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Lymphocyte to Monocyte Ratio Is an Independent Prognostic Factor in Patients With Esophageal Cancer Who Receive Curative Treatment

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Abstract. *Background/Aim: This study evaluated the clinical impact of the lymphocyte-to-monocyte ratio (LMR) in patients with esophageal cancer who received curative treatment and perioperative adjuvant treatment. The association between LMR and the clinicopathological characteristics of patients with esophageal cancer was also investigated. Patients and Methods: This study included 181 patients who underwent curative treatment for esophageal cancer between 2005 and 2020. The prognosis and clinicopathological parameters of patients with high and low LMR statuses were analyzed. Results: The OS rates at 3 and 5 years after surgery were significantly lower (40.6% and 33.8%, respectively) in the low-LMR group than in the high-LMR group (67.1% and 58.4%, respectively). The pretreatment LMR was selected as an independent prognostic factor in the multivariate analysis model [hazard ratio (HR)=2.606; 95%CI=1.504-4.516, p<0.001]. Similar results were observed for RFS. Furthermore, LMR was associated with the occurrence of postoperative surgical complications and hematological recurrence. The incidence of anastomotic leakage was 63.3% in the low-LMR group and 27.2% in the high-LMR group (p<0.001). Moreover, the hematologic recurrence rate in the low-LMR group was significantly higher than that in the high-LMR group (46.7% vs. 23.8%, p=0.011). Conclusion: The LMR may be a promising prognostic and predictive factor for esophageal cancer, and may be used to select optimal treatment strategies in the future.*

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Esophageal cancer is the eighth most common cancer and the sixth leading cause of cancer-related deaths in 2020 (1, 2). The standard treatment for resectable esophageal cancer is esophagectomy and perioperative adjuvant treatment (3, 4). However, more than half of patients experience recurrence even after curative treatment. Once a patient develops recurrent disease, their prognosis is poor (5, 6). Therefore, identification of prognostic and predictive factors is necessary for managing esophageal cancer treatment.

Recently, the perioperative inflammation status has been shown to affect both short- and long-term oncological outcomes (7-9). Cancer-related inflammation has been investigated in various malignancies and oncological outcomes. Considering these factors, various inflammation scores have been developed and evaluated for esophageal cancer. Among these, the neutrophil-lymphocyte ratio (NLR), neutrophil-monocyte ratio (NMR), and platelet-to-lymphocyte ratio (PLR) have been evaluated to clarify the prognostic factors for esophageal cancer (10-13). To date, limited studies have shown the prognostic role of the lymphocyte-to-monocyte ratio (LMR) in esophageal cancer (14, 15). We also investigated the mechanism underlying the effect of the LMR on both the short- and long-term oncological outcomes. An understanding of this mechanism would enable physicians to make better-informed treatment decisions and provide more aggressive treatment. The aim of

Table I. *Comparison of survival rates stratified by patient characteristics.*

Characteristics	No. of patients	1-year OS rate (%)	3-year OS rate (%)	5-year OS rate (%)	*p*-Value
Age (years)					0.470
<70	95	84.8	61.7	48.2	
≥70	86	83.7	63.6	57.9	
Sex					0.263
Male	156	84.4	60.1	52.2	
Female	25	82.4	72.4	66.8	
Site of tumor					0.636
Upper	37	77.1	56.1	56.1	
Middle	96	84.4	60.6	55.4	
Lower	48	89.0	72.1	49.8	
T status					<0.001
T1	80	94.9	79.3	74.9	
T2 to T3	101	75.4	48.8	38.0	
Lymph node metastasis					<0.001
Negative	96	89.1	76.1	70.5	
Positive	85	78.5	47.5	36.4	
Lymphocyte-Monocyte ratio					0.002
<1.7	30	71.4	40.6	33.8	
≥1.7	151	86.7	67.1	58.4	
Lymph-vascular invasion					<0.001
Negative	58	92.7	85.9	79.5	
Positive	123	80.0	51.2	42.0	
Postoperative surgical complications					0.826
No	52	89.9	63.6	51.2	
Yes	129	81.8	62.2	55.5	

OS: Overall survival.

the present study was to evaluate the clinical relationship between the pretreatment LMR and the oncological outcomes of resectable esophageal cancer.

Patients and Methods

Patients. We conducted a retrospective analysis of the medical records of consecutive patients who underwent curative resection for esophageal cancer at Yokohama City University between 2005 and 2020. Patients who met the following criteria were included in the study: 1) histologically-confirmed esophageal adenocarcinoma or squamous cell carcinoma, 2) clinical stage IB-III disease determined according to the tumor-node-metastasis classification, 7th edition (published by the Union for International Cancer Control (UICC), and 3) complete resection of esophageal cancer (classified as R0 resection).

Surgery and adjuvant treatment. The standard procedure involves performing a subtotal esophagectomy through a right thoracotomy, followed by reconstruction using a gastric tube. Two-field lymph node dissection is conducted for middle- to lower-thoracic tumors, whereas three-field dissection is undertaken for upper-thoracic tumors. Preoperative chemotherapy consists of two courses of 5-FU (800 mg/m^2, days 1-5) and CDDP (80 mg/m^2, day 1), with the cycle repeated every three weeks.

Definition of postoperative complications. The Clavien-Dindo classification was used to grade the severity of postoperative complications (POCs). Using the patient's records, we retrospectively identified grade 2-5 POCs that occurred during hospitalization and/or within 30 days after surgery (16).

Follow-up protocol. Patients underwent follow-up at outpatient clinics, with regular intervals of at least every three months for five years. During these appointments, hematological tests, including CEA and CA19-9 tumor marker levels, as well as physical examinations, were conducted. Additionally, CT examinations were performed every three months within the initial three years post-surgery and subsequently every six months until five years after the surgical procedure.

Measurement of preoperative lymphocyte to monocyte ratio. The preoperative lymphocyte to monocyte ratio (LMR) was calculated using the following formula:

LMR=Preoperative lymphocyte count/Preoperative monocyte count.

Evaluations and statistical analyses. The chi-squared test was employed to assess the significance of differences between the LMR and clinicopathological parameters. Overall survival (OS) and recurrence-free survival (RFS) curves were generated using the Kaplan–Meier method. Univariate and multivariate survival analyses were conducted utilizing a Cox proportional hazards model. Statistical significance was defined as $p<0.05$. All statistical analyses were performed using the SPSS software program (v27.0 J Win; IBM, Armonk, NY, USA). Approval for this study was

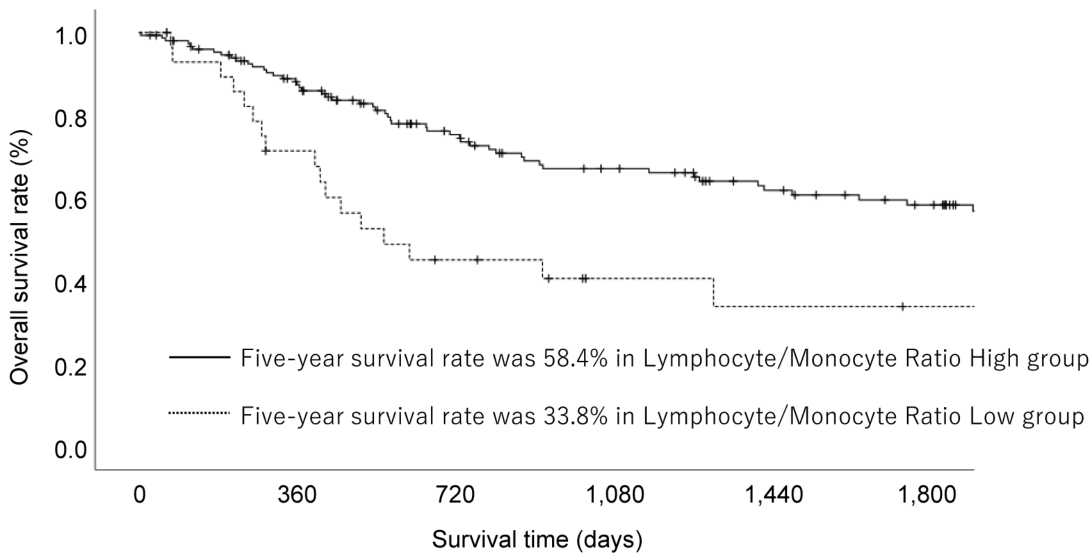

Figure 1. *Overall survival of patients with esophageal cancer in the high-lymphocyte-monocyte ratio (LMR) (≥1.7) and low-LMR (<1.7) groups.*

obtained from the Institutional Review Board (IRB) of Yokohama City University (IRB number: F220500064).

Results

Patient background. One-hundred eighty-one patients were evaluated in this study. The median age of the patients was 69 years (range=37-90 years). One-hundred fifty-six patients were male and 25 were female. Neoadjuvant chemotherapy was administered to 89 patients. According to the three- and five-year overall survival (OS) rates in the present study, an LMR of 1.7 was the optimal cutoff value (Table I). When comparing the patient backgrounds of the high-LMR (LMR ≥1.7) and low-LMR (LMR <1.7) groups, there were no significant differences in age, sex, pathological response after neoadjuvant chemotherapy, T status, N status, or lymphovascular invasion status.

Survival analysis. The OS rates at 3 and 5 years after surgery in the low-LMR group (40.6% and 33.8%, respectively) were significantly lower than those in the high-LMR group (67.1% and 58.4%, respectively). The OS curves are shown in Figure 1. Each clinicopathological factor was categorized, as shown in Table II, and analyzed for prognostic significance. Univariate analyses of factors associated with OS showed that pathological T factor, pathological N factor, pretreatment LMR, and vascular invasion were significant prognostic factors. The pretreatment LMR was therefore selected for the final multivariate analysis model [hazard ratio (HR)=2.606, 95%CI=1.504-4.516, p<0.001]. Similar results were observed in recurrence-free survival (RFS). The RFS rates at 3 and 5 years after surgery in the low-LMR group (31.8% and 25.5%, respectively) were significantly lower than those in the high-LMR group (66.7% and 58.4%, respectively). The RFS curves are shown in Figure 2. Each clinicopathological factor was categorized, as shown in Table III, and analyzed for prognostic significance. Univariate analyses of factors associated with RFS showed that pathological T factor, pretreatment LMR, and vascular invasion were significant prognostic factors. Therefore, the pretreatment LMR was selected for the final multivariate analysis model (HR=1.809; 95%CI=1.094-2.991, p=0.021).

Perioperative clinical course and recurrence pattern. Postoperative surgical complications (POCs) were compared between low-LMR and high-LMR groups. The overall incidence of POCs was similar between the two groups. The overall incidence of POCs was 80% in the low-LMR group and 69.5% in the high-LMR group (p=0.247). In contrast, the incidence of anastomotic leakage was 63.3% in the low-LMR group and 27.2% in the high-LMR group. There were significant differences between the two groups (p<0.001). In addition, when the sites of recurrence were compared, the rate of hematological recurrence in the low-LMR group was significantly higher than that in the high-LMR group (46.7% *vs*. 23.8%, p=0.011) (Table IV).

Discussion

The aim of the present study was to evaluate the clinical impact of preoperative LMR in patients with esophageal cancer who underwent curative surgery. The main finding

Table II. *Uni and Multivariate Cox proportional hazards analysis of clinicopathological factors for overall survival.*

Factors	No	Univariate analysis			Multivariate analysis		
		OR	95%CI	*p*-Value	OR	95%CI	*p*-Value
Age (years)				0.471			
<70	95	1.000					
≥70	86	1.186	0.746-1.886				
Sex				0.267			
Female	25	1.000					
Male	156	1.556	0.713-3.393				
T status				<0.001			0.006
T1	80	1.000			1.000		
T2 or T3	101	3.293	1.930-5.617		2.292	1.263-4.159	
Lymph node metastasis				<0.001			0.049
Negative	96	1.000			1.000		
Positive	85	2.550	1.577-4.123		1.656	1.002-2.737	
Lymphocyte-Monocyte ratio				<0.001			<0.001
<1.7	30	1.000			1.000		
≥1.7	151	2.266	1.327-3.867		2.606	1.504-4.516	
Lymph-vascular invasion				<0.001			0.045
Negative	58	1.000			1.000		
Positive	123	3.280	1.764-6.101		2.204	1.017-4.028	
Tumor location				0.348			
Middle, lower	144	1.000					
Upper	37	1.297	0.753-2.236				
Postoperative complications				0.826			
No	52	1.000					
Yes	129	1.058	0.641-1.746				

was that LMR was a significant prognostic factor for patients with esophageal cancer. Additionally, the LMR was found to be associated with the occurrence of postoperative surgical complications and hematologic recurrence. Our results suggest that preoperative LMR may be a useful tool in the treatment and management of esophageal cancer.

In the present study, the hazard ratio of the LMR for survival in patients with esophageal cancer was 2.606 (95%CI=1.504-4.516, $p<0.001$). Similar results have been reported in previous studies. Huang *et al*. clarified the prognostic impact of preoperative LMR in 348 patients with esophageal squamous cell carcinoma (17). Patients were divided into low-LMR (LMR ≤2.93) and high-LMR (LMR >2.93) groups. Patients with LMR <2.93 had a significantly poorer prognosis in comparison to those with LMR >2.93. The 5-year cancer-specific survival rate was 21.2% in the low-LMR group and 59.3% in the high-LMR group ($p<0.001$). The multivariate analysis demonstrated that the LMR was an independent predictive factor (HR for high-LMR=0.600; 95%CI=0.407-0.885, $p=0.010$). Han *et al*. evaluated the prognostic impact of the preoperative LMR in 218 patients with squamous cell carcinoma of the esophagus (14). Patients were divided into low-LMR (LMR ≤2.6) and high-LMR (LMR >2.6) groups. The survival analysis demonstrated that patients with LMR <2.6 had a significantly poorer prognosis than those with LMR >2.6. The mean DFS and OS was 24.7 months and 29.2 months, respectively, in the low-LMR group, and 26.5 months and 41.3 months in the high-LMR group. The multivariate analysis demonstrated that LMR was an independent predictive factor (HR for DFS=1.639; 95%CI=1.129-2.381, $p=0.009$) (HR for OS=1.759, 95%CI=1.201-2.576, $p=0.004$). Considering these factors, the LMR is a promising prognostic factor for patients with esophageal cancer who receive curative treatment.

There are some possible explanations for why the LMR affects the survival of patients with esophageal cancer. First, the preoperative LMR status was related to postoperative surgical complications. Our study demonstrated that the preoperative LMR status affects postoperative anastomotic leakage. Previously, we found that the occurrence of postoperative anastomotic leakage affects the survival of patients with esophageal cancer (18). Therefore, the preoperative LMR status affects postoperative anastomotic leakage, which results in a poor prognosis. Similar results have been reported in previous studies. Second, pretreatment LMR status has been related to chemotherapy response. Although no relationship was observed between pretreatment LMR and chemotherapy response in the present study,

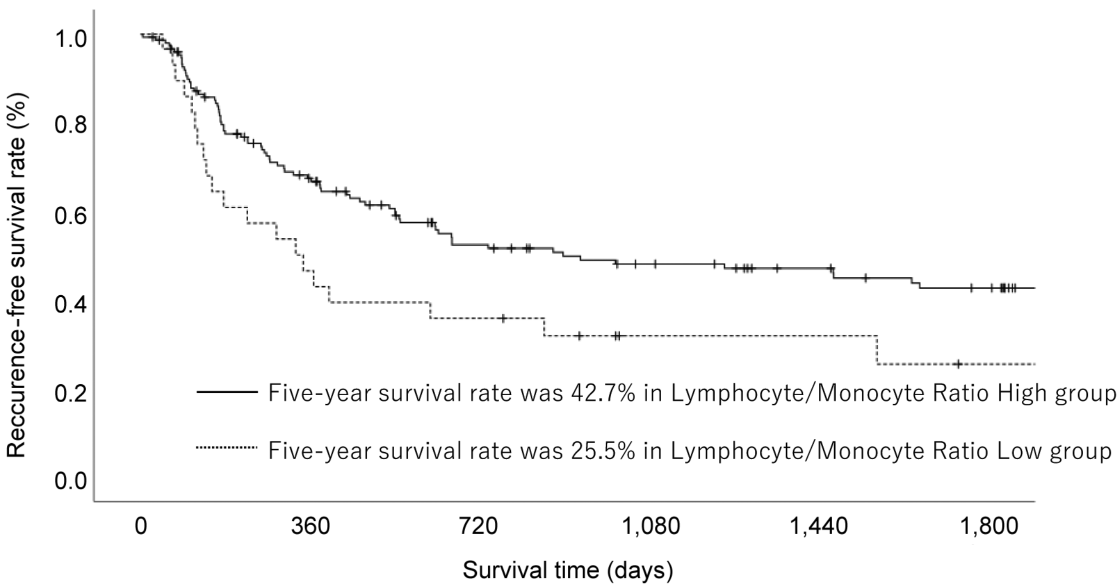

Figure 2. *Recurrence-free survival of patients with esophageal cancer in the high-lymphocyte-monocyte ratio (LMR) (≥1.7) and low-LMR (<1.7) groups.*

Table III. *Uni and Multivariate Cox proportional hazards analysis of clinicopathological factors for recurrence-free survival.*

Factors	No	Univariate analysis			Multivariate analysis		
		OR	95%CI	*p*-Value	OR	95%CI	*p*-Value
Age (years)				0.922			
<70	95	1.000					
≥70	86	1.020	0.682-1.527				
Sex				0.201			
Female	25	1.000					
Male	156	1.533	0.796-2.952				
T status				<0.001			<0.001
T1	80	1.000			1.000		
T2 or T3	101	4.139	2.578-6.645		2.724	1.619-4.582	
Lymph node metastasis				0.001			0.055
Negative	96	1.000			1.000		
Positive	85	2.508	1.659-3.790		1.526	0.990	2.352
Lymphocyte-Monocyte ratio				0.037			0.021
<1.7	30	1.000			1.000		
≥1.7	151	1.691	1.032-2.769		1.809	1.094-2.991	
Lymph-vascular invasion				<0.001			0.008
Negative	58	1.000			1.000		
Positive	123	3.897	2.240-6.780		2.272	1.241-4.159	
Tumor location				0.338			
Middle, lower	144	1.000					
Upper	37	1.262	0.784-2.032				
Postoperative complications				0.827			
No	52	1.000					
Yes	129	1.050	0.679-1.624				

previous studies have demonstrated a clinical relationship between the LMR and response to chemotherapy. Zhao *et al*. evaluated the value of the LMR and a complete pathological response (pCR) in 87 patients with locally advanced esophageal cancer who received neoadjuvant chemoradiation therapy (nCRT) (19). After nCRT, 26 (29.9%) patients

Table IV. *Patterns of recurrence according to lymphocyte-monocyte ratio*.

	Lymphocyte-monocyte ratio				
	<1.7 (n=30)		≥1.7 (n=151)		*p*-Value
Recurrence site	Number	%	Number	%	
Hematological recurrence	6	20.0	51	33.8	0.138
Lymph node recurrence	14	46.7	36	23.8	0.011
Peritoneal recurrence	1	3.3	9	6.0	0.565

achieved a pCR. When comparing the patient background factors between the pCR and non-pCR groups, there were significant differences in the mean pretreatment LMR (4.35±1.68 *vs*. 3.33±1.13, $p=0.002$). They set the cutoff value of the LMR at 3.73 according to the ROC curves. Univariate and multivariate logistic regression analyses demonstrated that the pretreatment LMR was an independent risk factor for pCR (odds ratio=5.093; 95%CI=1.658-15.646, $p=0.004$). The pCR rate was 53.1% for LMR ≥3.73, and 16.4% for LMR <3.73. Zhu *et al*. evaluated the clinical impact of LMR and chemotherapy response in 672 patients with advanced epithelial ovarian cancer who received neoadjuvant chemotherapy therapy and surgery (20). They set the cutoff value of the LMR at 3.45 according to the ROC curves. When comparing the patient background factors of the low-LMR and high-LMR groups, there were significant differences in chemosensitivity (60.0% *vs*. 72.3%, $p=0.001$). Furthermore, the CR rate in the low-LMR group was lower than that in the high-LMR group ($p<0.05$). Recent studies have demonstrated that sensitivity to chemotherapy is associated with long-term oncological outcomes (21). Therefore, LMR status affects chemotherapy sensitivity, resulting in a poor prognosis as a result of poor chemotherapy sensitivity.

To optimize the clinical use of LMR in daily clinical practice, it is necessary to establish the optimal cutoff value of the LMR for esophageal cancer. In the present study, we set the cutoff value to 2.93. Previously, various cutoff values have been reported. These include the cutoff values reported by Li *et al*. (3.03), Hirahara *et al*. (4.0), Han *et al*. (2.57), Song *et al*. (3.17), and Shang *et al*. (3.83) (14, 15, 22-24). These differences may be attributed to heterogeneity in patient numbers, patient background factors, and treatment methods for esophageal cancer. Recently, the SIS and Naples prognostic scores have been introduced and reported in the management of esophageal cancer treatment. Inflammation and nutritional scores, such as the Naples prognostic score, use the LMR, and set the cutoff value at 4.4. To utilize the LMR for esophageal cancer treatment, an optimal cutoff value is needed.

In the present study, we set the cutoff value of the LMR according to the 3- and 5-year survival rates. On the other hand, previous studies have set the optimal cutoff value using ROC curves (21-23). These differences might also affect the cutoff value of the LMR. Accordingly, further studies are needed to clarify the optimal cutoff value and optimal methods for evaluating the LMR.

With regard to suggestions on the clinical use of LMR for esophageal cancer treatment and management, recent studies have focused on perioperative changes in inflammation/ nutritional assessment scores, including the LMR, in esophageal cancer. For example, Song *et al*. evaluated the clinical impact of changes in the LNR (LMRc=pretreatment LMR – post-treatment LMR) in 674 patients with esophageal cancer who underwent esophagectomy (25). They found that a lower LMRc (≤1:59) was significantly associated with a poorer prognosis. A multivariate analysis demonstrated that the LMRc was independent predictor of both OS ($p=0,006$, HR=0,687, 95%CI=0.526-0.898) and DFS ($p=0,003$, HR=0,640, 95%CI=0.476-0.859). We will focus on this issue in future studies.

In conclusion, the LMR was a significant prognostic factor for patients with esophageal cancer. In addition, LMR is associated with the occurrence of postoperative surgical complications and hematological recurrence. Our results suggest that preoperative LMR is a promising tool for the treatment and management of esophageal cancer.

Conflicts of Interest

The Authors declare no conflicts of interest in association with the present study.

Authors' Contributions

TA, YM, and IH contributed substantially to concept and design. TA, YM, SK, JM, MT, KK1 (Keisuke Kazama), KH, SS, KO, KK2 (Keisuke Komori), AK, and MN made substantial contributions to the acquisition, analysis, and interpretation of data. TA, AT, HC, JM, NK, MT, TO, AS, NY, and YR were involved in drafting the article and revising it critically for important intellectual content. TA and IH approved the final version to be published.

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