ORIGINAL RESEARCH

Lymphocyte-to-monocyte ratio before chemoradiotherapy represents a prognostic predictor for locally advanced rectal cancer

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Abstract: Research indicates that cancer-triggered inflammation plays a pivotal role in carcinogenesis. Here, we aimed to evaluate the correlation of lymphocyte-to-monocyte ratio (LMR) before neoadjuvant chemoradiotherapy (CRT) with clinical outcomes in patients with locally advanced rectal cancer (LARC). We retrospectively enrolled 317 consecutive patients with LARC between 2004 and 2013. The optimal cutoff values of LMR were determined using receiver operating curve analysis. Overall survival (OS) and disease-free survival related to the LMR were analyzed using the log-rank test and multivariate Cox regression methods. We found that a low LMR (≤ 4.91) was prominently correlated with worse prognostic features and a shorter 3-year survival rate of LARC. Moreover, multivariate Cox analysis revealed that elevated LMR was an independent factor for better OS (hazard ratio 0.538, 95% confidence interval 0.292–0.991, P=0.047). In addition, univariate logistic regression analysis showed that the LMR was not associated with tumor pathologic regression. In conclusion, LMR is identified as a valuable prognostic marker for predicting the OS of LARC patients receiving CRT.

Keywords: rectal cancer, lymphocyte-monocyte ratio, prognosis, systemic inflammation

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the fourth leading cause of cancer-related mortality worldwide.[1] Rectal cancer accounts for approximately 30% of CRC and is associated with worse clinical outcomes.[2,3] Current treatment guidelines for locally advanced rectal cancer (LARC) include preoperative chemoradiotherapy (CRT), total mesorectal excision (TME) and postoperative adjuvant chemotherapy.[4] CRT combined with TME has been shown to significantly reduce the rate of local disease recurrence and improve the rectal cancer sphincter preservation rate.[5] However, not all patients benefit from CRT;[6] thus, identifying biomarkers that can predict the efficacy of CRT is essential for decision making in the management of patients with CRC. Research has shown that reduced E-cadherin, nucleic beta-catenin and reduced expression of mir200c were all significantly associated with nonresponse to neoadjuvant therapy,[7] but the inspection method is expensive. Previous studies have suggested that inflammation plays a critical role in the carcinogenesis and progression of cancer.[8,9] In addition, it has recently been reported that the lymphocyte-to-monocyte ratio (LMR) is an independent predictor of overall survival (OS) in patients with CRC undergoing curative resection,[10] and studies have reported that the preoperative LMR is a simple and useful prognostic indicator in patients with stage IV CRC who have undergone curative resection.[11] However, evidence of

preoperative LMR as a prognostic predictor in patients with LARC receiving CRT remains limited. Accordingly, this study investigated the association between LMR before CRT and clinical outcomes in patients with LARC.

Materials and methods
Patients
The present study retrospectively enrolled consecutive patients undergoing primary tumor resection and preoperative CRT with curative intent from April 2004 to June 2013 at Sun Yat-sen University Cancer Center, People's Republic of China. The enrolled patients met the following inclusion criteria: 1) histologically confirmed adenocarcinoma; 2) T3–4 or N+ disease initially; 3) preoperative chemotherapy with XELOX regimen (capecitabine plus oxaliplatin); and 4) completed radical resection. Patients were excluded from the analysis if they had metastatic disease before or during preoperative treatment, had other active malignancies, died within 1 month postoperatively, or had missing preoperative data on the number of blood cells. Patient demographics, primary tumor characteristics, preoperative treatment, and follow-up results were reviewed in detail from the medical records and the follow-up system. The present study was undertaken according to the ethical standards of the World Medical Association Declaration of Helsinki. Institutional Review Board approval was obtained from independent ethics committees at Sun Yat-sen University Cancer Center, with a waiver of informed consent as this research was retrospective and did not involve accessing any identifying patient data. The raw data in this paper has been successfully uploaded and locked onto Research Data Deposit with a RDD number of RDDA2017000378.

CRT and surgery
Patients were evaluated using a combination of colonoscopy, computed tomography (CT), ultrasonography, and magnetic resonance imaging (MRI) before CRT. Tumor stage was classified according to the seventh edition of the American Joint Committee on Cancer tumor node metastasis classification system. One to four cycles of XELOX regimen included oxaliplatin at 130 mg/m^2 on Day 1 and capecitabine at 1,000 mg/m^2 twice daily on Days 1–14 with an interval of 7 days. Radiotherapy consisted of 46.0–50.0 Gy delivered in 23–25 fractions of 2 Gy five times per week. The target field included the tumor bed, the surrounding intestines, and the presacral and iliac lymphatic drainage areas. Radical surgical resection was planned for 6–8 weeks after completing CRT. The primary tumor surgical types included Dixon, Miles,

TME, and other surgical procedures. Each surgical resection specimen was reviewed by an experienced pathologist. Pathologic response was classified in five categories as proposed by Mandard et al:[12] tumor regression grade (TRG) 1, no residual cancer cells; TRG 2, rare residual cancer cells; TRG 3, fibrosis outgrowing residual cancer; TRG 4, residual cancer outgrowing fibrosis; and TRG 5, absence of regressive change.

Inflammatory index calculation
The systemic inflammatory data (lymphocyte and monocyte counts), carcinoembryonic antigen (CEA) and cancer antigen 199 (CA199) were collected from routine blood tests that were taken before neoadjuvant therapy. Neutrophil and lymphocyte counts were determined by routine blood test using Sysmex XE-5000TM Automated Hematology System (Sysmex, Shanghai, People's Republic of China). The LMR was calculated by dividing the absolute number of circulating lymphocytes by the absolute number of monocytes. CEA and CA199 were detected using electrochemiluminescence immunoassay system (Elecsys 1601; Roche, Basel, Switzerland), and the cutoff values for CEA and CA199 were 5 ng/mL and 35 U/mL, respectively, according to the manufacturer's instructions. The values lower than the cutoff values were considered negative.

Follow-up
The follow-up protocol included evaluations every 3 months for the first 2 years after the completion of surgery, every 6 months for the third to fifth years and then once every year thereafter. Evaluations at each visit included complete blood count, CEA and CA199 measurements, and physical examination. Chest radiography, abdominal and pelvic CT, pelvic endoscopic ultrasonography or MRI were conducted every 12 months during follow-up. Colonoscopy was performed annually. OS was defined as the time from the date of surgery to the date of death or last follow-up, and disease-free survival (DFS) was defined as the time from the date of surgery to the date of disease recurrence or last follow-up. All follow-up statistics were reviewed by December 31, 2016.

Statistical analysis
The statistical analysis was performed using the IBM SPSS Statistics 20.0 software (SPSS, Chicago, IL, USA) and GraphPad Prism 7 software (GraphPad Software, Inc, San Diego, CA, USA). Receiver operating curve (ROC) analysis was performed to evaluate the sensitivity and specificity of the LMR for predicting 3-year OS. The Youden index was

estimated to select the optimal cutoff value of the LMR. We compared continuous variables that were normally distributed using Student's *t*-test and categorical variables using the chi square test or Fisher's test. The Kaplan–Meier method was used to estimate the survival rates for different groups, and the differences in the survival curves were compared with the log-rank test. The Cox proportional hazards model and the logistic regression model were used for univariate and multivariate survival analyses. *P*<0.05 was considered statistically significant.

Results
Patient characteristics and determination of the cutoff point
The optimal cutoff value of the LMR was 4.91, corresponding to maximum sensitivity and specificity (0.464 and 0.731, respectively) of the LMR for predicting 3-year OS in ROC analysis, and the Youden index was 0.182. The area under the curve was 0.584 for 3-year OS (95% confidence interval [CI], 0.513–0.654, *P*=0.036). Patients were then assigned either to the LMR-high (LMR >4.91) group or the LMR-low (LMR ≤4.91) group (Figure 1).

Among the 317 LARC patients, 64.7% (205/317) were males and 35.3% (112/317) were females, the median age was 55 years (range 15–78 years) and the average completed cycles of XELOX was 2.54 (range 1–8). In addition, among

the patients 34.3% (85/317) had a complete pathologic response, 25% (62/317) were diagnosed with stage 1 disease, 40.7% (101/317) were diagnosed with stage 2 disease and 21.8% (69/317) were diagnosed with stage 3 disease. The median interval days from radiotherapy to surgery was 49 days (range 7–168 days).

The associations of baseline characteristics with 3-year OS in LARC patients are listed in Table 1. As shown in Table 1, the high-LMR group had more female patients (*P*=0.022) and more cycles of XELOX treatment before surgery (*P*=0.002). Additionally, a higher proportion of the high-LMR group received intensity-modulated radiation therapy (*P*=0.002), and 50 Gy of radiotherapy dose (*P*=0.001) .

Association between patient characteristics and tumor pathologic regression
The association between patient characteristics and tumor pathologic regression after CRT is shown in Table 2. The univariate logistic regression analysis showed that the LMR was not associated with tumor pathologic regression. The multivariate analysis showed that well-differentiated histology (odds ratio, 7.453; 95% CI, 1.911–17.662; *P*=0.002) was associated with better pathologic response.

Analysis of the prognostic impact of the LMR on OS and DFS
To identify the association of the LMR before CRT with the clinical outcomes in patients with LARC, we evaluated the LMR and clinicopathologic factors in univariate and multivariate analyses. With a median follow-up time of 51 months (range 1–109 months), six (1.9%) patients were identified as having local recurrence, 68 (21.5%) patients were identified as having distant metastasis (liver metastases, 11; lung metastasis, 35; pelvic cavity metastasis, eight; bone metastases, eight; and other metastases, 11), 57 (21.1%) patients had cancer-related deaths and 10 (3.2%) were other causes of death. Kaplan–Meier analysis indicated that the 3-year OS rate in the high-LMR group was significantly higher than that in the low-LMR group (87.9% vs 74.3%, *P*=0.019; Figure 2A). By contrast, the 3-year DFS rates of the low- and high-LMR groups were 73.3% and 83.2%, respectively, and this rate was not significantly different between the subgroups (*P*=0.096; Figure 2B).

The univariate analysis revealed that the higher LMR was associated with better 3-year OS rates (hazard ratio [HR], 0.493; 95% CI, 0.269–0.904; *P*=0.022) (Table 3). In addition,
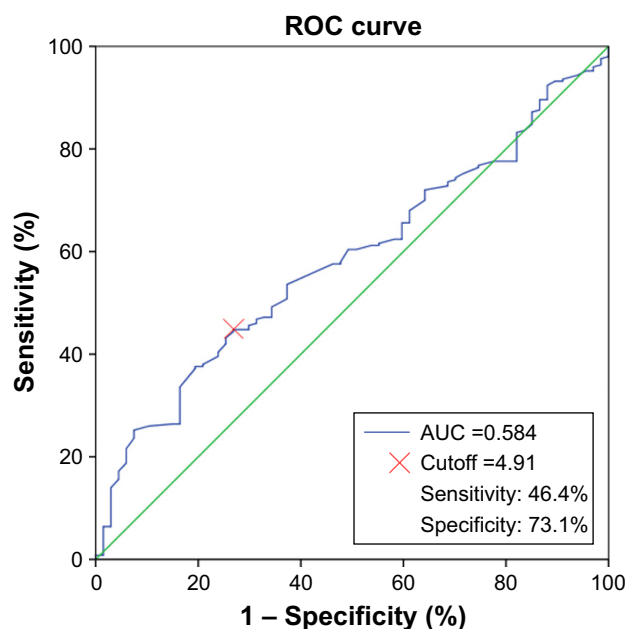

ROC curve

Figure 1 ROC for determination of the cutoff value for the LMR in patients with locally advanced rectal cancer with preoperative chemoradiotherapy.
Abbreviations: ROC, receiver operating curve; LMR, lymphocyte-to-monocyte ratio; AUC, area under the curve.

Table 1 Clinical characteristics of the patients stratified by LMR

Characteristics	Total n=317 (%)	LMR ≤4.91	>4.91	P-value
Age (years)				0.538
≤60	212 (66.9)	138	74	
>60	105 (33.1)	72	33	
Sex				0.022
Male	205 (64.7)	145	60	
Female	112 (35.3)	65	47	
Cycles of neoadjuvant XELOX regimen				<0.002
1	13 (4.1)	10	3	
2	162 (51.1)	117	45	
3	63 (19.9)	42	21	
4	79 (24.9)	41	38	
Radiotherapy model				<0.002
IMRT	154 (48.6)	87	67	
3D-CRT	146 (46.1)	110	36	
Conventional RT	17 (5.4)	13	4	
Radiation dose (Gy)				0.001
46	171 (53.9)	127	44	
50	146 (46.1)	83	63	
Interval from radiotherapy to surgery (days)				0.174
≤49	210 (66.2)	117	93	
>49	107 (33.8)	51	56	
Tumor size (cm)				0.133
≤3	226 (71.3)	144	82	
>3	91 (28.7)	66	25	
DAV (cm)				0.176
≤5	165 (52.1)	115	50	
>5	152 (47.9)	95	57	
Postoperative TNM stage				<0.191
pCR	85 (26.8)	53	32	
I	62 (19.6)	40	22	
IIA	59 (18.6)	35	24	
IIB	42 (13.2)	35	7	
IIIA	16 (5.0)	7	9	
IIIB	48 (15.1)	36	12	
IIIC	5 (2.0)	3	2	
TRG				0.097
1–2	160 (50.5)	99	61	
3–5	157 (49.5)	111	46	
Surgical type				<0.064
Anterior resection	203 (64.0)	125	78	
Abdominal perineal resection	106 (33.4)	79	27	
Others	8 (2.5)	6	2	
Tumor differentiation				0.841
Well differentiated	34 (10.7)	22	12	
Moderately or poorly differentiated	283 (89.3)	188	95	
Pre-CRT CEA (ng/mL)				0.528
≤5	161 (50.8)	104	57	
>5	156 (49.2)	106	50	
Pre-CRT CA199 (U/mL)				0.120
≤35	264 (83.3)	170	94	
>35	53 (16.7)	40	13	

Note: *P*-value, the correlation between clinical–pathological parameters and LMR was assessed by the chi-square test or Fisher's exact test.
Abbreviations: LMR, lymphocyte-to-monocyte ratio; XELOX, oxaliplatin 130 mg/m^2 administered intravenously on Day 1 and capecitabine administered orally 1,000 mg/m^2 twice daily on Days 1–14 for a 3-week cycle; IMRT, intensity-modulated radiation therapy; 3D-CRT, 3-dimensional conformal radiation therapy; RT, radiotherapy; DAV, distance of inferior tumor margin from the anal verge; TNM, tumor node metastasis; pCR, pathologic complete response; TRG, tumor regression grade; CRT, chemoradiotherapy; CEA, carcinoembryonic antigen; CA199, cancer antigen 199.

tumor size less than 3 cm, I/II stage, 1–2 of tumor regression grading and preoperative CA199 less than 35 U/mL were associated with better 3-year OS rates of LARC. On the other hand, tumor size less than 3 cm, I/II stage, 1–2 of tumor regression grading and preoperative CA199 less than 35 U/mL were associated with better 3-year DFS rates of LARC.

The multivariate analysis showed that I/II stage (HR, 3.004; 95% CI, 1.862–4.959; *P*<0.001), CA199 ≤35 U/mL (HR, 1.906; 95% CI, 1.116–3.254; *P*=0.018) and LMR >4.91 (HR, 0.538; 95% CI, 0.292–0.991; *P*=0.047) were significant prognostic factors for 3-year OS rate. Similarly, tumor ≤3 cm (HR, 1.927; 95% CI, 1.214–3.059; *P*=0.005) and CA199 ≤35 U/mL (HR, 3.182; 95% CI, 1.996–5.074; *P*<0.001) were also defined as independent factors for 3-year DFS rate.

Discussion

Nearly 150 years ago, Rudolf Virchow speculated that cancer is similar to the chronic inflammatory process of wound healing, as he noticed the presence of a large amount of leukocyte infiltration in tumor tissues.[8] Epidemiologic and clinical studies support his notion and show that approximately 25% of all human cancers in adults result from chronic inflammation.[13] Research has shown that inflammation plays an important role in the onset, development and therapeutic response of many tumors. It contributes to tumor proliferation, angiogenesis and metastasis and it defeats the adaptive immune responses.[9,10,14]

Systemic inflammation is achieved by the increased movement of plasma and leukocytes (includes lymphocytes and monocytes) from the blood into the inflamed tissue. Research has shown that cytotoxic T cells use two basic mechanisms to destroy their target cells: one is elicited by granule exocytosis (perforin [PRF1] and granule-associated enzymes [granzymes, GZM]) and the other occurs via the death ligand/death receptor system and is ultimately responsible for killing the cancer cells and eradicating the tumor.[15] Lymphocytes are key factors in immunosurveillance, and the occurrence of an immunologic antitumor reaction depends on lymphocytic infiltration into the tumor microenvironment.[16–18] However, tumor-induced systemic inflammation will depress cellular immunity significantly, resulting in a significant decrease of CD4$^+$ T lymphocytes and an increase of CD8$^+$ suppressor T lymphocytes.[19] Researchers have found that the lymphocyte-mediated immune reaction may play a positive role in achieving the complete eradication of tumor cells.[20] Accordingly, for patients with rectal cancer who underwent CRT, maintaining the number of lymphocytes is beneficial to the prognosis of the patients.[21] On the other hand, Augier

Table 2 The univariate and multivariate analyses of the factors influencing tumor pathologic regression response in locally advanced rectal cancer after preoperative chemoradiotherapy

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age (years)				
≤60	1 (reference)		–	
>60	0.941 (0.556–1.591)	0.820	–	
Sex				
Male	1 (reference)		–	
Female	0.934 (0.557–1.568)	0.797	–	
Cycles of preoperative XELOX regimen				
1–2	1 (reference)		–	
3–4	0.883 (0.536–1.453)	0.624	–	
Radiotherapy model				
IMRT	1 (reference)		–	
3D-CRT	1.504 (0.896–2.524)	0.122	–	
Conventional RT	1.054 (0.352–3.161)	0.925	–	
Radiation dose (Gy)				
46	1 (reference)		–	
50	0.685 (0.416–1.129)	0.138	–	
Interval from radiotherapy to surgery (days)				
≤49	1 (reference)		–	
>49	0.677 (0.411–1.115)	0.125	–	
Tumor size (cm)				
≤3	1 (reference)		–	
>3	2.060 (1.120–3.789)	0.020	–	
DAV (cm)				
≤5	1 (reference)		–	
>5	1.050 (0.638–1.727)	0.848	–	
Clinical TNM stage				
I/II	1 (reference)		–	
III	1.420 (0.832–2.423)	0.199	–	
Surgical type				
Anterior resection	1 (reference)	0.289	–	
Abdominal perineal resection	1.434 (0.831–2.474)		–	
Others	2.937 (0.354–24.393)		–	
Tumor differentiation				
Well differentiated	1 (reference)		1 (reference)	
Moderately or poorly differentiated	7.453 (3.445–16.125)	<0.001	7.453 (1.911–17.662)	0.002
Pre-CRT CEA (ng/mL)				
≤5	1 (reference)		–	
>5	3.113 (1.825–5.309)	<0.001	–	
Pre-CRT CA199 (U/mL)				
≤35	1 (reference)		–	
>35	1.487 (0.727–3.043)	0.277	–	
LMR				
≤4.91	1 (reference)		–	
>4.91	0.791 (0.471–1.328)	0.375	–	

Notes: *P*-value; in logistic regression analysis, variables found to be statistically significant (*P*<0.05) in univariate analysis were entered into a logistic regression multivariate model using a forward conditional method. '–' indicates multivariate analysis not performed.
Abbreviations: OR, odds ratio; CI, confidence interval; XELOX, oxaliplatin 130 mg/m² administered intravenously on Day 1 and capecitabine administered orally 1,000 mg/m² twice daily on Days 1–14 for a 3-week cycle; IMRT, intensity-modulated radiation therapy; 3D-CRT, 3-dimensional conformal radiation therapy; RT, radiotherapy; DAV, distance of inferior tumor margin from the anal verge; TNM, tumor node metastasis; CRT, chemoradiotherapy; CEA, carcinoembryonic antigen; CA199, cancer antigen 199; LMR, lymphocyte-to-monocyte ratio.

et al reported that inflammatory monocytes may contribute to cancer development.[22] Ozawa et al also reported that macrophages from within the tumor or those in peripheral locations and in the precursor blood of tumor-bearing mice are all targets of immunosuppressive strategies in tumor hosts, and within developing tumors, macrophages can help the progression of the disease.[11] Finally, a growing amount of evidence indicates that tumor growth is closely associated
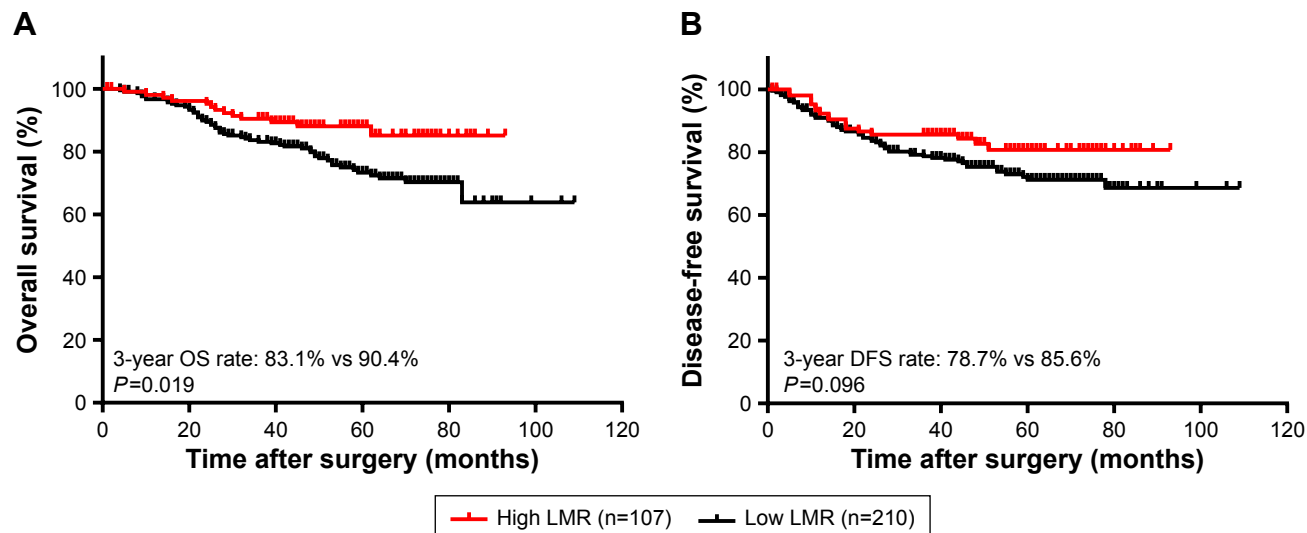
Figure 2 (**A**) Kaplan–Meier curves of LMR for 3-year OS, (**B**) Kaplan–Meier curves of LMR for 3-year DFS.
Abbreviations: LMR, lymphocyte-to-monocyte ratio; OS, overall survival; DFS, disease-free survival.

Table 3 The univariate and multivariate analyses of the factors influencing OS and DFS by the Cox proportional hazard model

	OS				DFS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (years)								
≤60	1 (reference)		–		1 (reference)		–	
>60	1.167 (0.711–1.915)	0.541	–		0.868 (0.530–1.420)	0.572	–	
Sex								
Male	1 (reference)		–		1 (reference)		–	
Female	0.874 (0.525–1.457)	0.606	–		1.095 (0.685–1.752)	0.704	–	
Cycles of preoperative XELOX regimen								
1–2	1 (reference)		–		1 (reference)		–	
3–4	0.931 (0.566–1.559)	0.785	–		1.007 (0.628–1.615)	0.977	–	
Radiotherapy model								
IMRT	1 (reference)	0.500	–		1 (reference)	0.732	–	
3D-CRT	1.101 (0.646–1.876)		–		1.005 (0.618–1.634)		–	
Conventional RT	1.685 (0.705–4.026)		–		1.406 (0.582–3.395)		–	
Radiotherapy dose (Gy)								
46	1 (reference)		–		1 (reference)		–	
50	0.922 (0.806–1.054)	0.231	–		0.787 (0.486–1.276)	0.331	–	
Interval from radiotherapy to surgery (days)								
≤49	1 (reference)		–		1 (reference)		–	
>49	0.714 (0.432–1.180)	0.189	–		0.658 (0.409–1.058)	0.084	–	
Tumor size (cm)								
≤3	1 (reference)		–		1 (reference)		1 (reference)	
>3	1.852 (1.138–3.013)	0.013	–		2.035 (1.284–3.225)	0.002	1.927 (1.214–3.059)	0.005
DAV (cm)								
≤5	1 (reference)		–		1 (reference)		–	
>5	0.705 (0.430–1.153)	0.163	–		1.067 (0.676–1.683)	0.782	–	
Postoperative TNM stage								
pCR I–II	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
III	3.253 (2.000–5.291)	<0.001	3.004 (1.837–4.912)	<0.001	3.300 (2.071–5.257)	<0.001	3.182 (1.996–5.075)	<0.001
TRG								
1–2	1 (reference)		–		1 (reference)		–	
3–5	2.062 (1.245–3.414)	0.005	–		1.926 (1.199–3.092)	0.007	–	

(Continued)

Table 3 (*Continued*)

	OS				DFS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Surgical type								
Anterior resection	I (reference)	0.017	–		I (reference)	0.099	–	
Abdominal perineal resection	1.702 (1.037–2.795)		–		1.347 (0.837–2.168)		–	
Others	3.503 (1.240–9.897)		–		2.805 (1.004–7.834)		–	
Tumor differentiation								
Well differentiated	I (reference)		–		I (reference)		–	
Moderately or poorly differentiated	2.754 (0.865–8.771)	0.087	–		2.393 (0.873–6.555)	0.090	–	
Pre-CRT CEA (ng/mL)								
≤5	I (reference)		–		I (reference)		–	
>5	1.581 (0.973–2.570)	0.064			1.530 (0.965–2.424)	0.070	–	
Pre-CRT CA199 (U/mL)								
≤35	I (reference)		I (reference)		I (reference)		–	
>35	2.332 (1.381–3.940)	0.002	1.906 (1.116–3.254)	0.018	2.025 (1.212–3.384)	0.007	–	
LMR								
≤4.91	I (reference)		I (reference)		I (reference)		–	
>4.91	0.493 (0.269–0.904)	0.022	0.538 (0.292–0.991)	0.047	0.640 (0.376–1.089)	0.100	–	

Notes: *P*-value; in Cox hazards regression analysis, variables found to be statistically significant (*P*<0.05) in univariate analysis were entered into a Cox regression multivariate model using a forward conditional method. '–' indicates multivariate analysis not performed.
Abbreviations: OS, overall survival; DFS, disease-free survival; HR, hazard ratio, CI, confidence interval; XELOX, oxaliplatin 130 mg/m² administered intravenously on Day 1 and capecitabine administered orally 1,000 mg/m² twice daily on Days 1–14 for a 3-week cycle; IMRT, intensity-modulated radiation therapy; 3D-CRT, 3-dimensional conformal radiation therapy; RT, radiotherapy; DAV, distance of inferior tumor margin from the anal verge; TNM, tumor node metastasis; pCR, pathologic complete response; TRG, tumor regression grade; CRT, chemoradiotherapy; CEA, carcinoembryonic antigen; CA199, cancer antigen 199; LMR, lymphocyte-to-monocyte ratio.

with myeloid cell recruitment, including macrophages. Under the influence of multiple microenvironmental signals, macrophages polarize towards phenotypes with pro-tumoral activities.[23] Through our analysis, we found that tumor-triggered inflammation resulted in reduced LMR. At the same time, systemic inflammation promoted cancer progression, eventually resulting in an unfavorable prognosis in LARC patients.

Our findings demonstrate that the LMR before CRT is an independent predictor of OS for patients with LARC. Our findings are consistent with previous studies on the relationship between the LMR and the prognosis of many other cancers, such as small cell lung cancer, ovarian cancer, esophageal cancer and nonmetastatic clear cell renal cell carcinoma.[24–27]

However, multivariate analysis in our study indicates that the LMR failed to play a predictive role in DFS. Similarly, researchers found that according to univariate analysis the LMR was not associated with recurrence-free survival.[28] This might be explained by the fact that the LMR is unable to predict postoperative recurrence of LARC after preoperative CRT.[29]

For patients with LARC, we can use MRI, abdominal CT, CEA and genetic testing to determine the patient's disease progression. However, these tests are both expensive and inconvenient. The LMR is a convenient and low-cost marker that is not only reproducible but also easily accessible. Therefore, the LMR biomarker may be helpful in differentiating high-risk from low-risk disease and in determining the form of adjuvant therapy to use in order to achieve maximum therapeutic effectiveness.

Several limitations of the present study should be addressed. First, this is a retrospective study with an uncontrolled methodology. Second, only 317 patients were enrolled in our study, which may have resulted in bias during analysis. Third, appropriate cutoff levels of LMR were calculated for OS using the ROC analysis. In fact, these cutoff variables were not consistent with those in previous studies. Thus, a reasonable cutoff value that could be used to prospectively predict the prognosis of LARC should be identified. Finally, several disease conditions, such as infection, ischemia and trauma, which may bias the blood-circulating cell counts, were not taken into consideration.

Conclusion

The findings of our study indicate that a lower LMR before preoperative CRT is an independent prognostic biomarker for OS in LARC patients. Therefore, based on the level of LMR,

the surgeon can assess the LARC patient's OS and formulate individualized strategies for preoperative treatment.

Disclosure

The authors report no conflicts of interest in this work.

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