



Postoperative ratio of the maximum C-reactive protein level to the minimum peripheral lymphocyte count as a prognostic indicator for gastric cancer patients

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Abstract

Purpose Inflammation, together with immune and nutritional status, are associated with the progression of various cancer types. We evaluated the prognostic significance of the postoperative ratio (post-CLR) of the maximum C-reactive protein value (post-CRP^{Max}) to the minimum peripheral lymphocyte count (post-LC^{Min}) in patients with gastric cancer (GC).

Methods The subjects of this retrospective study were 227 patients who underwent curative surgery for histopathologically diagnosed gastric adenocarcinoma.

Results The 5-year overall survival (OS) rates differed significantly between the post-CLR^{High} (≥ 152.6) group and the post-CLR^{Low} (< 152.6) group for all patients (45.0% vs. 68.4%, respectively; $P < 0.001$). The 5-year disease-specific survival (DSS) rates were also significantly related to post-CLR for all patients, (80.6% vs. 64.3% for the post-CLR^{Low} and the post-CLR^{High} groups, respectively; $P = 0.002$). Among patients without infectious complications, the CLR affected both the 5-year OS rate (48.4% vs. 69.2% for the post-CLR^{High} and the post-CLR^{Low} groups, respectively; $P = 0.006$) and the 5-year DSS rate (80.2% vs. 67.0% for the post-CLR^{Low} and the post-CLR^{High} groups, respectively; $P = 0.027$). Multivariate analysis revealed that post-CLR was an independent prognostic indicator for both the OS and DSS of all patients.

Conclusions Our finding show that the post-CLR can help predict the prognosis of GC patients.

Keywords CRP · Gastric cancer · Lymphocyte · Prognosis · Recurrence

Introduction

The prognosis of patients with gastric cancer (GC) has improved with advances in diagnostic techniques and better intraoperative and postoperative care. However, in 2012, GC was still the third-leading cause of cancer death of men and women in the world [1]. Gastrectomy with regional lymph node dissection is the standard curative treatment for GC, but recurrence is common, even after complete removal of the tumor (R0 resection) [2]. Early detection of recurrence may improve survival after curative gastrectomy for GC [3]. Recurrence usually arises from micrometastases,

which cannot be detected by ordinary diagnostics such as ultrasonography, computed tomography, and positron emission tomography. Therefore, identifying and carefully monitoring GC patients at high risk of recurrence after curative gastrectomy is important for optimizing their prognosis. To this end, reliable prognostic indicators for GC are indispensable. Various indices, such as the Glasgow prognostic score (GPS), the neutrophil–lymphocyte ratio (NLR), and the prognostic nutritional index (PNI) have been shown to predict the prognosis of GC patients [4–6]. These indicators are thought to reflect states of inflammation, immunocompetence, and nutrition in patients with cancer, signifying that their outcomes are determined not only by tumor-related factors, but also by systemic, patient-related factors.

Studies of these prognostic indicators are based mainly on pre-surgical measurements. However, surgery and postoperative infectious complications (post-ICs) may induce inflammation and immunosuppression. Post-ICs have been shown to worsen the prognosis of various cancers, including

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Table 1 Patient overview ($n=227$)

Variables	Mean \pm SD	Number (%)
Age (years)	68.8 \pm 11.8	
Gender		
Male		166 (73.1)
Female		61 (26.9)
Tumor size (cm)	5.5 \pm 3.0	
Histology ^a		
Differentiated		108 (47.6)
Undifferentiated		119 (52.4)
Depth of invasion ^b		
T1		22 (9.7)
T2		67 (29.5)
T3		105 (46.3)
T4		33 (14.5)
Lymph node metastasis ^c		
N0		87 (38.3)
N1		47 (20.7)
N2		56 (26.7)
N3		37 (16.3)
Lymphatic invasion ^d		
ly0		8 (3.5)
ly1		92 (40.5)
ly2		86 (37.9)
ly3		41 (18.1)
Venous invasion ^e		
v0		32 (14.1)
v1		103 (45.4)
v2		72 (31.7)
v3		20 (8.8)
Stage of disease		
I		50 (22.0)
II		103 (45.4)
III		74 (32.6)
Infectious complications ^f		
Absent		182 (80.2)
Present		45 (19.8)

^aDifferentiated, papillary, or tubular adenocarcinoma; undifferentiated, poorly differentiated, mucinous adenocarcinoma, and signet-ring cell carcinoma

^bDepth of invasion: T1: tumor has invaded the lamina propria or submucosa; T2: tumor has invaded the muscularis propria; T3: tumor has invaded the subserosa; T4: tumor invasion is contiguous to, or exposed beyond, the serosa or has invaded adjacent structures

^cN0: no regional lymph node metastases; N1: Metastasis in 1–2 regional lymph nodes; N2: Metastasis in 3–6 regional lymph nodes; N3: Metastasis in 7 or more regional lymph nodes

^dLymphatic invasion: ly0–ly3, grade of lymphatic invasion

^eVenous invasion: v0–v3, grade of venous invasion

^fGrade II or more according to the Clavien–Dindo classification

GC. We also recently reported finding that the postoperative peripheral lymphocyte count (LC) was a more useful indicator of GC prognosis than the preoperative LC [7]. These results suggest that surgery-related inflammation and immunosuppression may affect the prognosis of GC patients [8, 9] and that postoperative evaluations of C-reactive protein (CRP) and LC are probably more useful than preoperative evaluations for predicting the prognosis of GC patients. The postoperative values of CRP and LC change dramatically from the preoperative values because of surgical stress and the presence of an infectious complication. Saito et al. reported that the maximum postoperative CRP levels were significantly related to the prognosis of GC patients [9]. Therefore, in the current study, we used the maximum postoperative CRP level (post-CRP) and the minimum postoperative peripheral LC as representative postoperative values for CRP and LC. We then evaluated the correlation between the ratio (post-CLR) of the maximum post-CRP to the minimum postoperative peripheral LC (post-LC) and how this affected the prognosis of GC patients.

Materials and methods

The subjects of this retrospective study were 227 patients with stage IB–IIIC gastric adenocarcinoma, who underwent curative gastrectomy (R0 resection) at our institution between January, 2003 and April, 2014. Table 1 summarizes the patients' clinical characteristics. The median follow-up was 46.4 months at the time of analysis. The

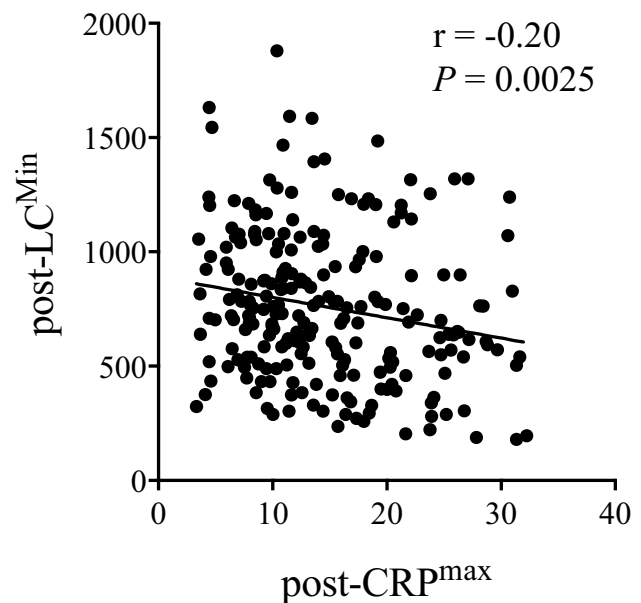


Fig. 1 Correlation between the maximum postoperative C-reactive protein level (CRP^{Max}) and the minimum postoperative peripheral lymphocyte count (LC^{Min}) ($r = -0.20$, $P = 0.0025$)

clinicopathologic findings were based on the Japanese Classification of Gastric Carcinoma [10]. All patients underwent either distal partial, proximal partial, or total gastrectomy with regional dissection of the lymph nodes. None of the patients received neoadjuvant chemotherapy or radiation therapy, but 62 patients received adjuvant chemotherapy. Patients were checked periodically for signs of early recurrence by diagnostic imaging, including chest X-ray, upper gastrointestinal endoscopy, ultrasonography, and/or computed tomography. Causes of death and patterns of recurrence were established by reviewing medical records, including laboratory data, ultrasonography, computed tomography, scintigrams, peritoneal punctures, and laparotomies, or by interviewing family members. In some cases, postmortems were done to determine the cause of death. Of the 102 deaths in this cohort, 65 were from recurrence of GC, and 42 were from unrelated malignancies, other diseases, or accidents.

The results of postoperative blood tests, including serum CRP and LC, were obtained from the patients' records. We measured serum CRP levels and absolute lymphocyte counts on postoperative days (PODs) 1, 3, 5 and 7 in principle, and additional measurements were taken based on the patients' condition. Each patient's maximum post-CRP value and minimum LC from surgery until hospital discharge were used as the post-CRP^{Max} and post-LC^{Min} values in this study, respectively. The post-CLR was calculated by dividing the post-CRP^{Max} (mg/dl) by the post-LC^{Min} × 10,000. The Clavien–Dindo classification was used to evaluate postoperative complications [11, 12]. The Institutional Review Board of our institution approved of this study and waived the informed consent requirement.

Statistical analysis

Differences between two groups were evaluated using the Mann–Whitney *U* test. The Youden index was calculated using a receiver operating characteristic (ROC) analysis to

determine optimal cutoffs for post-CLR in survival analyses. Survival curves were calculated according to the Kaplan–Meier method. Differences between curves were identified using the log-rank test. Multivariate analyses of factors considered prognostic of overall survival (OS) and disease-specific survival (DSS) were based on the Cox's proportional hazards model and a stepwise procedure. The covariates included in the current study were age, gender, histology, tumor size, depth of invasion, lymph node metastasis, lymphatic invasion, venous invasion, the presence of an infectious complication of grade II or more according to the Clavien–Dindo classification, and post-CLR. $P < 0.05$ was considered significant. GraphPad Prism (GraphPad Software, Inc., La Jolla, CA, USA) and SPSS statistics version 24.0 (SPSS Inc., Chicago, IL) software were used for the statistical analyses.

Results

The mean postoperative values were as follows: post-CRP^{Max}, 14.6 mg/dl (range 3.3–32.2); post-LC^{Min}, 760.1 (range 180.0–880.0); and post-CLR, 254.9 (range 27.3–1742). The post-CRP^{Max} and post-LC^{Min} had a significant, but weakly negative correlation ($r = -0.20$, $P = 0.0025$; Fig. 1). In the ROC analysis for OS, the AUCs were post-CRP^{Max}, 0.587; post-LC^{Min}, 0.593; and post-CLR, 0.618, which indicates that CLR was the most reliable predictor of the prognosis of GC patients among these markers (Fig. 2).

Table 2 shows the correlations between clinicopathological variables and post-CLR. The post-CLR was significantly higher in male patients, those aged ≥ 75 years, and those with post-ICs than in female patients, those younger than 75 years, and those with no post-ICs, respectively. ROC analysis showed the optimal post-CLR cut-off value to be 152.6 (AUC = 0.618, $P = 0.002$). Based on these results, we divided the patients into

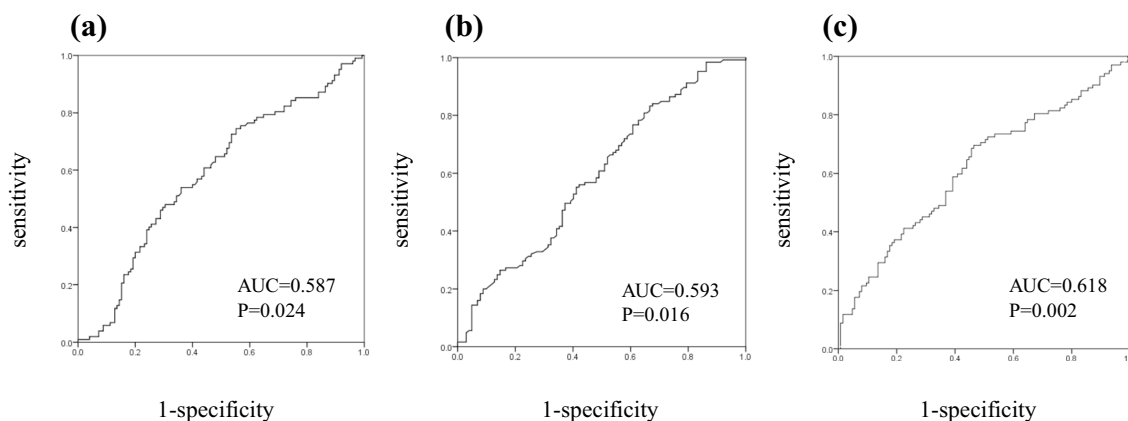


Fig. 2 Comparison of areas under the curves of the maximum postoperative C-reactive protein level (CRP^{Max}) (a), the minimum postoperative peripheral lymphocyte count (LC^{Min}) (b), and the ratio of postoperative CRP^{Max} to postoperative LC^{Min} (post-CLR) (c) for overall survival

Table 2 Relationships between the postoperative ratio of the maximum C-reactive protein level to the minimum peripheral lymphocyte count (post-CLR) and clinicopathological variables in patients with gastric cancer

Variables	Post-CLR	P value
Age (year)		0.018
< 75 (n = 152)	152.2 ± 232.7	
≥ 75 (n = 75)	202.6 ± 264.3	
Gender		0.007
Male (n = 166)	188.1 ± 268.8	
Female (n = 61)	137.2 ± 143.6	
Tumor size (cm)		0.143
< 4 (n = 77)	160.7 ± 147.9	
≥ 4 (n = 150)	182.0 ± 278.9	
Depth of invasion		0.414
T1 (n = 23)	184.6 ± 180.1	
T2/3/4 (n = 204)	178.8 ± 250.0	
Lymph node metastasis		0.549
Absent (n = 86)	159.4 ± 208.4	
Present (n = 141)	184.7 ± 264.9	
Histology		0.109
Differentiated (n = 108)	188.0 ± 283.4	
Undifferentiated (n = 119)	157.5 ± 201.8	
Lymphatic involvement		0.106
Absent (n = 8)	120.6 ± 268.2	
Present (n = 219)	181.9 ± 244.2	
Vascular involvement		0.118
Absent (n = 32)	138.8 ± 188.9	
Present (n = 195)	182.1 ± 252.3	
Infectious complication		< 0.001
Absent (n = 182)	151.3 ± 187.1	
Present (n = 45)	395.1 ± 329.2	
Stage of disease		0.27
Stage I/II (n = 153)	244.4 ± 228.2	
Stage III (n = 74)	276.6 ± 276.3	

All results expressed as means ± SD

See Table 1 for details of histology, depth of invasion, and infectious complications

a post-CLR^{High} group (post-CLR ≥ 152.6; n = 129) and a post-CLR^{Low} group (post-CLR < 152.6; n = 98). For all patients, the post-CLR^{High} and post-CLR^{Low} groups differed significantly, both in 5-year OS (post-CLR^{Low}: 70.7%; post-CLR^{High}: 48.7%; $P = 0.0003$, Fig. 3a) and 5-year DSS (post-CLR^{Low}: 79.5%; post-CLR^{High}: 62.0%; $P = 0.0022$; Fig. 3b). Fig. 4 shows the correlation between prognosis and post-CLR in each stage. The post-CLR^{High} and post-CLR^{Low} groups differed significantly in 5-year OS (post-CLR^{Low}: 80.0%; post-CLR^{High}: 58.8%; $P = 0.04$, Fig. 4c) for patients with stage II disease. The post-CLR^{High} and post-CLR^{Low} groups of patients with stage III disease differed significantly in both 5-year OS (post-CLR^{Low}: 49.8%; post-CLR^{High}: 32.3%; $P = 0.011$, Fig. 4e)

and 5-year DSS (post-CLR^{Low}: 64.8%; post-CLR^{High}: 41.4%; $P = 0.012$; Fig. 4f).

Figure 5 shows the correlation between prognosis and post-CLR in the GC patients without post-ICs. Among patients without post-ICs, the post-CLR^{High} and post-CLR^{Low} groups also differed significantly in 5-year OS (post-CLR^{Low}: 72.0%; post-CLR^{High}: 53.7%; $P = 0.0058$, Fig. 5a) and 5-year DSS (post-CLR^{Low}: 79.6%; post-CLR^{High}: 66.0%; $P = 0.027$, Fig. 5b).

Finally, multivariate analysis revealed that post-CLR was an independent prognostic indicator for both the OS and DSS of all patients (Table 3).

Discussion

Lymph node metastasis and depth of tumor invasion are generally regarded as the most important predictors of the prognosis of GC patients [13, 14]. According to recent reports, in addition to these tumor-related factors, patient-related factors such as inflammation, malnutrition, and immunity status also influence the prognosis of GC patients.

This study demonstrated that post-CLR is closely related to the prognosis of GC patients. High post-CLR reflects the increased serum concentration of post-CRP^{Max}. CRP is an acute-phase reactant synthesized by hepatocytes and regulated by proinflammatory cytokines, particularly IL-6 [15], and is commonly used to assess inflammation status. High pre-CRP levels are often observed in cancer patients, including those with GC, because the tumor itself and the surrounding cells produce interleukin 6 (IL-6), which regulates CRP synthesis by hepatocytes. Pre-CRP was proven to be an independent prognostic factor for the survival of patients with various malignancies, including GC [16].

High post-CRP levels in GC patients may be caused by post-ICs, which lead to prolonged inflammation. Therefore, higher post-CRP levels are likely to be observed over long periods in GC patients with post-ICs. Recent studies have shown post-ICs worsen the prognoses of patients with various cancers, including GC [17]. However, Saito et al. demonstrated that post-CRP^{Max} was a reliable indicator of survival after GC surgery [9]. Notably, post-CRP^{Max} was closely associated with the prognosis of GC patients without post-ICs, but not of those who suffered post-ICs, suggesting that post-operative CRP elevation is a more reliable indicator of survival than post-ICs after GC surgery. In the current study, we demonstrated that post-CLR was significantly associated with the prognosis of GC patients without post-ICs. Furthermore, post-CLR, but not the presence of IC, was an independent prognostic indicator for DSS, which indicates that post-CLR is also a more reliable indicator of DSS after GC surgery than

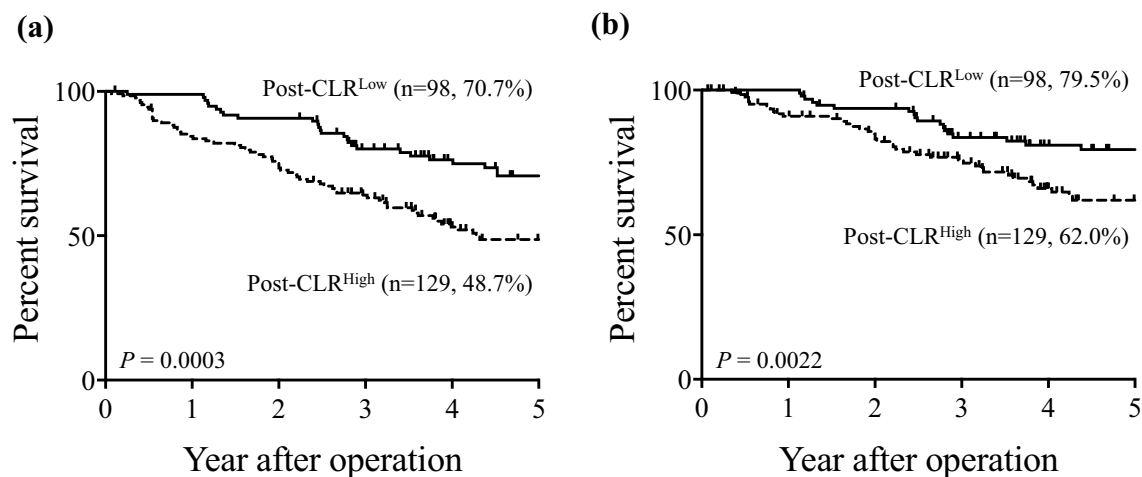


Fig. 3 **a** Overall survival curves and **b** disease-specific survival curves, according to the postoperative ratio of the maximum C-reactive protein level to the minimum peripheral lymphocyte count (post-CLR)

postoperative complications. There are two possible reasons for a high post-CRP in patients without a post-IC. One is that residual micrometastatic cancer cells produce IL-6, which could increase the post-CRP levels; and the other is that the stress of surgery elevates the post-CRP levels.

Increased post-CLR also reflects a decreased post- LC^{Min} . We reported observing a rapid and significant decrease in total lymphocyte numbers after surgery for GC in a previous study [18]. The number of lymphocytes was lowest on postoperative day (POD) 1 and although they gradually increased, they were still significantly lower than the pre-surgical levels on PODs 3 and 7. As lymphocytes are part of cell-mediated immunity and play an important role in host anticancer defense mechanisms, the lymphopenia observed after GC surgery may place a patient at higher risk of tumor recurrence due to decreased cell-mediated tumor immunity for residual micrometastasis. We recently demonstrated that the postoperative LC is a useful predictor of the prognosis of GC patients [7]. In that study, we measured the LC on POD1 and defined that as the postoperative LC. However, we noticed that the LC was lowest later than POD1 in some patients. Therefore, in the current study, we defined the lowest LC as the LC^{Min} , because we think that the lowest LC is a more reliable indicator of prognosis. We then determined the post-CLR and compared the prognostic significance of each indicator. The AUC of post-CLR was the highest among these indicators, which suggests that the post-CLR is a more accurate predictor of the prognosis of GC patients than either the post- LC^{Max} or the post- LC^{Min} alone. In this study, the post-CLR was closely related to the prognosis of GC patients, especially those with stage III tumors. Therefore, this parameter can

be used to select which patients with stage III GC are at high risk of recurrence and need intensive adjuvant chemotherapy and follow-up. However, because the post-CLR can be obtained postoperatively, it cannot be used to make preoperative decisions about treatment strategy.

GC can be further subdivided into intestinal and diffuse types according to the Lauren classification [19]. An alternative system, proposed by the Japanese Classification of Gastric Carcinoma, divides gastric cancer into papillary, tubular, mucinous, poorly differentiated, and signet ring cell carcinomas [10]. It is possible that the effect of post-CLR on prognosis differs according to the type of GC. Therefore, we investigated the correlation between prognosis and post-CLR in both differentiated (papillary, or tubular adenocarcinoma) and undifferentiated (poorly differentiated, mucinous adenocarcinoma, and signet-ring cell carcinoma) types and found a close correlation in both types (data not shown). A recent study demonstrated that GC could be subdivided into four molecular subtypes; namely, EBV-infected tumors, MSI tumors, genomically stable tumors, and chromosomally unstable tumors [20]. Further investigations should be carried out to establish the correlation between prognosis and post-CLR in these molecular subtypes.

This study has a few limitations. First, it was a retrospective analysis, which would generate some bias. Second, lymphocytes include some regulatory cells such as regulatory T cells, reported to have negative effects on cancer prognoses [21], although the scope of these effects is beyond the current study. Third, the number of patients in this study was small; thus a large-scale, prospective study is needed to verify our results.

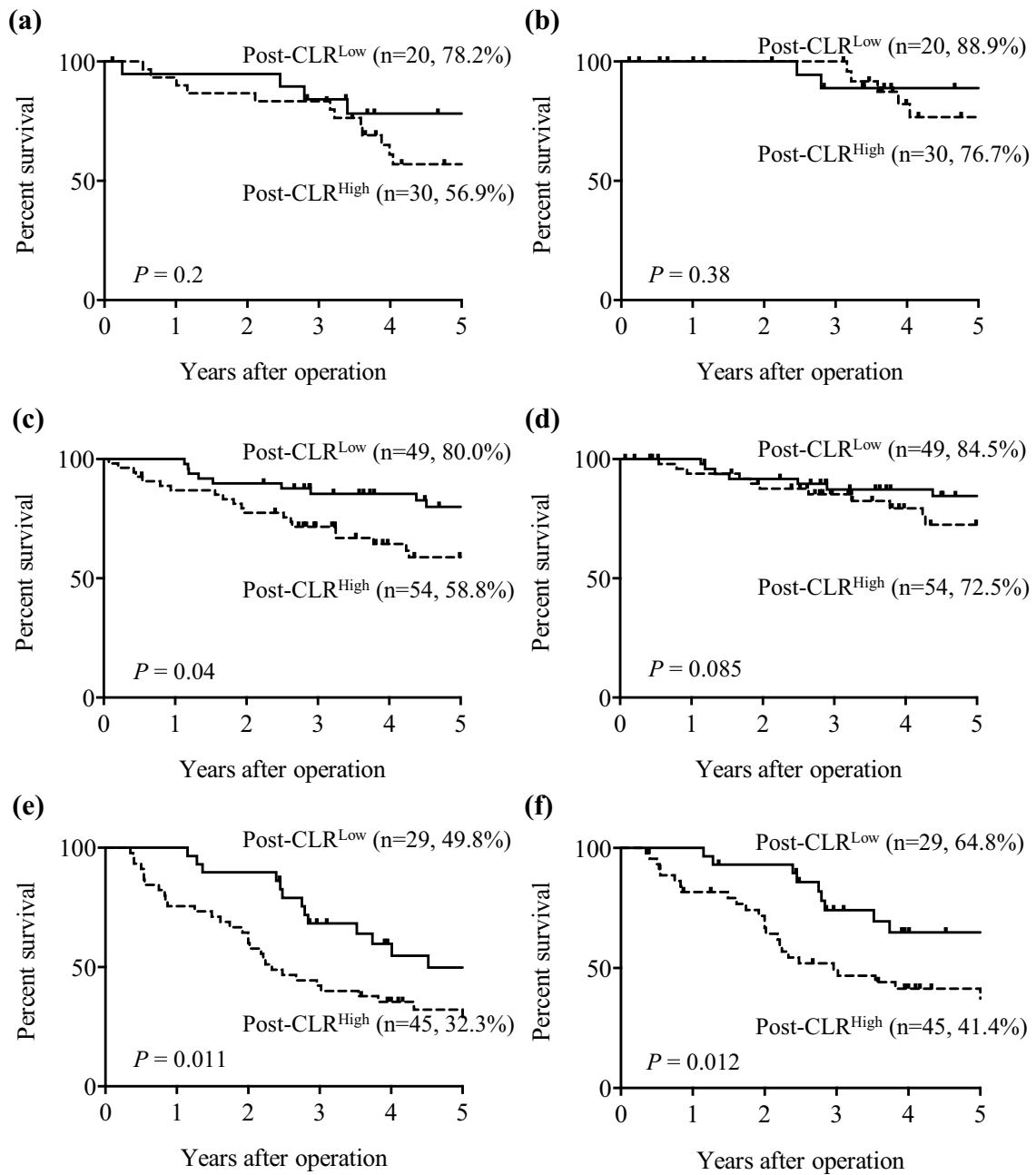


Fig. 4 Overall survival curves of patients with stage I (a), II (c), and III (e) gastric cancer and disease-specific survival curves of patients with stage I (b), II (d), and III (f) gastric cancer according to the post-

operative ratio of the maximum C-reactive protein level to the minimum peripheral lymphocyte count (post-CLR)

In conclusion, post-CLR is thought to reflect the status of postoperative maximum inflammation and immune suppression in each patient and can help predict the prognosis

of GC patients. Because serum markers can be measured quickly, easily, and non-invasively, post-CLR is a convenient biological marker in the routine clinical setting.

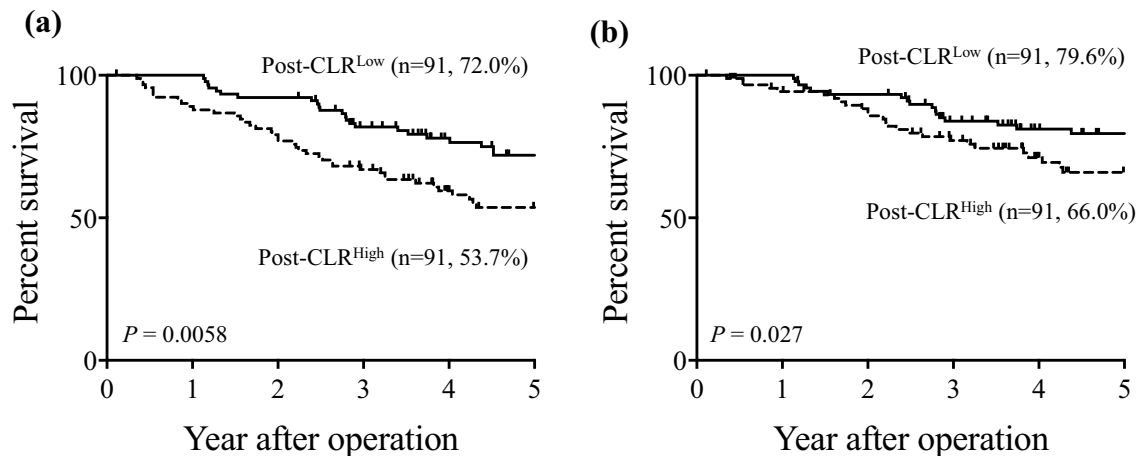


Fig. 5 **a** Overall survival curves and **b** disease-specific survival curves, according to the postoperative ratio of the maximum C-reactive protein level to the minimum peripheral lymphocyte count (post-CLR) of patients without postoperative infectious complications

Table 3 Multivariate analyses of prognostic factors associated with overall survival and disease-specific survival

Variables	Overall survival			Disease-specific survival		
	<i>P</i> value	HR	95% CI	<i>P</i> value	HR	95% CI
Age (years) ^a	<0.001	1.046	1.026–1.066	–	–	–
Tumor size (cm) ^a	0.003	1.100	1.033–1.170	–	–	–
Lymph node metastasis (N0–N3) ^b	<0.001	1.445	1.210–1.725	<0.001	1.609	1.284–2.017
Depth of invasion (T1–T4) ^c	–	–	–	0.027	1.450	1.043–2.015
Infectious complication (presence vs. absence)	0.007	1.894	1.187–3.021	–	–	–
Post-CLR (high group vs. low group)	0.023	1.667	1.073–2.591	0.019	1.953	1.119–3.413

See Table 1 for the detail of lymph node metastasis, depth of invasion, and infectious complication

CI Confidence interval, *HR* hazard ratio

^aContinuous variable

Funding We received no grants, equipment or funding for this study.

Compliance with ethical standards

Conflict of interest We have no real or potential conflicts of interest to declare.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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