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Lymphocyte-to-C-reactive Protein Ratio as an Independent Prognostic Factor for Patients With Gastric Cancer Who Received Curative Treatment

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Abstract

Background/Aim: Lymphocyte-to-C-reactive protein ratio (LCR) is a useful biomarker for predicting the prognosis of various cancers. This study examined the effect of LCR on the oncological prognosis of patients with gastric cancer who underwent curative resection at our institution and considered the mechanisms involved.

Patients and Methods: In this retrospective cohort study, 258 subjects were selected from the medical records of patients who underwent curative resection for gastric cancer at Yokohama City University between 2005 and 2020. The LCR was calculated using the following formula: LCR=lymphocyte count (number/μl)/C-reactive protein (mg/dl).

Results: The cutoff value for LCR was set at 9,000, and 258 patients were classified into the LCR-low (<9,000) (58 patients) and LCR-high (>9,000) (200 patients) groups. The overall survival (OS) and recurrence-free survival (RFS) rates of the two groups were compared. The 5-year overall survival rate was 54.2% in the LCR-low group and 75.2% in the LCR-high group (p<0.001), and a multivariate analysis showed that it was a useful prognostic factor [hazard ratio (HR)=1.744, 95% confidence interval (CI)=1.009-3.014, p=0.046]. In addition, with regard to RFS, there was a significant difference in the 5-year RFS between the LCR-low group (50.4%) and the LCR-high group (72.3%) (p<0.001). Regarding the comparison of the postoperative clinical course between the two groups, the peritoneal recurrence rate was 24.1% in the LCR-low group and 7.5% in the LCR-high group (p<0.001).

Conclusion: Preoperative LCR is a useful prognostic factor for predicting the oncological prognosis of patients with gastric cancer undergoing curative resection. Thus, the LCR may be a useful tool for the treatment and perioperative management of patients with gastric cancer.

Keywords: LCR, gastric cancer, survival, prognostic factor.

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Introduction

Although the incidence of gastric cancer is decreasing worldwide, by 2022 the number of new cases is expected to exceed 968,000 and the number of deaths is expected to reach nearly 660,000 (1). Although the incidence is expected to continue to decrease owing to a decrease in the rate of *H. pylori* infection, which is the main cause, it is still one of the malignant tumors with the highest incidence and mortality rates (2).

For patients with resectable gastric cancer, the standard treatment is tumor resection, appropriate lymph node dissection, and perioperative chemotherapy (3). Even with the above standard treatment, it is not possible to prevent cancer recurrence in all cases, and once recurrence occurs, the prognosis is extremely poor (4, 5). Therefore, it is important to appropriately assess the prognosis and risk of recurrence in patients with resectable gastric cancer before surgery. Evaluating these factors allows us to provide the most appropriate treatment for each patient, considering their individual circumstances.

Recently, various studies have reported that systemic inflammatory markers are useful prognostic factors for patients with gastric cancer (6-8). This is because inflammatory response values are closely related to the oncological prognosis of cancer patients (9, 10). Several studies have reported the usefulness of the lymphocyte-to-C-reactive protein ratio (LCR) as a prognostic predictor (11-13). Lymphocytes play an important role in tumor immunity, and C-reactive protein (CRP) is a typical marker of inflammatory reactions. Few studies have examined the usefulness of LCR as a prognostic factor in patients with gastric cancer who have undergone curative resection and subsequently received postoperative adjuvant chemotherapy. In this study, we investigated the effect of the LCR on oncological prognosis in these patients.

Patients and Methods

Patients. We identified patients who had undergone curative resection for gastric cancer at Yokohama City University between 2005 and 2020 by reviewing their medical records. The following conditions were met: 1) histologically diagnosed as adenocarcinoma, 2) clinical stage I to III [according to the 15th edition of the Japanese Gastric Cancer Association's "Gastric Cancer Treatment Guidelines" (14)], 3) cases in which curative resection was performed as initial treatment, and 4) cases in which complete resection (R0) and radical lymph node dissection of gastric cancer were achieved.

Surgical and adjuvant therapy. In this study, all the patients underwent gastrectomy with D1+ or D2 lymphadenectomy. S-1 was administered as a postoperative adjuvant chemotherapy for patients with pathological stage I or II disease (15, 16).

Calculation of the LCR. The LCR was calculated using the following formula: LCR=Lymphocytes (number/μl) / C-reactive protein (mg/dl).

Follow-up. As a postoperative follow-up evaluation, patients underwent physical examinations and hematological tests, including tumor marker measurements, once every three months for five years after surgery. In addition, patients underwent computed tomography (CT) scans once every three months for three years after surgery and then every six months until five years after surgery.

Statistical analysis. The chi-squared test was used to evaluate the significance of the association between LCR and clinicopathological factors. The Kaplan–Meier method was used to create and evaluate overall survival and recurrence-free survival curves. Univariate and multivariate survival analyses were performed using a Cox proportional hazards model. *p*-Values of <0.05 were considered to indicate statistical significance. All statistical analyses were performed using SPSS (ver. 27.0 J Win; IBM Corp., Armonk, NY, USA).

Ethical approval. The present study was approved by the review board of Yokohama City University.

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)					<0.001
<75	179 (69.3)	96.9	82.8	78.6	
≥75	79 (30.7)	96.0	65.9	52.7	
Sex					0.416
Male	183 (70.9)	97.6	75.7	69.8	
Female	75 (29.1)	94.3	80.8	72.2	
Site of tumor					0.009
Upper	63 (24.4)	93.4	62.6	55.2	
Middle	113 (43.8)	96.0	81.3	78.1	
Lower	82 (31.8)	97.3	84.5	73.2	
T status					<0.001
T1	138 (53.5)	99.1	94.9	91.7	
T2 to T3	120 (46.5)	93.0	59.4	50.0	
Lymph node metastasis					<0.001
Negative	168 (65.1)	98.0	93.0	85.9	
Positive	90 (34.9)	93.1	53.5	46.2	
Lymphocyte-CRP ratio					<0.001
<9,000	58 (22.5)	94.1	57.1	54.2	
>9,000	200 (77.5)	97.3	83.0	75.2	
Lymphatic invasion					<0.001
Negative	168 (65.1)	98.0	93.0	85.9	
Positive	90 (34.9)	93.1	53.5	46.2	
Vascular invasion					<0.001
Negative	154 (59.7)	98.5	90.5	85.1	
Positive	104 (40.3)	92.9	60.8	51.6	
Postoperative surgical complications					0.003
No	160 (62.0)	98.5	90.5	85.1	
Yes	98 (38.0)	92.9	60.8	51.6	
Histological type					0.106
Intestinal	137 (53.1)	97.5	83.3	75.0	
Diffuse	121 (46.9)	94.8	72.1	66.3	

OS: Overall survival; CRP: C-reactive protein.

Results

Patients. The study included 258 patients [median age, 75 years; male, n=183 (70.9%); female, n=75 (29.1%)]. In this study, the 3-year and 5-year overall survival (OS) rates were lower when LCR was <9,000: the 3-year and 5-year OS were 57.1% and 53.6%, respectively, in patients with LCR <9,000, and 83.0% and 74.7% in patients with LCR >9,000 (Table I). Therefore, the cutoff value of the LCR was set at 9,000 in this study. Using this cutoff value, 258 patients were classified into the LCR-low (n=58) and LCR-high (n=200) groups. When comparing the patient backgrounds of the LCR-low and LCR-high groups, the LCR was significantly correlated with age, tumor-related factors (*e.g.*, tumor depth, lymph node metastasis, and stage progression), comorbidities (*e.g.*, diabetes and chronic obstructive pulmonary disease), perioperative blood transfusion history, and preoperative albumin.

Survival analysis. In this study, several clinicopathological factors were analyzed to determine their influence on overall survival (Table II). The 5-year OS rate was 54.2% in the LCR-low group and 75.2% in the LCR-high group ($p<0.001$), indicating that LCR was a significant prognostic factor (Figure 1). In the univariate analysis of clinicopathological factors other than LCR, there were significant differences in age, T status, lymph node metastasis, lymphatic invasion, vascular invasion, and

Table II. U*ni 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)				0.002			
<75	179	1.000					
≥75	79	2.288	1.351-3.875				
Sex				0.467			
Male	183	1.000					
Female	75	1.252	0.683-2.293				
T status				<0.001			0.002
T1	138	1.000			1.000		
T2 or T3	120	8.932	4.043-19.730		4.138	1.715-9.987	
Lymph node metastasis				<0.001			0.001
Negative	168	1.000			1.000		
Positive	90	6.583	3.588-12.079		2.976	1.521-5.826	
Lymphocyte-CRP ratio				<0.001			0.046
>9,000	200	1.000			1.000		
<9,000	58	2.614	1.526-4.477		1.744	1.009-3.014	
Lymphatic invasion				<0.001			
Negative	149	1.000					
Positive	109	4.790	2.610-8.792				
Vascular invasion				<0.001			
Negative	154	1.000					
Positive	104	4.915	2.681-9.010				
Histological type				0.140			0.055
Intestinal	137	1.000			1.000		
Diffuse	121	1.489	0.877-2.529		1.690	0.989-2.890	
Postoperative complications				0.003			0.043
No	160	1.000			1.000		
Yes	98	2.273	1.334-3.873		1.743	1.018-2.986	

CI: Confidence interval; OR: Odds ratio; CRP: C-reactive protein.

postoperative complications, which were identified as prognostic factors. The LCR was also identified as a prognostic factor in the multivariate analysis of overall survival [hazard ratio (HR)=1.744, 95% confidence interval (CI)=1.009-3.014, p=0.046]. T status, lymph node metastasis, and postoperative complications were identified as prognostic factors in the multivariate analysis of OS. In the univariate analysis of recurrence-free survival (RFS), the 5-year RFS was 50.4% in the LCR-low group and 72.3% in the LCR-high group (p<0.001), indicating that LCR is a significant prognostic factor (Figure 2). In the univariate analysis of RFS, there were significant differences in T status, lymph node metastasis, lymphatic invasion, vascular invasion, and postoperative complications. T status, lymph node metastasis, and postoperative complications were identified as significant prognostic factors in the multivariate analysis of RFS (Table III).

Comparison of postoperative clinical course. A comparison of the postoperative clinical course between the low and high LCR-low groups revealed a significant difference in the peritoneal recurrence rate, which was 24.1% in the LCR-low group and 7.5% in the LCR-high group (p<0.001) (Table IV). The peritoneal recurrence rate was significantly higher in the LCR-low group than in the LCR-high group (p<0.001). However, there were no significant differences between the two groups in hematological recurrence, lymph node recurrence, or local site recurrence.

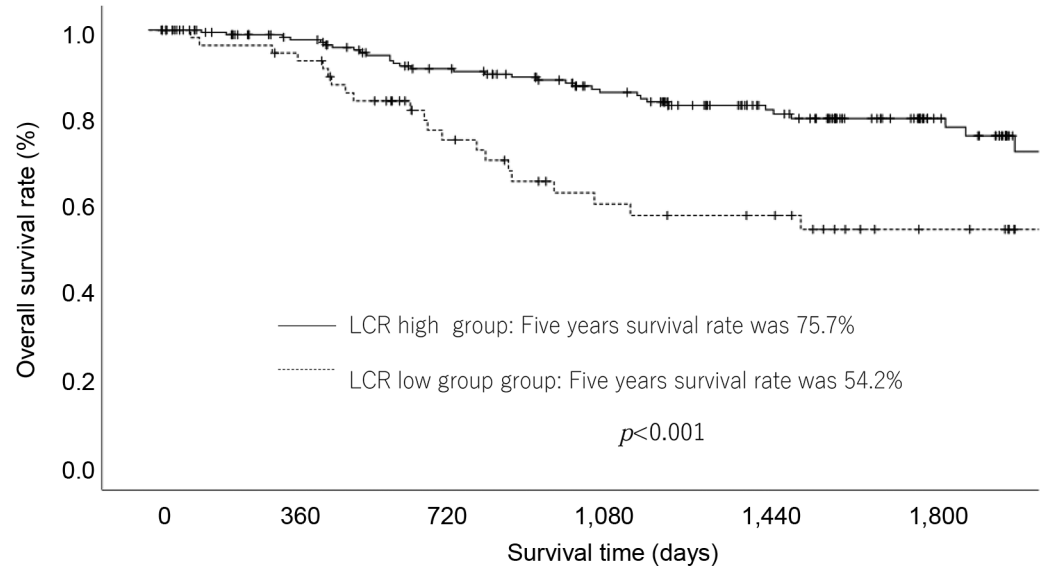

Figure 1. *Overall survival of gastric cancer patients in the lymphocyte-to-C-reactive protein ratio (LCR)-high and LCR-low groups.*

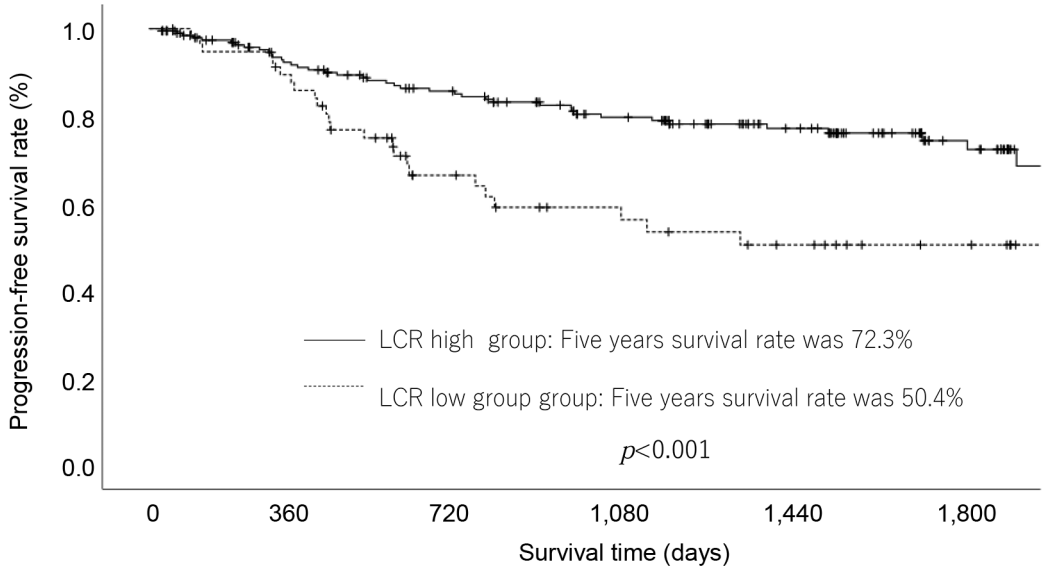

Figure 2. *Recurrence-free survival of gastric cancer patients in the lymphocyte-to-C-reactive protein ratio (LCR)-high and LCR-low groups.*

Discussion

In this study, we investigated the impact of the LCR on the postoperative course of gastric cancer patients who underwent curative resection. In terms of survival analysis, OS was significantly higher in the LCR-high group than in the LCR-low group, and RFS was significantly longer in the LCR-high group than in the LCR-low group. In addition, the peritoneal recurrence rate was significantly higher in the LCR-low group than in the LCR-

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)				0.008			
<75	179	1.000					
≥75	79	1.941	1.186-3.175				
Sex				0.301			
Male	183	1.000					
Female	75	1.347	0.766-2.370				
T status				<0.001			0.020
T1	138	1.000			1.000		
T2 or T3	120	7.642	3.892-15.005		2.612	1.160-3.005	
Lymph node metastasis				<0.001			<0.001
Negative	168	1.000			1.000		
Positive	90	7.642	4.333-13.476		3.490	1.822-6.685	
Lymphocyte-CRP ratio				0.001			
>9,000	200	1.000					
<9,000	58	2.310	1.392-3.832				
Lymphatic invasion				<0.001			
Negative	149	1.000					
Positive	109	4.285	2.483-7.392				
Vascular invasion				<0.001			0.069
Negative	154	1.000			1.000		
Positive	104	5.112	2.935-8.903		1.831	0.954-3.513	
Histological type				0.368			
Intestinal	137	1.000					
Diffuse	121	1.251	0.768-2.038				
Postoperative complications				0.001			0.017
No	160	1.000			1.000		
Yes	98	2.234	1.367-3.650		1.831	1.116-3.005	

CI: Confidence interval; OR: Odds ratio; CRP: C-reactive protein.

high group. Based on the above findings, it is clear that LCR has an impact on the oncological prognosis of patients with gastric cancer.

In the multivariate analysis of this study, LCR was identified as an independent prognostic factor for OS. Similar results have been reported previously. In 2021, Aoyama *et al.* investigated the involvement of the LCR in the survival and recurrence of 480 gastric cancer patients who underwent curative resection and subsequent adjuvant chemotherapy (17). They set the cutoff value of the LCR at 7,000 and analyzed survival and recurrence in the LCR-high and LCR-low groups. A statistically significant difference was found between the two groups in terms of OS (p=0.031), with the LCR-high group having significantly greater OS in comparison to the LCR-low group. The two groups also showed a statistically significant difference in RFS (p=0.048), and the LCR-high group was found to have significantly greater RFS in comparison to the LCR-low group. Furthermore, this study demonstrated that the LCR was an independent prognostic factor for OS and RFS in the multivariate analysis. Miyatani *et al.* investigated the correlation between preoperative and postoperative LCR and OS in 455 patients with gastric adenocarcinoma who underwent curative resection in 2022 (18). The 5-year OS rate was significantly higher in the preoperative high-dose group than in the preoperative low-dose group (65.4% *vs.* 83.9%, p<0.0001). Similarly, the 5-year OS rate was significantly higher in the postoperative LCR-high group than that in

Table IV. *Patterns of recurrence according to systemic inflammation score.*

	Lymphocyte-to-C-reactive protein ratio				*p*-Value
	>9,000 (n=200)		<9,000 (n=58)		
Recurrence site	Number	%	Number	%	
Peritoneal recurrence	15	7.50%	14	24.1%	<0.001
Hematological recurrence	17	8.50%	10	17.2%	0.056
Lymph node recurrence	9	4.50%	5	8.62%	0.223
Local site	6	3.00%	5	8.62%	0.062

the postoperative LCR-low group (67.0% *vs.* 84.1%, $p<0.0001$). In addition, 5-year OS was found to be lower in the subgroup of patients whose LCR was low both preoperatively and postoperatively in comparison to the group with a high LCR both preoperatively and postoperatively or in the group with a low LCR either preoperatively or postoperatively. Furthermore, the combination of the preoperative and postoperative LCR was identified as an independent prognostic factor in the multivariate analysis.

It is clear from this study and previous reports that the LCR has an impact on the long-term oncological prognosis of patients with gastric cancer who have undergone curative resection. However, in previous studies, the relationship between the LCR and oncological outcomes in patients with gastric cancer was unclear. Therefore, we examined this issue and found several associations between the LCR and postoperative outcomes. First, the LCR may be correlated with postoperative complications. Aoyama *et al.* reported that the incidence of intra-abdominal abscess and ileus after surgery was significantly higher in the LCR-low group than in the LCR-high group (17). Chen *et al.* also reported that the incidence of postoperative complications was significantly higher in the LCR-low group than in the LCR-high group, in terms of the correlation between LCR and postoperative complications in patients with gastric cancer (19). Maezawa *et al.* showed that postoperative infectious complications affected the oncological prognosis of patients with gastric cancer who underwent radical resection (20). The correlation between the LCR and postoperative complications may affect the oncological prognosis of patients with gastric cancer. In this study, there was no significant difference in postoperative complications between the two groups; however, a significant difference may have been detected in a larger cohort study. Second, the LCR was associated with peritoneal recurrence in the postoperative recurrence pattern, and the LCR-low group had a significantly higher rate of peritoneal recurrence relative to the LCR-high group. Patients with peritoneal recurrence after gastric cancer surgery have a poor prognosis. The effect of postoperative adjuvant chemotherapy may be the reason for the significant difference in the rate of peritoneal recurrence between the two groups. The ATCS-GC study showed that the use of S-1 as postoperative adjuvant chemotherapy significantly reduces the rate of peritoneal recurrence in patients who have undergone surgery for gastric cancer (15). In this study, 51.7% and 29.0% of the patients in the LCR-low and LCR-high groups, respectively, were eligible for postoperative adjuvant chemotherapy. In contrast, the actual rate of postoperative adjuvant chemotherapy in the LCR-low and LCR-high groups was 66.7% and 84.5%, respectively. In other words, it is possible that the LCR-low group did not fully benefit from postoperative adjuvant chemotherapy. Thus, the LCR was thought to be associated with the rate of postoperative adjuvant chemotherapy, which affected the rate of peritoneal recurrence and, in turn, the oncological prognosis. Third,

the LCR is associated with perioperative blood transfusion. In this study, the LCR-low group had a significantly higher rate of perioperative blood transfusion than the LCR-high group (20.7% *vs.* 8.5%, p=0.010). Many studies have confirmed that perioperative blood transfusions have an impact on the prognosis of patients after gastric cancer surgery (21). Perioperative blood transfusions have also been reported to increase the incidence of postoperative infectious complications and promote tumor recurrence (22). In this study, there was a correlation between the LCR, perioperative blood transfusions, and postoperative infectious complications, which are thought to have an impact on OS and RFS. In addition, Aoyama *et al.* reported that perioperative anemia in patients with gastric cancer who underwent curative resection in 2024 affected the patients' oncological prognosis. In this study, patients with hemoglobin levels below 11 g/dl had significantly lower OS than those with hemoglobin levels above 11 g/dl, and univariate and multivariate analyses showed that perioperative anemia was an independent prognostic factor. Therefore, in this study, it is also possible that perioperative anemia, as well as perioperative blood transfusions, may have affected the oncological prognosis of gastric cancer patients (23).

There are several points that need to be addressed in future research. First, this study was a retrospective analysis conducted at a single institution, and it was not possible to completely eliminate selection bias. Second, although the cutoff value for the LCR was set at 9,000 in this study, the optimal cutoff value for the LCR remains unclear. In a previous study, Aoyama *et al.* studied the usefulness of the LCR as a prognostic factor in 480 patients with gastric cancer who underwent curative resection between 2013 and 2017. In their study, the LCR was calculated as the number of lymphocytes (number/μl)/CRP (mg/dl), and the cutoff value was set at 7,000 (17). Miyatani *et al.* also conducted a study to investigate whether preoperative and postoperative LCR is useful for predicting the prognosis of patients with gastric cancer, using 455 patients who were pathologically diagnosed with gastric adenocarcinoma between 2005 and 2018. In their study, LCR was calculated as the number of lymphocytes (number/μl)/CRP (mg/dl) and based on a receiver operating characteristic (ROC) analysis of OS, the cutoff values were set at 23,800 preoperative and 13,033 postoperative (18). The different cutoff values in each study are thought to be due to variations in patient backgrounds, perioperative treatments, and the number of patients enrolled in each study. To calculate the optimal cutoff value for the LCR, it is necessary to conduct a larger cohort study. Third, the timing of the LCR calculation was based on blood sampling 1-7 days before surgery, and there was a range of evaluation times for each patient. The bias caused by the evaluation time may have affected this study. Accordingly, it is necessary to clearly set the evaluation time in future studies.

Conclusion

The results of this study suggest that the LCR may be a useful prognostic factor for patients with gastric cancer who have undergone curative resection. The LCR was correlated with postoperative complications, peritoneal recurrence, and blood transfusions, suggesting that it may be useful for perioperative treatment and management.

Conflicts of Interest

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

Authors' Contributions

SY and TA contributed substantially to the study design. TA, YM, IH, SY, RE, KK, KS, AT, MH and MF made substantial contributions to data acquisition, analysis, and interpretation. TA, MN, AS, and NY were involved in drafting and critically revising the manuscript for important intellectual content. TA and YM approved the final version of the manuscript.

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