

Research Paper

# A Low Lymphocyte-to-Monocyte Ratio Predicts Unfavorable Prognosis in Pathological T3N0 Rectal Cancer Patients Following Total Mesorectal Excision

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## Abstract

Neoadjuvant radio-chemotherapy followed by total mesorectal excision (TME) is the standard treatment option for stage II and III rectal cancer. However, for pT3N0 rectal cancer patients who receive upfront TME, the lack of an efficient method to predict their prognosis hampers post-operative treatment. A low lymphocyte-to-monocyte ratio (LMR) is associated with an unfavorable prognosis for certain malignancies; however, this association has not been investigated in rectal cancer. The purpose of this study was to evaluate whether LMR can predict the prognosis of pT3N0 rectal cancer patients following TME. Rectal cancer patients who received radical TME without preoperative treatment between June 2004 and Nov. 2011 at the Sun Yat-sen University Cancer Center were retrospectively reviewed. Counts for pre-surgery peripheral absolute lymphocytes and monocytes were obtained and used to calculate the LMR. A retrospective cohort of 280 pT3N0 rectal cancer patients who received TME was recruited. Significantly worse disease-free survival can be observed in patients with lower LMR levels (<3.78) using univariate and multivariate analyses ( $P=0.01$  and  $P=0.015$ , respectively). Subgroup analysis in patients with elevated carcinoembryonic antigen (CEA) and LMR <3.78 exhibited an accumulated 5-year disease failure rate of approximately 40%, whereas patients with normal CEA regardless of LMR and patients with LMR  $\geq 3.78$  exhibited accumulated 5-year disease failure rates of only approximately 15%. Low pre-surgery peripheral LMR was significantly unfavorable for pT3N0 rectal cancer patient prognosis, especially in patients with elevated CEA. This easily obtained variable might serve as a valuable marker to predict the outcomes of pT3N0 rectal cancer and indicate appropriate postoperative management.

Key words: Rectal cancer, Pathological T3N0, Lymphocyte-to-monocyte ratio, Total mesorectal excision

## Introduction

Neoadjuvant chemoradiotherapy followed by total mesorectal excision (TME) has gradually been accepted as the standard treatment for patients with

locally advanced rectal cancer. However, controversy remains regarding the peri-operative treatment strategy of patients with stage II rectal cancer, espe-

cially in patients with pathological T3N0 (pT3N0) after upfront TME. Due to the varied prognosis of pT3N0 disease, it is critical to define receivable prognostic factors that may help these patients benefit from postoperative adjuvant therapy. Prognostic factors that have been identified in previous studies include carcinoembryonic antigen (CEA), vascular invasion, tumor size, and perineural invasion [1].

Emerging evidence indicates that cancer-associated inflammation plays a key role in the development and survival of a broad range of cancers [2]. Peripheral blood cells might reflect the inflammatory status of patients and the response of patients to malignant tumors, and these cells hold great promise for improving the predictive ability of known prognostic factors. Lymphocytes and monocytes are key immune cells in the inflammatory response and are independently associated with the prognosis of various malignancies, such as breast cancer [3], gastric cancer [4], hepatocellular carcinoma [5], acute lymphoblastic leukemia [6], and lymphoma [7].

Interestingly, a lower pretreatment lymphocyte-monocyte ratio (LMR) is associated with unfavorable prognosis in some hematology malignancies [8,9], although relevant studies in non-hematology malignancies have only been performed recently. Some studies have demonstrated a prognostic role for peripheral LMR at diagnosis in limited cancers, such as soft tissue sarcomas [10] and nasopharyngeal carcinoma [11].

To date, the prognostic value of the LMR in rectal cancer has not been reported. Therefore, we hypothesized that LMR might also play an important role in rectal cancer. The aim of this study was to investigate the prognostic value of baseline LMR for patients with pT3N0 rectal cancer. To our knowledge, this study is the first to examine the association between LMR and rectal cancer.

## Materials and Methods

### Ethics statement

This research was approved by the Ethical Committee of Sun Yat-sen University Cancer Center, and written informed consent was obtained from participants for the use of their clinical records in this study. The study complies with current Chinese law and was performed in accordance with the principles of Declaration of Helsinki.

### Patients

We conducted a retrospective study on consecutive patients with rectal cancer who underwent curative TME at Sun Yat-sen University Cancer Center between June 2004 and Nov. 2011. The main inclusion criteria were as follows: pathologically proven pT3N0

rectal cancer, complete surgical resection, and no preoperative therapy. Patients were excluded if they died of postoperative complications or with positive margins.

### Evaluation and staging

Clinical stage was assessed according to endorectal ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) examinations. In our cancer center, endorectal ultrasound is recommended for every patient because it provides accurate T staging. Abdominal CT and pelvic CT or MRI are examined routinely. Other tests, such as complete blood count (CBC) and liver function tests were also performed. Tumor stage was based on the 7th edition of the TNM Classification.

### Treatment

Surgical resection was defined as radical when there was no evidence of distant metastases and tumor clearance was both macroscopically and histologically complete. All operations were conducted according to TME principles by colorectal surgeons, and the methods included low anterior resection (LAR) and abdominoperineal resection (AR).

### Laboratory data

As part of pretreatment evaluation, peripheral blood was collected before any treatment, and peripheral lymphocytes and monocytes were counted using an automated hematology analyzer. The baseline peripheral LMR was calculated as the ratio of absolute counts between peripheral lymphocytes and monocytes. All patients had no self-reported acute infections, indicating that the cell counts represented a normal baseline value.

### Follow-up

Follow up was performed every 3 months for the first 2 years after treatment and every 6 months thereafter. Evaluations included a CBC, liver function test, serum levels of CEA and CA19-9, physical examination and digital rectal examination at each visit. Chest radiography, CT scanning of the abdomen and pelvis and colonoscopy were conducted every 6 months after surgery. PET/CT is not regularly recommended, although some patients preferred its advantages regarding the early detection of recurrence. Each patient follow-up appointment was recorded in a database.

### Statistical analysis

The primary endpoint of the present study was disease-free survival (DFS), which was defined as the time between operation and failure (including recurrence and/or distant metastasis). All statistical anal-

yses were performed using SPSS software, version 19.0 (SPSS Inc., Chicago, IL, USA). The distributions of LMR were compared using the chi-square test or Fisher's exact test. DFS was analyzed and compared using the Kaplan-Meier method and the log-rank test. Multivariate analysis was performed using Cox proportional hazards regression, and all possible clinical factors were entered in the analysis. A two-tailed P value of <0.05 was considered significant.

## Results

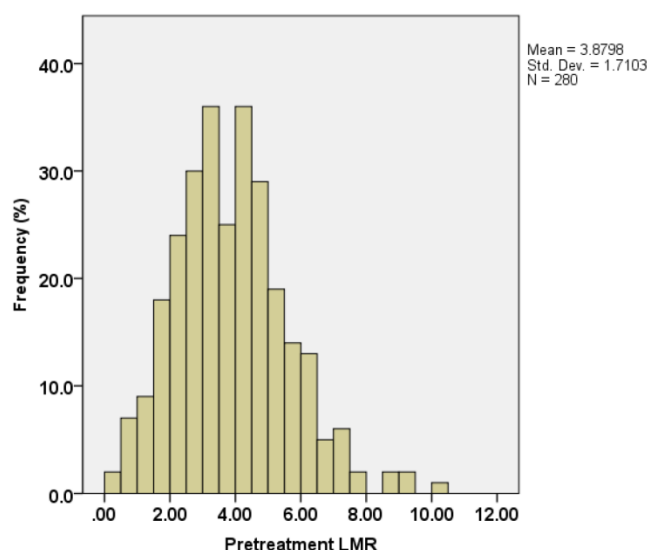
### Patient characteristics

In our study, 280 patients were enrolled; the median follow-up period for all patients was 52 months (range, 0.5-106.37 months). The basic clinicopathological characteristics of the patients are presented in Table 1. Fifty patients (17.8%) experienced disease recurrence. Thirty-two patients (11.4%) died after the last follow-up.

Absolute lymphocyte count (ALC) and absolute monocyte count (AMC) at time of initial diagnosis were derived from CBC counts. The distribution of the LMR is shown in Figure 1. The median value of LMR was 3.78, with an inter-quartile range of 2.73-4.82.

### Correlations between LMR and clinicopathological factors

The correlations between LMR and clinicopathological factors are shown in Table 1. Using the median value of LMR (3.78) for the patient group, significant correlations were observed between LMR and sex ( $P=0.001$ ) and between LMR and operation type ( $P=0.047$ ). No significant correlation was observed between LMR and CEA level.



**Figure 1.** Distribution of lymphocyte-to-monocyte ratios (LMRs) in 280 pT3N0M0 rectal cancer patients.

**Table 1.** Characteristics of 280 patients with pathological T3N0 rectal cancer according to LMR

Characteristic	Overall	LMR<3.78	LMR≥3.78	Chi-Square	P value
<b>Gender</b>					
Male	175	101	74	11.109	<b>0.001</b>
Female	105	39	66		
<b>Age, y</b>					
<61	133	69	64	0.358	0.550
≥61	147	71	76		
<b>CEA level</b>					
Normal	163	78	85	0.719	0.396
Elevated	117	62	55		
<b>Tumor location</b>					
≤5 cm	73	35	38	0.167	0.683
>5 cm	207	105	102		
<b>Operation</b>					
AR	227	107	120	3.933	<b>0.047</b>
APR	53	33	20		
<b>Tumor grade</b>					
I	19	11	8	1.205	0.547
II	239	120	119		
III	22	9	13		
<b>Adjuvant treatment</b>					
No	84	43	41	0.068	0.794
Chemotherapy	196	97	99		

Bold values are significant ( $P<0.05$ ). LMR, lymphocyte-to-monocyte ratio; CEA, carcinoembryonic antigen; AR, anterior resection; APR, abdominoperineal resection

### Survival analyses

As shown in Table 2, the correlation between DFS and each clinicopathological variable was examined using univariate analysis; normal CEA level (hazard ratio [HR]=0.470; 95% CI, 0.266-0.830;  $P=0.009$ ), higher LMR (as a continuous variable) (HR=0.790; 95%CI, 0.661-0.945;  $P=0.010$ ) and female gender (HR=0.506; 95% CI, 0.264-0.970;  $P=0.040$ ) were associated with a significantly lower risk of disease recurrence.

**Table 2.** Univariate and multivariate analyses of LMR for DFS in patients with pT3N0M0 rectal cancer

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
CEA level	0.470 (0.266-0.830)	<b>0.009</b>	0.508 (0.287-0.900)	<b>0.021</b>
LMR	0.790 (0.661-0.945)	<b>0.010</b>	0.805 (0.675-0.959)	<b>0.015</b>
Gender	0.506 (0.264-0.970)	<b>0.040</b>		
Age	1.026 (1.000-1.053)	0.052		
Operation	0.760 (0.356-1.621)	0.477		
Tumor location	0.731 (0.402-1.327)	0.303		
Tumor grade	0.939 (0.463-1.903)	0.862		
Adjuvant treatment	0.987 (0.531-1.835)	0.967		

Bold values are significant ( $P<0.05$ ). DFS, disease-free survival; HR, hazard ratio; CI, confidence interval

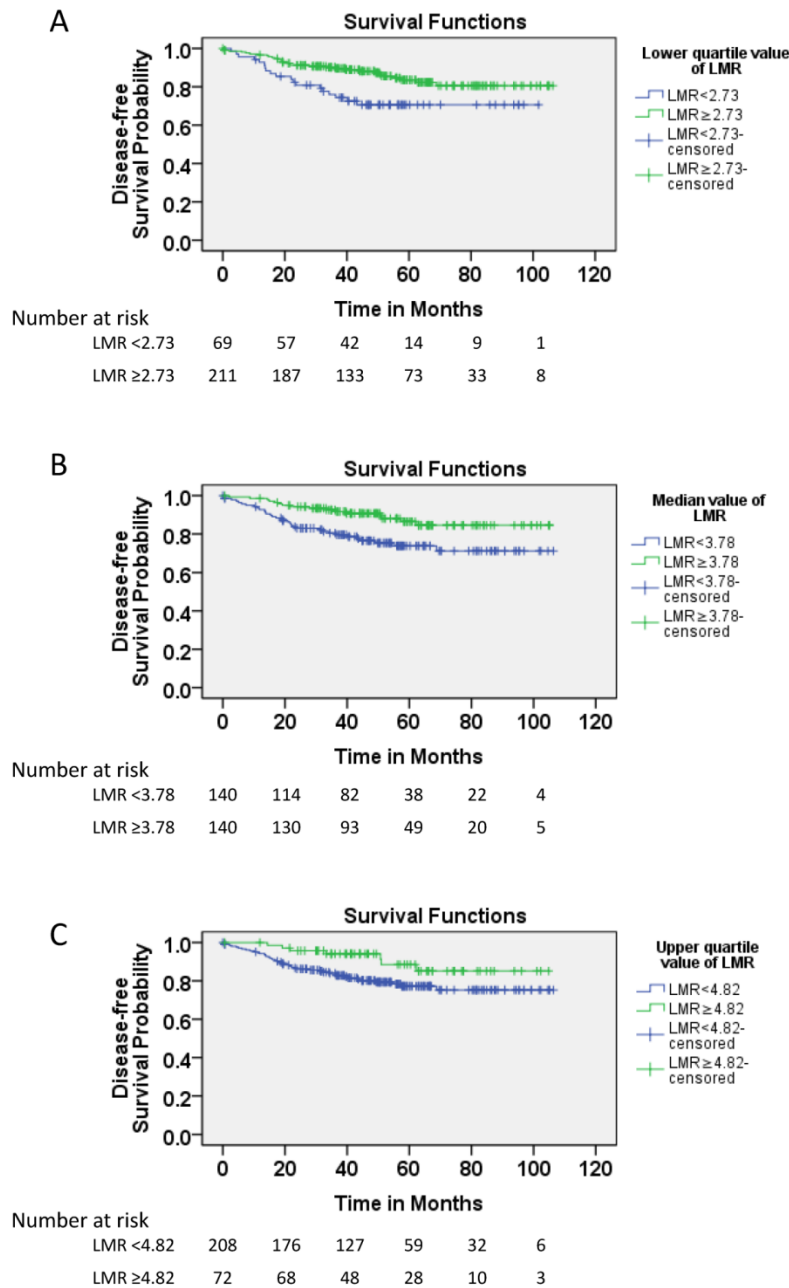
The following parameters were included in the Cox proportional hazards model by backward elimination: LMR as a continuous variable, CEA level (elevated vs. normal), age as a continuous variable, gender (male vs. female), operation (APR vs. AR), tumor location (low rectal cancer vs. high rectal cancer), tumor grade (highly differentiated vs. moderately differentiated vs. poorly differentiated), and adjuvant treatment (adjuvant chemotherapy vs. no chemotherapy).

When DFS was compared between patients with higher and lower LMR ( $\geq 2.73$  vs.  $< 2.73$ ;  $\geq 3.78$  vs.  $< 3.78$ ;  $\geq 4.82$  vs.  $< 4.82$ ), a significance difference was detected regardless of the cutoff point used (respective 5-year DFS rates: 83.6% vs. 70.6%,  $P=0.009$ ; 86.5% vs. 73.8%,  $P=0.005$ ; and 88.5% vs. 77.2%,  $P=0.041$ ; Figure 2).

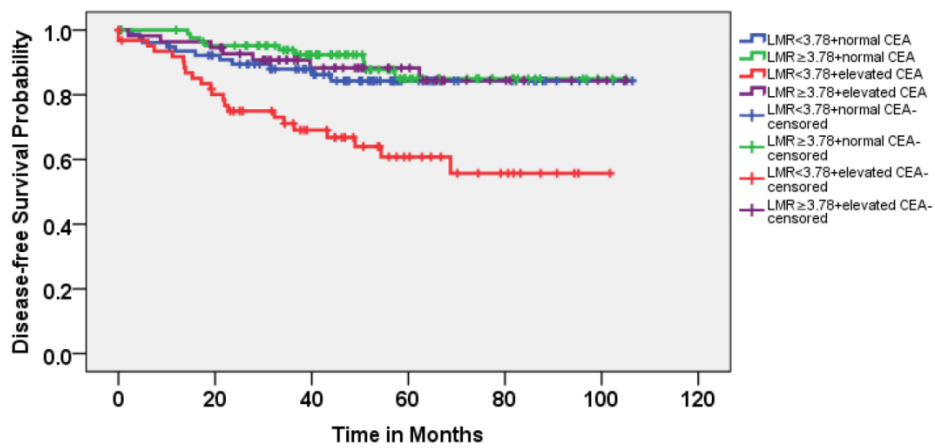
Using multivariate analysis, CEA level (HR=0.508; 95% CI, 0.287-0.900;  $P=0.021$ ) and LMR (HR=0.805; 95% CI, 0.675-0.959;  $P=0.015$ ) remained significantly associated with DFS.

Because the CEA level was not significantly correlated with LMR and both of these factors were

significantly associated with DFS in patients with pT3N0 rectal cancer, the patients were divided into four subgroups according to CEA level (elevated vs. normal) and LMR ( $\geq 3.78$  vs.  $< 3.78$ ). As shown in Figure 3, 22% of the patients with pT3N0 exhibited both elevated CEA and lower LMR before treatment; these patients exhibited lower DFS rates than the other three subgroups (Table 3). The 5-year accumulated disease recurrence rate was approximately 40% for patients with elevated CEA and lower LMR. In contrast, it was approximately 15% for the other three groups.



**Figure 2. Elevated LMR indicates a favorable disease-free survival (DFS) in pT3N0M0 rectal cancer patients.** A. Cumulative DFS curves of patients with pT3N0M0 rectal cancer with high or low LMR based on the median value (number of patients, 280; number of events, 49). B. Cumulative DFS curves of patients with pT3N0M0 rectal cancer with high or low LMR based on the lower quartile value (number of patients, 280; number of events, 49). C. Cumulative DFS curves of patients with pT3N0M0 rectal cancer with high or low LMR based on the upper quartile value (number of patients, 280; number of events, 49).



Number at risk	Time in Months					
	0	20	40	60	80	100
LMR <3.78+normal CEA	78	67	51	22	14	3
LMR ≥3.78+normal CEA	85	78	57	25	11	2
LMR < 3.78+elevated CEA	62	47	31	16	8	1
LMR ≥3.78+elevated CEA	55	52	36	24	9	3

Figure 3. Kaplan-Meier estimates of DFS according to LMR and carcinoembryonic antigen (CEA) level.

Table 3. Comparison of DFS in patients with pT3N0 rectal cancer according to LMR and CEA

Subgroup	LMR<3.78+normal CEA	LMR≥3.78+normal CEA	LMR<3.78+elevated CEA	LMR≥3.78+elevated CEA	Chi-Square	P value
N (%)	78 (27.9)	85 (30.4)	62 (22.1)	55 (19.6)	20.303	<0.001
5-year DFS	84.3%	84.9%	60.8%	88.3%		
LMR<3.78+normal CEA	-	-	-	-		
LMR≥3.78+normal CEA	$\chi^2=0.569$ P=0.451	-	-	-		
LMR<3.78+elevated CEA	$\chi^2=8.486$ P=0.004	$\chi^2=14.237$ P<0.001	-	-		
LMR≥3.78+elevated CEA	$\chi^2=0.122$ P=0.727	$\chi^2=0.074$ P=0.785	$\chi^2=8.676$ P=0.003	-		

Bold values are significant (P<0.05)

### Discussion

Current guidelines issued by the National Comprehensive Cancer Network recommend that all patients with clinical stage II/III rectal cancer should be treated with preoperative radio-chemotherapy followed by TME. However, whether patients with pT3N0 rectal cancer who received upfront TME should undergo adjuvant therapy remains controversial.

An increasing number of studies suggest a strong link between inflammation and cancer, and the pretreatment of peripheral inflammatory cells, including neutrophils, lymphocytes and monocytes, has been significantly associated with progression and prognosis in various types of cancers.

The peripheral blood lymphocyte count is an important surrogate marker of immunological reconstitution following stem cell transplantation in non-Hodgkin lymphoma, and lymphopenia is a surrogate marker of host immunological incompetence

[9]. Lymphopenia prior to the initiation of systemic treatment is a powerful predictor of clinical outcome in hematologic and solid malignancies [12]. Lymphopenia prior to the initiation of systemic treatment is also a poor-risk feature in patients with stage II and III rectal cancer who have been treated with neoadjuvant chemoradiotherapy [13-15]. The induction of programmed cell death, antibody-dependent cellular cytotoxicity, and complement-dependent cytotoxicity play important roles in slowing or preventing disease progression and distant metastasis in rectal cancer [16]. Lymphopenia might impair the efficacy of the immune system by impairing antibody-dependent cell-mediated cytotoxicity due to a lack of effector cells.

Monocyte-associated macrophages might contribute to the suppression of host anti-tumor immunity and the promotion of tumor angiogenesis [17]. Furthermore, monocytes might also provide trophic factors that directly promote the growth and survival of cancer cells [18]. Wilcox et al. have shown that pe-

peripheral blood monocytes and their progeny within the tumor microenvironment express the T-cell co-inhibitory ligand B7-H1 (PD-L1), which stimulates the expansion of suppressive regulatory T cells [19]. Monocytes are direct precursors of hematopoietic stem cell-derived macrophages. After recruitment into the tumor tissue, monocytes can differentiate into tumor-associated macrophages, which are an important component of infiltrating inflammatory cells, and might interact with tumor cells to promote tumor development by producing various cytokines and chemokines [20]. Therefore, it is not surprising that peripheral blood monocytosis is an adverse prognostic factor for various tumors [21-25].

In hematology malignancies [8,21] and solid tumors [10,11,26-32], including lung cancer, bladder cancer, breast cancer, oropharyngeal cancer, pancreatic adenocarcinoma, gastric cancer and renal cell carcinoma, literature reports show that a low pre-treatment peripheral LMR level is significantly unfavorable and represents a useful marker for predicting outcomes.

To our knowledge, this is the first large-scale study to evaluate the prognostic significance of LMR in patients with rectal cancer and pT3N0 rectal cancer in particular. We performed a retrospective cohort study on 280 patients with pT3N0 rectal cancer who had received TME with or without adjuvant chemotherapy to evaluate the prognostic values of pre-treatment peripheral LMR and other clinical factors. Our results confirmed previous findings that normal CEA levels were associated with a favorable prognosis for patients with rectal cancer [33]. More importantly, we found that a lower LMR was significantly associated with a high probability of disease failure and inferior DFS and was able to predict patient prognosis for pT3N0 rectal cancer after TME independently of other variables.

Interestingly, we also found that LMR was not significantly associated with CEA level. Moreover, LMR <3.78 was associated with inferior DFS in patients with elevated CEA but was not associated with a survival difference in patients with normal CEA. These results suggest that host immune status affects survival in patients with pT3N0, especially in patients with elevated CEA. Patients with rectal cancer who are staged as pT3N0 with elevated CEA level might already have micrometastases and are more likely to relapse after curative treatment. In those patients, an immune reaction, indicated by elevated LMR, might be sufficient to eradicate the micrometastases and afford good disease control, as with patients exhibiting normal CEA. Thus, in patients with both elevated CEA and LMR <3.78 at diagnosis, adjuvant radio-chemotherapy appears strongly recommended. In

patients with normal CEA or LMR  $\geq 3.78$ , radical surgery might suffice, and postoperative adjuvant treatment might not lead to improved treatment outcomes.

## Conclusions

Taken together, these findings show for the first time that pre-surgery low peripheral blood LMR predicts unfavorable prognosis in patients with pT3N0 rectal cancer, especially in patients with elevated CEA at initial diagnosis. This biomarker can be derived directly from routine blood cell counts and can easily be applied as a prognostic marker and as an individual treatment index for pT3N0 rectal cancer in the clinical setting. Further studies in a multicenter or prospective manner are warranted.

## Abbreviations

TME: total mesorectal excision; pT3N0: pathological T3N0; CEA: carcinoembryonic antigen; LMR: lymphocyte-monocyte ratio; CT: computed tomography; MRI: magnetic resonance imaging; LAR: low anterior resection; AR: abdominoperineal resection; DFS: disease-free survival; CBC: complete blood count; HR: hazard ratio; ALC: absolute lymphocyte count; AMC: absolute monocyte count

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## Competing interests

The authors declare no competing interest.

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