

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

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Abstract. A correlation between the lymphocyte-to-monocyte ratio (LMR) and the survival of patients with hematological malignancies has been reported previously. However, there have been few studies investigating the prognostic significance of LMR in patients with solid tumors. The aim of the present study was to evaluate the prognostic significance of preoperative LMR in patients with colorectal cancer (CRC). A total of 189 patients undergoing potentially curative surgery for CRC were enrolled. The LMR was calculated from preoperative blood samples by dividing absolute lymphocyte count by absolute monocyte count. A cut-off value of 4.8 was set based on the receiver operating characteristic curve; 116 patients were classified as high-LMR, and 73 patients classified as low-LMR. The high-LMR group exhibited significantly better relapse-free survival ($P=0.0018$) and overall survival ($P=0.0127$) rates than the low-LMR group. According to the multivariate analysis of survival, preoperative LMR was identified as an independent prognostic factor for relapse-free survival ($P=0.041$) and overall survival ($P=0.031$). Therefore, preoperative LMR is a useful prognostic marker in patients with CRC.

Introduction

Colorectal cancer (CRC) is the third most common cancer and fourth leading cause of cancer-associated mortality worldwide (1). Despite advances in surgical procedures and adjuvant chemotherapy, 20-25% of patients still experience relapse following curative surgery (2). The Union for International Cancer Control (UICC) tumor node metastasis (TNM) staging system (3) is currently the most reliable indicator of patient prognosis and is widely used amongst practitioners. However, there are differences in patient prognosis even

within the same TNM stage. Therefore, more reliable markers are required to improve predictions of cancer recurrence and patient survival.

It has previously been reported that inflammation is important in determining cancer progression (4,5). Inflammation-based indices, such as the C-reactive protein level, Glasgow prognostic score, and neutrophil-to-lymphocyte ratio; are useful for predicting the prognosis of patients with CRC as well as various other types of cancer (6-9). Recent studies investigating various types of malignancies have demonstrated a correlation between the lymphocyte-to-monocyte ratio (LMR), which also reflects the degree of systemic inflammation, and patient survival (10-14). However, the prognostic value of the LMR has mainly been investigated in patients with hematological malignancies, with few reports focusing on patients with solid tumors. Therefore, the aim of this retrospective study was to evaluate the prognostic significance of preoperative LMR in patients with CRC who are able to undergo potentially curative surgery.

Materials and methods

Patients. A total of 189 patients with CRC were enrolled. All patients underwent potentially curative surgery for CRC in the Department of Surgical Oncology, Osaka City University, between January 2007 and December 2009. Patients who received preoperative therapy, underwent emergency surgery for perforation/obstruction, or who had inflammatory bowel disease were excluded from the study.

The patient characteristics are presented in Table I. Included in the study were 107 males and 82 females, and median patient age at initial surgery was 68 years old (range, 26-86 years old). A total of 112 patients had primary tumors located in the colon and 77 had primary tumors located in the rectum. Resected specimens were pathologically classified according to the UICC TNM classification of malignant tumors, ver. 7 (3). The distribution of cancer stages was as follows: stage I, 63; stage II, 65; stage III, 61 patients. All patients underwent regular physical examinations and blood tests. The levels of tumor markers, such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9), were measured, and mandatory screening was performed using colonoscopy and computed tomography until December 2014 (60 months following surgery) or patient mortality.

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Key words: colorectal cancer, prognosis, lymphocyte-to-monocyte ratio, inflammation, biomarker

Table I. Patient characteristics.

Characteristic	No. patients
Gender	
Male	107
Female	82
Age, years	
Median (range)	68 (26-86)
Location of primary tumor	
Colon	112
Rectum	77
Tumor depth	
T1-3	150
T4	39
Tumor diameter, cm	
Median (range)	4.0 (0.2-11.0)
Histological type	
Well or moderately differentiated	169
Poorly differentiated or mucinous	16
Lymphatic involvement	
Negative	76
Positive	113
Venous involvement	
Negative	163
Positive	21
Lymph node metastases	
Negative	126
Positive	63
Stage ^a	
I	63
II	65
III	61
Lymphocyte count, per mm ³	
Median (range)	1690 (432-3891)
Monocyte count, per mm ³	
Median (range)	324 (28-792)

^aAccording to the Union for International Cancer Control Tumor-Node-Metastasis Classification of Malignant Tumors (3).

Blood sample analysis. Preoperative blood samples were obtained at the time of diagnosis prior to surgery. The differential white blood cell count was analyzed using the Sysmex XE-5000 automated hematology analyzer™ (Sysmex, Kobe, Japan) following the manufacturer protocol. LMR was calculated from the preoperative blood samples by dividing the absolute lymphocyte count by the absolute monocyte count.

Statistical analysis. A receiver operating characteristic (ROC) curve was used to determine an appropriate cut-off value. All patients were classified into two groups according to the preoperative LMR. The significance of associations between preoperative LMR and clinicopathological characteristics

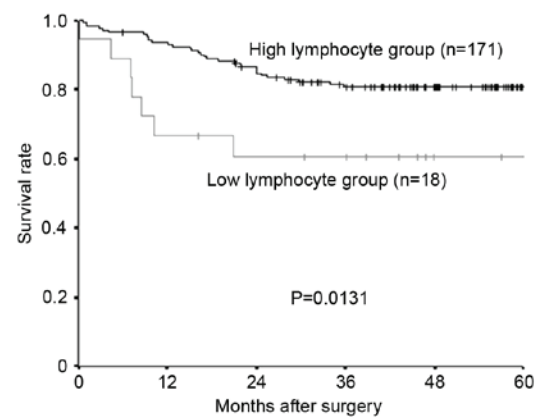


Figure 1. Kaplan-Meier survival curves for the relapse-free survival of different lymphocyte groups. The relapse-free survival rate was significantly lower in the low-lymphocyte group compared with the high-lymphocyte group ($P=0.0131$).

was analyzed using χ^2 test and Fisher's exact test. Duration of survival was calculated according to the Kaplan-Meier method. Differences between survival curves were assessed with the log-rank test. A multivariate analysis was performed according to the Cox proportional hazards model, and all statistical analyses were performed using the SPSS software package (SPSS Inc., Tokyo, Japan). $P<0.05$ was considered to indicate a statistically significant difference.

Ethical considerations. The current study conformed to the provisions of the Declaration of Helsinki and was approved by the ethics committee of Osaka City University. All patients were informed of the investigational nature of this study and provided written informed consent.

Results

Survival analysis according to the lymphocyte/monocyte count. The median preoperative lymphocyte count was 1,690/mm³ (range, 432-3,891), and 1,000 mm³ was set as the cut-off value, in accordance with previous studies (15). Following the lymphocyte count, 171 patients were placed into the high-lymphocyte group and 18 patients into the low-lymphocyte group. Relapse-free survival rate and overall survival rate were significantly lower in the low-lymphocyte group compared with the high-lymphocyte group (Fig. 1, relapse-free survival; $P=0.0131$; Fig. 2, overall survival; $P=0.0314$).

The median preoperative monocyte count was 324/mm³ (range, 28-792), and 300 was set as the cut-off value, based on previous reports (16). A total of 76 patients were placed into the high-monocyte group and 113 patients into the low-monocyte group. Both the relapse-free survival rate and the overall survival rate were significantly lower in the high-monocyte group compared with the low-monocyte group (Fig. 3, relapse-free survival; $P=0.0243$; Fig. 4, overall survival; $P=0.0444$).

Cut-off value for the LMR. The median preoperative LMR was 5.429 (range, 1.494-57.500). The continuous variable LMR was used as the test variable and the 5-year rate survival as the state variable. The cut-off value for the preoperative LMR was investigated using the ROC curve, and was determined as

Table II. Associations between preoperative LMR and clinicopathological factors.

Factors	LMR		P-value
	High	Low	
Age, years			0.073
<70	70	34	
≥70	46	39	
Gender			0.099
Male	60	47	
Female	56	26	
Tumor location			0.880
Colon	68	44	
Rectum	48	29	
Tumor depth			0.196
T1-3	96	54	
T4	20	19	
Tumor diameter, cm			0.063
<5	75	37	
≥5	38	34	
Histological type			0.789
Well/moderately differentiated	105	64	
Poorly differentiated/mucinous	9	7	
Lymphatic involvement			0.013
Negative	52	19	
Positive	61	52	
Venous involvement			0.352
Negative	98	65	
Positive	15	6	
Lymph node metastasis			0.156
Negative	82	44	
Positive	34	29	
Preoperative CEA (>5 ng/ml)			1.000
Negative	77	47	
Positive	38	24	
Stage ^a			0.139
I	44	19	
II	40	25	
III	32	29	
Adjuvant chemotherapy			0.881
No	64	39	
Yes	52	34	

LMR, lymphocyte-to-monocyte ratio; CEA, carcinoembryonic antigen. ^aAccording to the Union for International Cancer Control Tumor-Node-Metastasis Classification of Malignant Tumors (3). Bold indicates a statistically significant difference (P<0.05).

4.8 (the sensitivity was 64.1% and the specificity was 63.2%; Fig. 5). Based on this cut-off value, 116 patients were classified into the high-LMR group and 73 patients were classified into the low-LMR group.

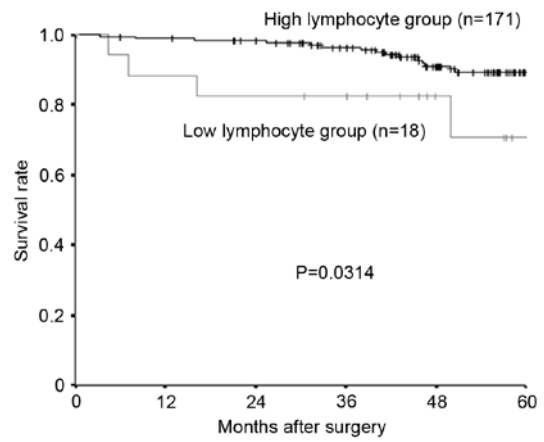


Figure 2. Kaplan-Meier survival curves for the overall survival. The overall survival rate was significantly lower in the low-lymphocyte group than in the high-lymphocyte group (P=0.0314).

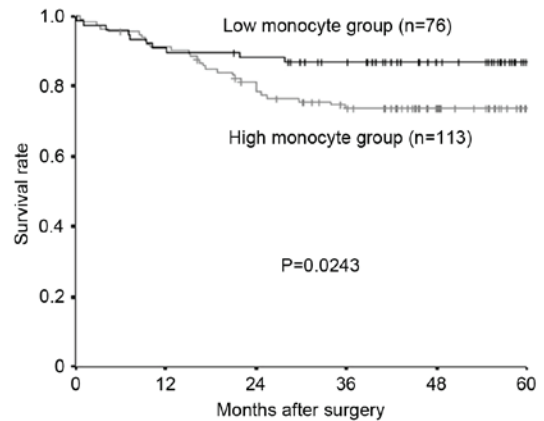


Figure 3. Kaplan-Meier survival curves for the relapse-free survival of different monocyte groups. The relapse-free survival rate was significantly lower in the high-monocyte group compared with the low-monocyte group (P=0.0243).

Correlation between the LMR and clinicopathological parameters. The associations between preoperative LMR and clinicopathological parameters are shown in Table II. The only significant relationship identified was between preoperative LMR and lymphatic involvement (P=0.013, Table II).

Survival analysis according to the LMR. The relapse-free survival rate was significantly lower in the low-LMR group compared with that of the high-LMR group (P=0.0018; Fig. 6), as was overall survival rate (P=0.0127; Fig. 7).

Furthermore, even in an analysis limited to the patients with a normal lymphocyte count (>1,000/mm³), relapse-free survival rate was significantly lower in the low-LMR group than in the high-LMR group (P=0.0071; Fig. 8), and overall survival rate tended to be lower in the low-LMR group than in the high-LMR group, though this difference was not significant. (P=0.0792; Fig. 9).

Prognostic factors influencing relapse-free/overall survival. The associations between relapse-free survival and various clinicopathological factors are presented in Table III. According

Table III. Associations between relapse-free survival and various clinicopathological factors.

Factors	Univariate analysis			Multivariate analysis		
	Hazard Ratio	95% CI	P-value	Hazard Ratio	95% CI	P-value
Age (>70 years vs. ≤70 years)	1.433	0.764-2.685	0.262			
Gender (female vs. male)	1.575	0.809-3.064	0.181			
Location of primary tumor (rectum vs. colon)	1.545	0.824-2.985	0.175			
Tumor depth (T4 vs. T1-3)	1.396	0.680-2.865	0.363			
Tumor diameter (>5 cm vs. ≤5 cm)	2.421	1.256-4.669	0.008	1.259	0.597-2.655	0.546
Histological type (poor, mucinous vs. well, moderately)	2.777	1.222-6.308	0.015	1.607	0.678-3.805	0.281
Lymphatic involvement (positive vs. negative)	3.211	1.417-7.276	0.005	1.946	0.676-5.600	0.217
Venous involvement (positive vs. negative)	1.782	0.787-4.039	0.166			
Lymph node metastasis (positive vs. negative)	3.362	1.775-6.366	<0.001	2.041	0.904-4.606	0.086
Preoperative CEA (>5 ng/ml vs. ≤5 ng/ml)	2.590	1.369-4.899	0.003	1.923	0.913-4.054	0.086
Preoperative LMR (≥4.8 vs. <4.8)	2.657	1.403-5.033	0.003	2.051	1.028-4.090	0.041

CI, confidence interval; CEA, carcinoembryonic antigen; LMR, lymphocyte-to-monocyte ratio. Bold denotes a statistically significant result (P<0.05).

Table IV. Correlations between overall survival and various clinicopathological factors.

Factors	Univariate analysis			Multivariate analysis		
	Hazard Ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
Age (>70 years vs. ≤70 years)	1.386	0.562-3.416	0.479			
Gender (female vs. male)	1.713	0.651-4.508	0.275			
Location of primary tumor (rectum vs. colon)	1.909	0.767-4.748	0.164			
Tumor depth (T4 vs. T1-3)	0.689	0.201-2.365	0.553			
Tumor diameter (>5 cm vs. ≤5 cm)	1.224	0.492-3.047	0.664			
Histological type (poor, mucinous vs. well, moderate)	1.172	0.271-5.078	0.832			
Lymphatic involvement (positive vs. negative)	2.379	0.790-7.169	0.124			
Venous involvement (positive vs. negative)	2.663	0.959-7.396	0.060			
Lymph node metastasis (positive vs. negative)	2.814	1.132-6.996	0.026	2.533	1.014-6.328	0.047
Preoperative CEA (>5 ng/ml vs. ≤5 ng/ml)	2.008	0.815-4.946	0.130			
The preoperative LMR (≥4.8 vs. <4.8)	3.081	1.212-7.830	0.018	2.805	1.098-7.163	0.031

CI, confidence interval; CEA, carcinoembryonic antigen; LMR, lymphocyte-to-monocyte ratio. Bold denotes a statistically significant result (P<0.05).

to a univariate analysis, there were significant correlations between relapse-free survival and tumor diameter, histological type, lymphatic involvement, lymph node metastasis, preoperative CEA levels and the preoperative LMR (all P<0.05). Multivariate analysis indicated that only preoperative LMR was an independent risk factor for a poor relapse-free survival. The associations between overall survival and various clinicopathological factors are presented in Table IV. According to a univariate analysis, there were significant correlations between overall survival and both lymph node metastasis and preoperative LMR. In addition, a multivariate analysis indicated that lymph node metastasis and preoperative LMR were independent risk factors for poor overall survival.

Discussion

Inflammation and cancer are closely related. Inflammation is caused not only by the systemic reaction of the host to the tumor, but also by inflammatory cytokines and chemokines released by cancer cells, and tumor-associated leukocytes that cause tumor growth, invasion, metastasis and suppression of the host immune system (4,5,17,18). Thus, inflammation reflects cancer progression, and the significance of systemic inflammatory markers in predicting the survival of patients with CRC, as well as other malignancies, has previously been reported. LMR, which consists of the peripheral lymphocyte and monocyte counts, also reflects systemic inflammation.

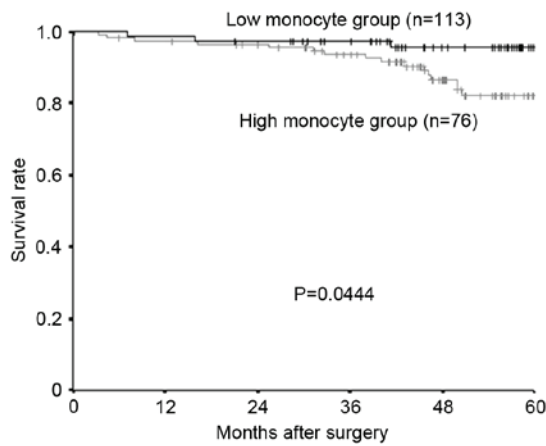


Figure 4. Kaplan-Meier survival curves for the overall survival of different monocyte groups. The overall survival rate was significantly worse in the high-monocyte group than in the low-monocyte group ($P=0.0444$).

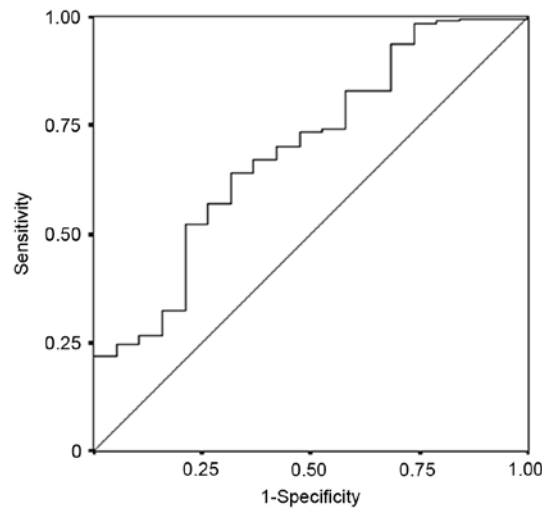


Figure 5. The results of a receiver operating characteristic curve analysis of the LMR in patients with colorectal cancer who underwent potentially curative surgery. Area under the curve, 0.694; 95% confidence interval, 0.568-0.819; $P=0.006$. LMR, lymphocyte-to-monocyte ratio.

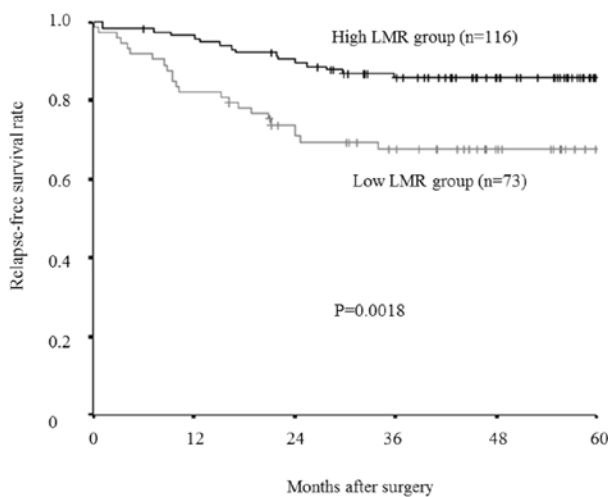


Figure 6. Kaplan-Meier survival curves for the relapse-free survival of different LMR groups. The relapse-free survival rate was significantly lower in the low-LMR group compared with the high-LMR group ($P=0.0018$). LMR, lymphocyte-to-monocyte ratio.

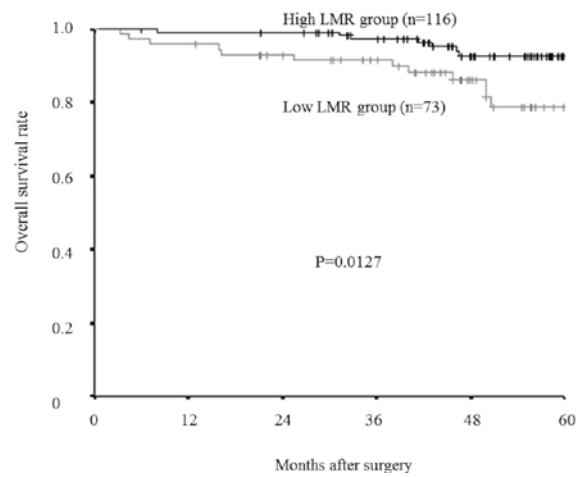


Figure 7. Kaplan-Meier survival curves for the overall survival rate of different LMR groups. The overall survival rate was significantly lower in the low-LMR group than in the high-LMR group ($P=0.0127$). LMR, lymphocyte-to-monocyte ratio.

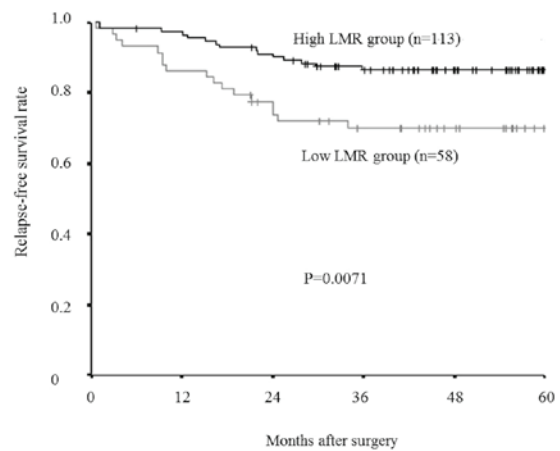


Figure 8. Kaplan-Meier survival curves for the relapse-free survival in an analysis limited to the patients with a normal lymphocyte count. The relapse-free survival rate was significantly lower in the low-LMR group than in the high-LMR group ($P=0.0071$). LMR, lymphocyte-to-monocyte ratio.

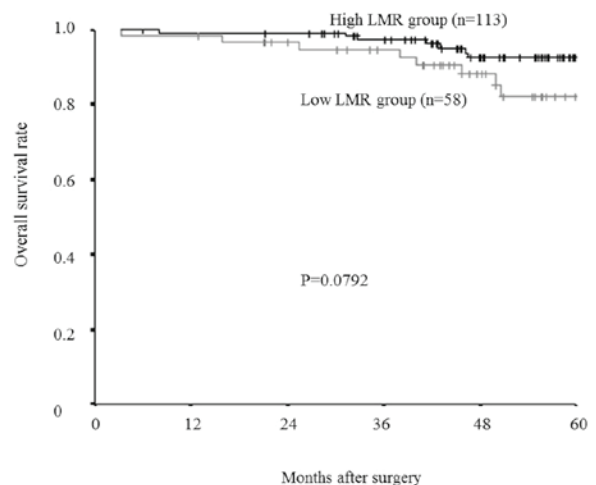


Figure 9. Kaplan-Meier survival curves for the overall survival in an analysis limited to the patients with a normal lymphocyte count. The overall survival rate tended to be lower in the low-LMR group compared to the high-LMR group, however the difference was not significant ($P=0.0792$). LMR, lymphocyte-to-monocyte ratio.

Lymphocytes serve an important role in tumor suppression. Previous studies have demonstrated a correlation between lymphopenia and poor prognosis of patients with various types of cancer (15,19). Lymphocytes induce cytotoxic cell death and produce cytokines that inhibit cancer cell proliferation and metastatic activity (4,20,21). The absolute peripheral lymphocyte count is assumed to reflect the degree of responsiveness of the entire immune system of a patient (15,22). Therefore, a low peripheral lymphocyte count may result in a weak and insufficient immunological reaction to the tumor, thus promoting tumor progression and metastasis (23).

By contrast, monocytes play an important role in tumor progression (4,24). A correlation between monocytosis and poor prognosis in different types of cancer has previously been observed (16,25-27). Monocytes represent a source of chemokines and cytokines that contribute to inflammation (28). Inflammation in the cancer microenvironment promotes tumor progression and metastasis (29). Moreover, tumor-associated macrophages (TAMs), derived from circulating monocytes (30), cause migration, intravasation, tumor cell invasion, tumor-associated angiogenesis, and the suppression of the anti-tumor immune system (4,31-33). The absolute peripheral monocyte count reflects the formation and/or presence of TAMs (34), thus a high peripheral monocyte count is responsible for a high tumor burden. Therefore, low LMR reflects insufficient antitumor immunity and an elevated tumor burden, and is associated with poor patient prognosis.

In previous studies, both the lymphocyte and the monocyte count have been reported as prognostic factors for the survival of patients with various malignancies, and this was confirmed in the present study. Furthermore, the prognostic significance of LMR was investigated, and was demonstrated to be an accurate prognostic marker. Even in an analysis limited to patients with a normal lymphocyte count, the LMR identified patients with a poor prognosis. Therefore, the LMR is considered to be a more accurate prognostic marker than the lymphocyte count alone.

The cut-off value for the LMR used in the present study was different from that of previous studies. A cut-off value of 4.8 was set based on a ROC analysis, and was higher than cut-off values used in previous studies, which ranged between 2.14-4.19 (12-14,35). Thus, although LMR is a useful prognostic marker for various solid tumors, the optimum cut-off value for the LMR may differ according to the organ, stage or end point (such as disease-free survival, progression-free survival or overall survival).

There are several limitations associated with the present study: i) A relatively small number of patients were evaluated; ii) the study design was retrospective; iii) the results obtained were not validated in another population; iv) potential confounding factors, such as infection, ischemia or acute coronary disease, which may affect the white blood cell count, were not assessed; v) the optimum cut-off value for the preoperative LMR remains unknown, although 4.8 was set as the cut-off value using the results of a ROC analysis. Therefore, a large prospective study is required to confirm the findings of the current study.

In conclusion, preoperative LMR may be a useful prognostic marker in patients with CRC able to undergo potentially curative surgery, and assessing the LMR may enable more informed decisions regarding choice of therapeutic strategies to be made. It is quick and easy to obtain a peripheral blood cell count,

therefore, measuring preoperative LMR may become a novel clinical biomarker for patients with CRC.

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