	0.764
KRAS			
Wild type	15	10	
Mutant type	15	10	1.000
Peritoneal dissemination			
Negative	53	32	
Positive	13	6	0.793
Number of organs affected by metastasis			
One organ	39	19	
More than one organ	27	19	0.416
Pre-treatment CEA (ng/mL)			
≤ 5	10	3	
> 5	54	35	0.362
Average relative dose intensity (%)			
Median (range)	100 (60.0-100)	96.2 (50.0-100)	0.697
Molecular targeted therapy			
No	15	13	
Yes	51	25	0.253
Pre-treatment NLR			
< 2.8	48	5	
≥ 2.8	18	33	< 0.001

CEA: Carcinoembryonic antigen; LMR: Lymphocyte to monocyte ratio; NLR: Neutrophil to lymphocyte ratio.

survival.

Correlation between normalization of LMR/NLR eight weeks after chemotherapy and survival

We evaluated the prognostic significance of normalization of the LMR/NLR eight weeks after the initiation of chemotherapy. We categorized the patients into three groups according to the combination of their pre-treatment and post-treatment LMR values. Patients with high pre-treatment LMR were categorized into group A. Patients with low pre-treatment LMR and normalization of the LMR eight weeks after the initiation of chemotherapy were categorized into group B. Patients with low pre-treatment and post-treatment LMR value were categorized into group C. The patients in group C exhibited a worse prognosis than those in groups A and B (A vs C, $P < 0.0001$; B vs C, $P = 0.0308$) (Figure 2B). We categorized the patients into three groups according to the combination of their pre-treatment and post-treatment NLR values.

Patients with low pre-treatment LMR were categorized into group D. Patients with high pre-treatment NLR and normalization of the NLR eight weeks after the initiation of chemotherapy were categorized into group E. Patients with high pre-treatment and post-treatment NLR value were categorized into group F. There was no significant difference between groups E and F (Figure 2C).

Pre-treatment and post-treatment absolute neutrophil/lymphocyte/monocyte counts

The absolute neutrophil count tended to decrease after chemotherapy. However, the absolute lymphocyte count did not change after chemotherapy, while the absolute monocyte count tended to increase after chemotherapy (Table 5).

DISCUSSION

In this study, we investigated the prognostic significance of pre-treatment LMR as a marker for predicting chemotherapeutic response and survival time in patients with unresectable metastatic CRC. Moreover, we demonstrated that normalization of the LMR after chemotherapy resulted in improved overall survival. Recently, systemic inflammation has been recognized to correlate with tumor progression and inflammatory markers have been reported to be useful for predicting the prognosis^[9-13]. The LMR is an inflammatory marker, and a correlation between the LMR and survival has been reported^[14-21]. However, most analyses in previous studies targeted patients with hematological malignancies^[14-18]. To the best of our knowledge, this is the first study to assess the prognostic significance of the LMR in patients with unresectable metastatic CRC who received palliative chemotherapy.

Lymphocytes play an important role in the anti-tumor immunity of the host, including cytotoxic cell death and the inhibition of tumor cell proliferation and migration^[9,24-26]. The absolute lymphocyte count is assumed to reflect the degree of responsiveness of the immune system of the host^[26-28]. A decreased number of lymphocytes is therefore considered to be responsible for an insufficient immunologic reaction to the tumor, thus promoting tumor progression and metastasis^[20].

On the other hand, monocytes play an important role in tumor progression and metastasis^[9,29]. Tumor-associated macrophages (TAMs), which are derived from circulating monocytes, suppress adaptive immunity and promote angiogenesis, invasion, migration, and tumor growth^[9,30-32]. The circulating level of monocytes in the peripheral blood is reported to reflect the formation and/or presence of TAMs^[20,22]. Therefore, an increased level of monocytes reflects a high tumor burden in patients with cancer.

As mentioned above, the LMR reflects both the immune status of the host and the degree of tumor

Table 3 Treatment response to chemotherapy according to the pre-treatment lymphocyte to monocyte ratio/neutrophil to lymphocyte ratio

Response	LMR			NLR		
	High (<i>n</i> = 64)	Low (<i>n</i> = 38)	<i>P</i> value	High (<i>n</i> = 51)	Low (<i>n</i> = 51)	<i>P</i> value
CR	2	2		2	2	
PR	20	9		12	17	
SD	31	13		22	22	
PD	11	14		15	10	
Objective response rate	34.4%	28.9%	0.664	27.5%	37.3%	0.397
Disease control rate	82.8%	63.2%	0.033	70.6%	80.4%	0.357

CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; LMR: Lymphocyte to monocyte ratio; NLR: Neutrophil to lymphocyte ratio.

Table 4 Correlations between overall survival and various clinicopathological factors

	Univariate analysis			Multivariate analysis		
	HR	95%CI	<i>P</i> value	HR	95%CI	<i>P</i> value
Performance status (≥ 1)	3.821	1.805-8.087	< 0.001	3.345	1.558-7.182	0.002
Location of primary tumor (colon)	1.405	0.857-2.304	0.177			
Detection of unresectable tumor (synchronous)	1.407	0.852-2.312	0.182			
Histological type (poorly, mucinous)	1.283	0.644-2.556	0.478			
Peritoneal dissemination (yes)	0.981	0.534-1.802	0.951			
Number of organs affected by metastasis (≥ 2)	1.637	1.012-2.648	0.045	1.270	0.737-2.187	0.389
Pre-treatment CEA (> 5 ng/mL)	1.949	0.841-4.521	0.120			
Resection of primary tumor (no)	1.716	0.948-3.104	0.074	1.736	0.871-3.459	0.117
Molecular targeted therapy (yes)	0.496	0.289-0.853	0.011	0.462	0.263-0.813	0.007
Response to chemotherapy (CR, PR)	0.459	0.264-0.797	0.006	0.432	0.244-0.765	0.004
Pre-treatment LMR (< 3.38)	2.273	1.368-3.777	0.002	1.734	0.942-3.192	0.077
Pre-treatment NLR (< 2.8)	2.578	1.569-4.237	< 0.001	1.734	0.947-3.178	0.075

CEA: Carcinoembryonic antigen; CR: Complete response; PR: Partial response; LMR: Lymphocyte to monocyte ratio; NLR: Neutrophil to lymphocyte ratio.

Table 5 Pre-treatment and post-treatment absolute neutrophil/lymphocyte/monocyte counts

	Pre-treatment value	Post-treatment value	<i>P</i> value
All patients			
Neutrophil (mean \pm SD)	4538.5 \pm 200.4	2798.0 \pm 190.0	< 0.001
Lymphocyte (mean \pm SD)	1664.3 \pm 649.1	1610.5 \pm 671.0	0.247
Monocyte (mean \pm SD)	422.1 \pm 19.0	471.7 \pm 24.6	0.027
Patients receiving chemotherapy based on oxaliplatin			
Neutrophil (mean \pm SD)	4455.8 \pm 1962.6	2791.7 \pm 1859.9	< 0.001
Lymphocyte (mean \pm SD)	1694.9 \pm 695.4	1639.2 \pm 677.8	0.365
Monocyte (mean \pm SD)	412.4 \pm 181.0	457.3 \pm 248.4	0.001
Patients receiving chemotherapy based on irinotecan			
Neutrophil (mean \pm SD)	4567.6 \pm 1873.2	2879.4 \pm 2007.3	0.038
Lymphocyte (mean \pm SD)	1307.5 \pm 440.8	1238.6 \pm 342.1	0.394
Monocyte (mean \pm SD)	466.9 \pm 221.0	427.0 \pm 134.2	0.174

progression. Since both a low lymphocyte count and a high monocyte count reflect insufficient anti-tumor immunity and an elevated tumor burden, a low LMR is associated with a poorer prognosis.

In this study, normalization of the LMR eight weeks after the initiation of chemotherapy tended to correlate with an improvement in overall survival. Based on this result, the post-treatment LMR is considered to reflect the responsiveness of chemotherapy. The LMR is therefore a useful marker for monitoring tumor progression in patients with unresectable metastatic CRC who receive palliative chemotherapy.

The NLR, which has been reported to correlate with survival in patients with CRC, is quite similar to the LMR, as both results can be easily obtained from an examination of the peripheral blood. Although the pre-treatment NLR significantly correlated with the pre-treatment LMR and similar results regarding the long-term survival were obtained, only the LMR significantly correlated with the chemotherapeutic response. Moreover, in relation to the normalization of the value after chemotherapy, only the LMR significantly correlated with survival. Since the absolute neutrophil count tends to decrease after chemotherapy, the NLR

tends to improve regardless of whether the tumor is controlled. On the other hand, because the absolute monocyte count tends to increase, the LMR tends to worsen, regardless of whether the tumor progresses. The normalization of the LMR after chemotherapy despite such situations is considered to reflect tumor control. This is because the prognostic significance of normalization after chemotherapy varied between the LMR and NLR. Therefore, the LMR is considered to be superior to the NLR.

There are some possible limitations associated with this study. First, we evaluated a relatively small number of patients and the study design was retrospective. Second, factors such as infection, ischemia, and coronary syndrome, which may affect the white blood cell count, were not taken into consideration. Third, the appropriate cut-off value for the LMR was not uniform in previous studies, although we set 3.38 as the cut-off value in the current study based on the ROC curve. Large prospective studies should therefore be performed to confirm our findings.

COMMENTS

Background

Despite recent major advances in the development of new cytotoxic and molecular targeted therapies, patients with unresectable metastatic colorectal cancer (CRC) still have a poor prognosis. According to the guidelines of the European Society for Medical Oncology, it is recommended that the treatment of patients with metastatic CRC be individualized based on their tumor- and disease-related characteristics. It is therefore necessary to detect biomarkers for predicting survival.

Research frontiers

The lymphocyte to monocyte ratio (LMR) is a useful marker for predicting survival and chemotherapeutic response. This marker can therefore be used for the individualization of treatment in patients with unresectable metastatic CRC. By using this marker, the authors can identify patients with a high risk of a poor prognosis, and thereby choose the most appropriate intensive therapy.

Innovations and breakthroughs

It is difficult to predict the prognosis of patients with unresectable metastatic CRC. A few markers for predicting patient survival have been reported previously. Survival prediction is important for planning an appropriate course of treatment. The LMR was revealed to correlate with both survival and the chemotherapeutic response in the present study. The LMR makes a useful clinical biological marker because its measurement by peripheral blood cell count is a quick and easy assay to perform.

Applications

The results of the present study suggest that the LMR is a useful prognostic marker for predicting survival and chemotherapeutic response in patients with unresectable metastatic CRC who undergo palliative chemotherapy.

Terminology

The LMR was calculated from a blood sample by dividing the absolute lymphocyte count by the absolute monocyte count. The LMR reflects the immune status and systemic inflammatory response of the host. Immune status and systemic inflammation have been reported to correlate with tumor progression, invasion, and metastasis. The LMR is thus considered to correlate with the survival of patients with CRC.

Peer-review

This is a good descriptive study in which the authors evaluated the prognostic significance of the lymphocyte to monocyte ratio in patients with unresectable metastatic colorectal cancer who underwent palliative chemotherapy. The study is well structured and the subject is clear and interesting. The manuscript is correctly written and the conclusions are justified by the results found in the study.

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