Prognostic role of the lymphocyte-to-monocyte ratio in patients undergoing resection for nonmetastatic rectal cancer

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Abstract
Lymphocyte-to-monocyte ratio (LMR) was associated with survival benefit in some types of cancer. The relationship between LMR and rectal cancer has not been investigated. We conducted a retrospective cohort study to assess the prognostic significance of LMR in patients with nonmetastatic rectal cancer. Patients with rectal cancer who underwent potentially curative resection between January 2009 and December 2013 were enrolled. The LMR was calculated from preoperative blood test by dividing the absolute lymphocyte counts by the absolute monocyte counts. The optimal cut-off value for LMR was calculated as the median value. On the basis of the cut-off value, patients were divided into 2 groups: low group and high group. A total of 543 patients with rectal cancer were eligible for this study. The median follow-up time for all patients was 55 months (range 6–85 months). The cut-off value of LMR was 5.13 and patients were divided into 2 groups: low group (LMR $<$ 5.13) and high group (LMR $\geq$ 5.13). In the univariate and multivariate analysis, the LMR was not significantly associated with overall survival (OS) [hazard ratio (HR): 1.034, 95% confidence intervals (CIs): 0.682–1.566, $P = 0.876$]. When disease-free survival (DFS) was compared, univariate and multivariate analysis also indicated that the LMR was not significantly associated with DFS (HR: 0.988, 95% CI: 0.671–1.453, $P = 0.950$). In addition, in the subgroup analysis by tumor-node-metastasis stage, there existed no significance between LMR and OS and DFS. Although as an easy access and highly efficient laboratorial inflammatory marker, LMR cannot predict the prognosis of nonmetastatic rectal cancer patients.

Abbreviations: AUC = area under curve, CI = confidence intervals, CRC = colorectal cancer, CT = computed tomography, DFS = disease-free survival, HR = hazard ratio, LMR = lymphocyte-to-monocyte ratio, MRI = magnetic resonance imaging, OS = overall survival.

Keywords: disease-free survival, lymphocyte-to-monocyte ratio, overall survival, prognosis, rectal cancer

1. Introduction

Colorectal cancer (CRC) is the third most common cancer and fourth leading cause of cancer-related deaths worldwide.[1] Although treatment strategies for CRC have been developed, surgery is still the main option for nonmetastatic disease. However, the outcomes for patients who underwent curative surgery were not satisfied because about 40% of those patients died of it.[2] Generally, outcomes following surgery are mainly determined by pathological tumor characteristics, such as tumor-node-metastasis (TNM) stage system. Patients with same TNM stage, however, may have different oncologic outcomes.[3] It is increasingly recognized that not only TNM stage but also neo-adjuvant therapy, adjuvant therapy, and systemic inflammatory response is connected with CRC outcomes.

Since Virchow[4] in 1863 first reported the link between inflammation and tumorigenesis, many other studies have shown that systemic inflammatory response played a critical role in the pathogenesis and progression of cancer, including CRC.[5–8] Approximately 20% of tumor occurrence was associated with chronic inflammation, and even about 15% of cancer-related deaths were closely associated with chronic inflammation or unresolved infection.[6,9] As a marker of systemic inflammatory response, recent studies have proved that the elevated pretreatment lymphocyte-to-monocyte ratio (LMR) was associated with favorable survival in hematologic malignancies.[10–12] In addition, it has been proved for the first time that preoperative LMR was a good prognostic marker in patients with colon cancer by Stotz et al in 2014.[13] Since then, several other studies also showed that LMR was a prognostic factor for patients with metastatic CRC.[14–18] Besides, Xiao et al[19] focused on rectal cancer patients with pT3N0 and suggested that elevated LMR can predict a favorable prognosis. However, to the best of our knowledge, there is no report that investigated LMR and nonmetastatic rectal cancer with a large sample size. Thus, we conducted this retrospective study to investigate the prognostic

significance of LMR in patients with nonmetastatic rectal cancer with a large sample size.

2. Methods

2.1. Patients

Patients with rectal cancer underwent potentially curative resection between January 2009 and December 2013 at the Department of Gastrointestinal Surgery, West China Hospital, Sichuan University, and were enrolled in this retrospective study. The inclusion criteria were histologically confirmed rectal carcinoma and checked blood test in 2 weeks before surgery and LMR could be calculated. Exclusion criteria were as follows: Neoadjuvant therapy, Presence of metastatic disease, Presence of infection, Beyond 85 years old, and Died within 1 month after surgery. Ethical approval was not necessary because this study was a retrospective study.

Patient demographics and clinicopathological characteristics were collected, including gender, age, pretreatment carcinoembryonie antigen (CEA), tumor location, tumor size, differentiation, TNM stage, vascular invasion, perineural invasion, adjuvant therapy, and lymphocyte and monocyte counts. TNM stage was assessed according to the American Joint Committee on Cancer TNM staging standard, 7th edition. The LMR was calculated from blood test by dividing the absolute lymphocyte counts by the absolute monocyte counts.

2.2. Follow-up

Follow-up was performed every 3 months intervals for the first 2 years, every 6 months intervals in the next 3 years, and every 12 months intervals after 5 years after surgery. The examinations included physical examination, blood test, CEA levels, computed tomography (CT) of chest, and CT or magnetic resonance imaging (MRI) of abdominal and pelvic (every 6 months within the first 2 years and every 12 months after 2 years after surgery) and colonoscopy (every 2 years). Local recurrence was defined as the recurrent disease in the pelvis or at the incision, while the distant recurrence was defined as the recurrence beyond the above parts. Both of them were confirmed by biopsy, CT, or MRI. Follow-up data of all enrolled patients were available.

2.3. Statistical analysis

The primary endpoint and the secondary endpoint of this study were overall survival (OS) and disease-free survival (DFS), respectively. OS was the time of surgery to the date of death from any causes or the date of follow-up, while DFS was calculated from the surgery to the recurrence or end of follow-up.

The optimal cut-off value for LMR was calculated as the median value. The Chi-square test or Fisher exact test was used to analyze the association between clinicopathologic characteristics and LMR. The OS and DFS were analyzed and compared by using the Kaplan–Meier method and the log-rank test. Multivariate analysis was performed using Cox proportional hazards regression. Data analyses were all carried out using SPSS software (version 22.0; SPSS Inc., Chicago, IL). A P value <0.05 was recognized as statistical significance.

3. Results

3.1. Patient characteristics

A total of 543 patients with rectal cancer who underwent potentially curative resection were eligible for this study. All patients were followed up until January 31, 2016. And the median follow-up time was 55 months (range 6–85 months). The cut-off value of LMR, based on the median value, was 5.13. According to the cut-off value, patients were divided into 2 groups: low group (LMR <5.13) and high group (LMR ≥5.13).

3.2. Correlations between LMR and clinicopathological factors

A comparison of the basic clinicopathological characteristics of those 2 groups is summarized in Table 1. The CEA, tumor location, difference, TNM stage, vascular invasion, perineural invasion, and adjuvant treatment were not statistically different between the 2 groups, while the gender ($P=<0.001$), age ($P=0.005$), and tumor size ($P=0.003$) existed statistically different between the 2 groups.

3.3. Survival outcomes

As summarized in Tables 2, in the univariate and multivariate analysis, the LMR was not significantly associated with OS [hazard ratio (HR): 1.034, 95% confidence intervals (CIs): 0.682–1.566, $P=0.876$; Fig. 1A], while age, CEA, tumor location, difference, and TNM stage were associated with OS. When DFS was compared in Table 3, univariate and multivariate analysis indicated that the LMR was also not significantly

Table 1

Patient clinicopathological characteristics.

Characteristics	Total = 543			P
	Overall	Low	High	
Gender				**<0.001**
Female	212	85 (40.1%)	127 (59.9%)	
Male	331	186 (56.2%)	145 (43.8%)	
Age, y				**0.005**
<65	342	155 (45.3%)	187 (54.7%)	
≥65	201	116 (57.7%)	85 (42.3%)	
CEA, ng/mL				0.140
<5	355	183 (51.5%)	172 (48.5%)	
≥5	168	75 (44.6%)	93 (55.4%)	
Tumor location				0.387
Low	253	124 (49.0%)	129 (51.0%)	
Middle	213	103 (48.4%)	110 (51.6%)	
High	77	44 (57.1%)	33 (42.9%)	
Tumor size				**0.003**
<5	414	192 (46.4%)	222 (53.6%)	
≥5	125	77 (61.6%)	48 (38.4%)	
Differentiation				0.296
G1+ G2	400	205 (51.3%)	195 (48.7%)	
G3+ G4	143	66 (46.2%)	77 (53.8%)	
TNM				0.986
I	156	77 (49.4%)	79 (50.6%)	
II	166	83 (50.0%)	83 (50.0%)	
III	221	111 (50.2%)	110 (49.8%)	
Vascular invasion				0.631
No	498	247 (49.6%)	251 (50.4%)	
Yes	45	24 (53.3%)	21 (46.7%)	
Perineural invasion				0.358
No	523	259 (49.5%)	264 (50.5%)	
Yes	20	12 (60.0%)	8 (40.0%)	
Adjuvant treatment				0.445
No	176	92 (52.3%)	84 (47.7%)	
Yes	367	179 (48.8%)	188 (51.2%)	

CEA = carcinoembryonie antigen, TNM = tumor-node-metastasis.
Bold values mean $P < 0.05$.

Table 2

Univariate and multivariate analyses of LMR for OS in patients with nonmetastatic rectal cancer.

Characteristic	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Gender				
Female	1 (reference)		1 (reference)	
Male	1.441 (0.957–2.170)	0.080	1.389 (0.906–2.130)	0.132
Age, y				
<65	1 (reference)		1 (reference)	
≥65	1434 (0.982–2.094)	0.062	1.673 (1.118–2.502)	**0.012**
CEA, ng/mL				
<5	1 (reference)		1 (reference)	
≥5	2.936 (1.999–4.313)	**<0.001**	2.109 (1.397–3.184)	**<0.001**
Tumor location, cm				
Low	1 (reference)		1 (reference)	
Middle	0.799 (0.540–1.182)	0.261	0.858 (0.566–1.300)	0.470
High	0.200 (0.073–0.549)	**0.002**	0.199 (0.027–0.555)	**0.002**
Tumor size, cm				
<5	1 (reference)		1 (reference)	
≥5	1.352 (0.883–2.071)	0.165	0.881 (0.559–1.390)	0.586
Differentiation				
G1+ G2	1 (reference)		1 (reference)	
G3+ G4	3.603 (2.467–5.261)	**<0.001**	2.396 (1.574–3.647)	**<0.001**
TNM				
I	1 (reference)		1 (reference)	
II	4.775 (1.971–11.567)	**0.001**	3.394 (1.371–8.406)	**0.008**
III	10.644 (4.633–24.457)	**<0.001**	6.346 (2.624–15.350)	**<0.001**
Vascular invasion				
No	1 (reference)		1 (reference)	
Yes	2.268 (1.367–3.763)	**0.002**	0.942 (0.537–1.652)	0.835
Perineural invasion				
No	1 (reference)		1 (reference)	
Yes	3.348 (1.686–6.648)	**0.001**	1.986 (0.964–4.093)	0.063
Adjuvant treatment				
No	1 (reference)		1 (reference)	
Yes	0.829 (0.558–1.230)	0.352	0.713 (0.470–1.084)	0.113
LMR				
LMR ≥5.13	1 (reference)		1 (reference)	
LMR <5.13	0.964 (0.661–1.406)	0.848	1.034 (0.682–1.566)	0.876

CEA = carcinoembryonie antigen, CI = confidence intervals, HR = hazard ratio, LMR = lymphocyte-to-monocyte ratio, TNM = tumor-node-metastasis.
Bold values mean $P < 0.05$.

associated with DFS (HR: 0.988, 95% CI: 0.671–1.453, $P=$ 0.950; Fig. 1B) (Table 2). In addition, in the subgroup analysis by TNM stage, there existed no significance between LMR and OS and DFS (Fig. 2).

4. Discussion

In the present study, we evaluated the prognostic significance of LMR in patients with nonmetastatic rectal cancer who underwent potentially curative resection. Our study cohort demonstrated that there was no association between LMR and OS (HR: 1.034, 95% CI: 0.682–1.566, $P=0.876$) or DFS (HR: 0.988, 95% CI: 0.671–1.453, $P=0.950$). There was no significance between LMR and OS or DFS in the subgroup analysis by TNM stage, either.

The association between inflammation and tumorigenesis was first reported by Virchow.[4] Since then, strong evidence suggests that inflammation plays a critical role in cancer onset, development, and therapeutic response.[6,7,20,21] As a marker of systemic inflammatory response, the LMR, which can be easily gained from peripheral blood test, is drawing increasing attention.

Although lymphopenia usually predicts disease severity[22] and can cause immune escape of tumor cells from tumor-infiltrating lymphocytes,[23] different subtypes of lymphocyte can have a different influence on tumor. Even the same type of lymphocyte may have different function. It has been already shown that elevated levels of tumor-infiltrating lymphocytes predicted a better survival in patients with CRC.[24] However, regulatory T cells, which are kind of lymphocytes, may play a positive,[25–27] negative,[28–30] or nonpredictive[31,32] role in combating CRC.

Similarly, monocytes can also have a different influence on tumor. Monocyte-associated macrophages are suggested to have a crucial role in host antitumor immunity suppression, tumor cell migration, and invasion.[33–35] Moreover, monocytes and their progeny can produce factors promoting the growth and survival of tumor cells.[36,37] Nevertheless, Forssell et al[38] showed that a dense macrophage infiltration at the tumor invasive margin was a good prognostic factor for colon cancer patients. From the above, the relationship between LMR and the prognosis of CRC is not clear.

Different to these aforementioned reports which indicated that elevated LMR predicted a significantly favorable OS and/or DFS in CRC patients,[13–19] our study suggested that LMR was not

Table 3

Univariate and multivariate analyses of LMR for DFS in patients with nonmetastatic rectal cancer.

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Gender				
Female	1 (reference)		1 (reference)	
Male	1.359 (0.928–1.989)	0.115	1.320 (0.887–1.965)	0.171
Age, y				
<65	1 (reference)		1 (reference)	
≥65	1.021 (0.707–1.474)	0.912	1.156 (0.784–1.705)	0.464
CEA, ng/mL				
<5	1 (reference)		1 (reference)	
≥5	2.293 (1.597–3.291)	**<0.001**	1.660 (1.129–2.441)	**0.010**
Tumor location, cm				
Low	1 (reference)		1 (reference)	
Middle	0.765 (0.526–1.114)	0.162	0.790 (0.532–1.173)	0.242
High	0.302 (0.139–0.658)	**0.003**	0.322 (0.146–0.711)	**0.005**
Tumor size, cm				
<5	1 (reference)		1 (reference)	
≥5	1.371 (0.918–2.047)	0.123	1.038 (0.676–1.595)	0.864
Differentiation				
G1+ G2	1 (reference)		1 (reference)	
G3+ G4	3.523 (2.464–5.037)	**<0.001**	2.278 (1.536–3.379)	**<0.001**
TNM				
I	1 (reference)		1 (reference)	
II	3.347 (1.584–7.071)	**0.002**	2.476 (1.144–5.358)	**0.021**
III	8.114 (4.077–16.150)	**<0.001**	4.808 (2.295–10.076)	**<0.001**
Vascular invasion				
No	1 (reference)		1 (reference)	
Yes	3.202 (2.032–5.045)	**<0.001**	1.287 (0.773–2.143)	0.332
Perineural invasion				
No	1 (reference)		1 (reference)	
Yes	3.951 (2.119–7.365)	**<0.001**	2.206 (1.133–4.294)	**0.020**
Adjuvant treatment				
No	1 (reference)		1 (reference)	
Yes	1.037 (0.706–1.522)	0.853	0.856 (0.571–1.282)	0.450
LMR				
LMR ≥5.13	1 (reference)		1 (reference)	
LMR <5.13	1.019 (0.714–1.456)	0.915	0.988 (0.671–1.453)	0.950

CEA = carcinoembryonie antigen, CI = confidence intervals, HR = hazard ratio, LMR = lymphocyte-to-monocyte ratio, TNM = tumor-node-metastasis.
Bold values mean $P < 0.05$.

associated with either OS or DFS in rectal cancer patients, as well subgroup analysis by TNM stage. Although we did not measure the subtype cells of lymphocyte or monocyte, we thought that those subtype cells could have an influence on rectal cancer survival. This is the first study demonstrating that LMR is not associated with the survival of rectal cancer. In addition, a previous study focusing on CRC demonstrated that LMR could not be used as a potential diagnostic biomarker because its area under the curve of the cut-off value was <0.50, but the survival data were not presented.[39] Another 2 studies showed that LMR
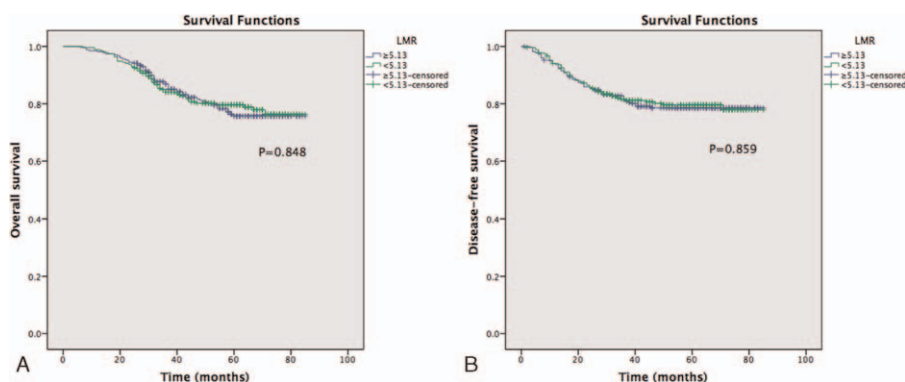
Figure 1. Preoperative LMR and OS and DFS: (A) OS, (B) DFS.
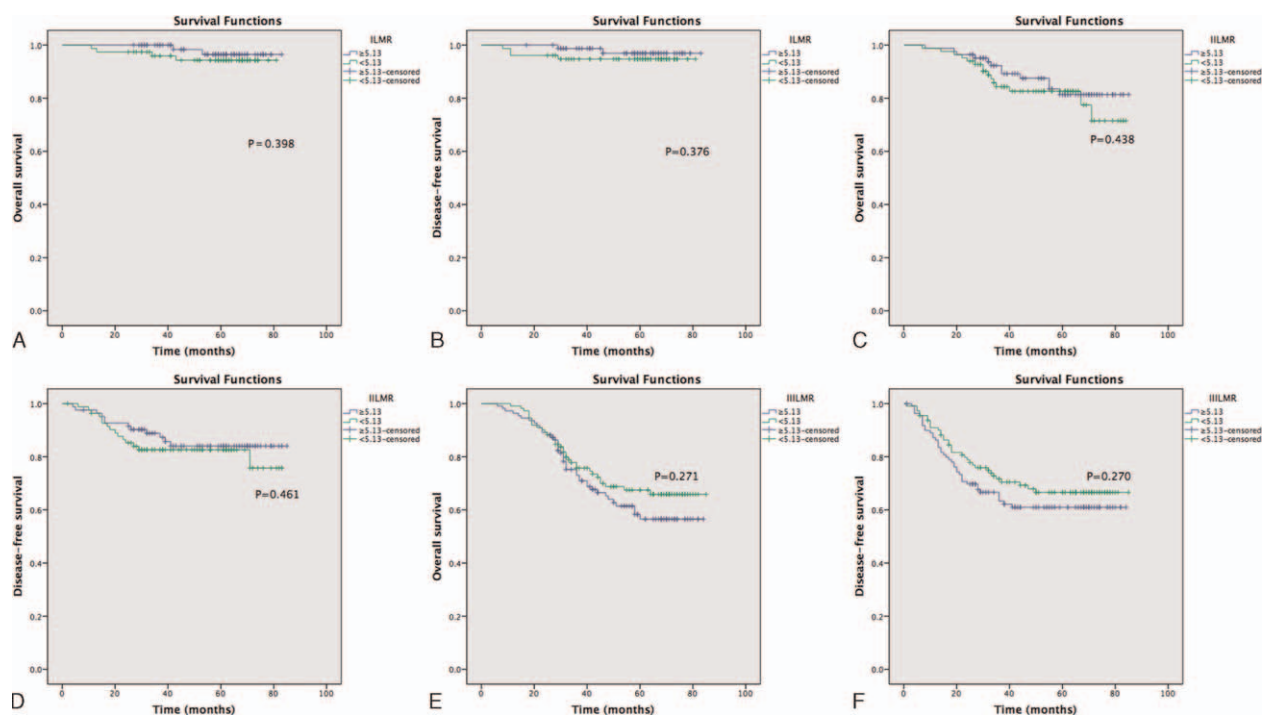
Figure 2. Preoperative LMR and OS and DFS in different TNM stages: (A) OS for stage I, (B) DFS for stage I, (C) OS for stage II, (D) DFS for stage II, (E) OS for stage III, (F) DFS for stage III. TNM = tumor-node-metastasis.

could be a prognostic factor for CRC.[17,40] However, both of them did not present the data of rectal cancer and colon cancer, separately. Besides, there is a report focused on pT3N0 rectal cancer, and the result was positive.[19] But it enrolled older patients, which might influence the result, because as our results, age could also influence the LMR. Besides, in our study, patients' blood test was checked in 2 weeks before surgery, which was not mentioned in that report.

This is the first large-scale cohort study demonstrating that there is no association between LMR and either OS or DFS in rectal cancer. Unfortunately, this study was a retrospective study. Still, a prospective cohort study is needed to evaluate the association between LMR and OS and DFS in rectal cancer patients.

In conclusion, although as an easy access and highly efficient laboratorial inflammatory marker, LMR cannot predict the prognosis of nonmetastatic rectal cancer patients.

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