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ORIGINAL ARTICLE

Clinical implications of the preoperative lymphocyte C-reactive protein ratio in esophageal cancer patients

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Abstract

Purpose We recently revealed the preoperative lymphocyte C-reactive protein ratio (LCR) to be a new marker for predicting various outcomes in malignancies. The aim of our present study was to clarify the potential utility of the preoperative LCR for predicting the perioperative risk and oncological outcome in esophageal cancer patients.

Methods We analyzed the preoperative LCR from 153 esophageal cancer patients to clarify its clinical relevance.

Results The preoperative LCR was significantly decreased in a stage-dependent manner, and a decreased preoperative LCR was significantly associated with the occurrence of postoperative surgical site infection. Esophageal cancer patients with a low LCR showed a poor outcome in both the overall survival and disease-free survival compared with those who had a high LCR. Multivariate analyses showed that a decreased LCR was an independent prognostic factor for both a poor overall survival and disease-free survival. A decreased preoperative LCR was an independent predictive factor for postoperative surgical site infection and significantly correlated with nutritional and inflammatory indicators. In addition, the LCR was useful for identifying esophageal cancer patients likely to have a poor outcome among patients with and without neoadjuvant chemotherapy.

Conclusions Assessing the preoperative LCR might help physicians identify populations at high risk for perioperative complication and oncological outcomes, and determine individualized perioperative therapeutic strategies.

Keywords Esophageal cancer · Chemoradiation · Lymphocyte C-reactive protein ratio · Recurrence · Prognosis

Introduction

Esophageal cancer (EC) is the sixth-most common cause of cancer-related death worldwide [1]. With advances in our understanding of tumor biology, new evidence has been uncovered that provides further insight into this disease. Recent advances in multimodality therapy have provided survival benefits to EC patients. However, the long-term prognosis of patients undergoing potentially curative esophageal resection remains poor [2]. The ability to predict tumor behavior would be informative for patients and clinician during the decision-making process. Therefore, there is a clear need for prognostic biomarkers that identify high-risk EC patients to provide each patient with favorable intensive therapy.

The inflammatory response is intimately related to tumorigenesis, and an elevated inflammatory response is correlated with a poor survival in numerous cancers [3–5]. In esophageal squamous cell carcinoma in particular, the pathogenesis is robustly related to chronic inflammation caused by alcohol drinking and cigarette smoking. Chronic inflammation from these sources can lead to mucosal injury and subsequent DNA damage [6, 7]. In addition, inflammatory processes are thought to affect various steps of carcinogenesis and play a pivotal role in the underlying biological mechanisms of resistance to chemotherapeutic treatment for EC patients [8]. Furthermore, previous studies have shown that perioperative complications are associated with an unfavorable

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short-term quality of life and long-term oncology outcome of early recurrence and a poor survival after esophagectomy [9, 10]. Therefore, a biomarker that also evaluates the risk of perioperative complications would be useful.

Our previous study showed that several scoring systems for inflammatory status have potential utility for predicting the perioperative risk and oncological outcome in gastrointestinal cancer patients [11–19]. Recently, our newly developed biomarker of the lymphocyte C-reactive protein ratio (LCR) was shown to be a predictive biomarker for recurrence, the prognosis, and postoperative morbidity in CRC patients, and it proved useful for perioperative management and as a postoperative oncological follow-up strategy [20].

In this study, we explored the clinical significance of the LCR as a prognostic biomarker for EC patients receiving surgery and identified patients whose prognosis was likely to improve according to the choice of postoperative therapeutic strategy.

Methods

Patients

In this study, we enrolled 153 patients who underwent surgery for EC at our institution between 2002 and 2017. All patients were classified according to the International Union against Cancer TNM Classification (seventh edition). Before treatment, 18 patients (11.8%) had clinical stage 0 disease, 41 (26.8%) had stage I, 47 (30.7%) had stage II, 30 (19.6%) had stage III, and 17 (11.1%) had stage IV disease. The surgical approaches included thoracoscopic esophagectomy and both left and right transthoracic esophagectomy. Sixty-five patients (42.4%) received neoadjuvant chemotherapy (NAC) before surgery (with or without radiation therapy). Preoperative treatment options were determined based on the tumor stage and operability, including the patient's age and history. Neoadjuvant chemotherapy was performed as 5-fluorouracil and cisplatin for two cycles. Chemoradiotherapy schedules consisted of three cycles of 5-fluorouracil and cisplatin weekly and 2.0 Gy per fraction for a total dose of 30 Gy.

Patients were followed up using our standard protocol every 12–16 weeks for at least 1 year. This protocol included tumor-marker studies, computed tomography, endoscopic examinations, ultrasonography, and chest radiography. Bone scans were performed when bone metastasis was indicated. Data collected from inpatient and outpatient records included demographic data (age and sex), tumor-specific data, pathologic data [including *T* classification, lymph-node metastasis, distant metastasis, histology, and tumor markers, including carcinoembryonic antigen (CEA) and squamous cell carcinoma antigen (SCC), at the diagnosis], and survival data [disease-free survival (DFS) and overall survival (OS)].

Postoperative surgical site infection (SSI) as a primary short-term post-operative outcome was defined as that occurring within 30 days of surgery. Details of SSI were obtained from a prospectively collected database and, where necessary, from patient medical records. Postoperative SSI included wound infection (superficial or deep infection requiring treatment with antibiotic agents or wound drainage) and intra-abdominal abscess (intra-abdominal fluid collection associated with a fever or leucocytosis that discharged spontaneously or required surgical or radiologically guided drainage, with positive blood or fluid culture).

Written informed consent was obtained from all patients, and the study was approved by the Institutional Review Board of Mie University Hospital.

Laboratory measurements

Each patient's blood specimen was obtained within 1 day prior to surgery. A full blood count (FBC) and blood molecules, including albumin (ALB), choline esterase (Ch-E), CRP levels, and tumor markers, were evaluated during a routine blood examination. The LCR was calculated as follows: lymphocyte count/C-reactive protein. The cut-off value for the LCR was defined according to the receiver-operating characteristic (ROC) curve analysis with Youden's index for the survival. The cut-off value for ALB was 3.5 g/dl and for Ch-E was 240 U/l depending on the upper limit of the normal range in our institute. In addition, the cut-off values for CEA (5 ng/ml) and SCC (1.5 ng/ml) were the upper limit of the normal range in our institute.

Statistical analyses

The association between the LCR and clinicopathological findings was analyzed using the Kruskal–Wallis test to clarify the clinical significance as both a prognostic and predictive biomarker of treatment. Results are expressed as the median ± interquartile range (IQR). F tests were conducted to assess the equality of variance for comparable groups. For time-to-event analyses, survival estimates were calculated using a Kaplan–Meier analysis, and groups were compared using the log-rank test. The OS was measured from the date the patient underwent surgery until the date of death resulting from any cause or until the last known follow-up in patients who were still alive. The DFS was measured from the date the patient underwent curative surgery to the date of disease recurrence, death from any cause (i.e., cancer-unrelated deaths were not censored), or until the last contact with the patient. ROC curves were established to discriminate the patients who died from those who survived for the OS and those who did have recurrence from those who did not have it for the DFS. Youden's index was used to determine the optimal

cut-off threshold of the LCR from our EC cohort for predicting the OS and DFS. Cox's proportional hazards model was used to estimate hazard ratios (HRs) for the OS and DFS. The assumption of proportionality was confirmed for the Cox proportional hazard analyses by generating Kaplan–Meier survival curves (e.g., LCR low group and LCR high group) and by ensuring that the two curves did not intersect.

Multivariate logistic regression models were used to predict factors influencing postoperative infectious complication. Multivariate analyses were performed using the factors that were significant in univariate analyses. Clinical variables that were considered for univariate and multivariate analyses, in addition to the target LCR, were previously identified confounding factors with an impact on the prognosis and perioperative complications in patients with EC: sex, age at the diagnosis, histology, pathological *T* stage (T1/2 or T3/4), lymph-node metastasis (present or absent), distant metastasis (present or absent), neutrophil–lymphocyte ratio (NLR; < 2.5 or ≥ 2.5), modified Glasgow prognostic score (mGPS; 2 or 0,1), CEA levels (≥ 5.0 ng/mL or < 5.9 ng/mL), SCC levels (≥ 1.5 ng/mL or < 1.5 ng/mL), body mass index (BMI; < median or ≥ median), ALB (< 3.5 g/dl or ≥ 3.5 g/dl), Ch-E (< 240 U/l or ≥ 240 U/l), operation time (< median or ≥ median), and blood loss (< median or ≥ median). All *p* values were two-sided, and $P < 0.05$ was considered statistically significant. All statistical analyses were carried out using the JMP 13.1 software program (SAS Institute Inc., Cary, North Carolina, USA).

Results

Association between the LCR and disease progression in patients with EC

The median value of the preoperative LCR was 11,750 [95% confidence interval (CI): 17,469–28,018]. Table 1 shows the association between the clinicopathological findings and the preoperative LCR in EC patients. A lower LCR was significantly associated disease progression factors, such as advanced *T* classification (T3/4, $P = 0.02$) and TNM stage (stage III/IV, $P = 0.02$). Furthermore, the preoperative LCR was significantly decreased in EC patients with a history of neoadjuvant treatment compared with those with no such history in this cohort ($P < 0.0001$). This finding suggested that patients who underwent neoadjuvant treatment had more advanced disease and thus a lower LCR (Supplementary Table 1). Regarding postoperative complications, a lower LCR was associated with SSI ($P = 0.02$).

Table 1 Association between clinicopathological variables and LCR in EC patients

Variables	*n*	LCR (median ± IQR)	*P* value
Sex			
Male	128	11,430 ± 23,501	0.17
Female	25	20,923 ± 37,176	
Age (years)[#]			
> 69	72	11,105 ± 23,033	0.50
≤ 69	81	12,000 ± 26,929	
Neoadjuvant therapy			
Yes	64	6385 ± 14,205	< 0.0001*
No	89	19,125 ± 28,789	
Histological type			
SCC	136	11,618 ± 23,826	0.23
Others	17	24,250 ± 32,860	
T classification			
pT0/1/2	102	155,489 ± 27,795	0.02*
pT3/4	50	8040 ± 17,373	
Node involvement			
Present	73	8700 ± 23,046	0.08
Absent	80	15,116 ± 27,896	
Distant metastasis			
Present	7	8700 ± 17,561	0.34
Absent	146	11,803 ± 26,197	
TNM stage			
0/I/II	106	15,116 ± 28,431	0.02*
III/IV	46	8040 ± 21,292	
Surgical site infections			
Yes	27	6576 ± 11,380	0.02*
No	126	14,763 ± 30,949	

LCR lymphocyte C-reactive protein ratio, *EC* esophageal cancer, *IQR* interquartile range, *TNM* tumor node metastasis

*$P < 0.05$ Kruskal–Wallis test

[#]The median age was 69 years (range = 35–90 years) in this cohort

EC patients with a low LCR showed a poor outcome for both the OS and DFS

Next, we investigated the prognostic impact of the preoperative LCR on the OS and DFS of EC patients. To generate Kaplan–Meier curves subdivided by the preoperative LCR, we first performed ROC analyses to define the optimal cut-off value of the preoperative LCR. ROC analyses for the OS showed that 7842 was the cut-off value of the LCR that could discriminate EC patients with a poor prognosis from those without a poor prognosis, with an area under the curve (AUC) of 0.65 (sensitivity: 0.60, specificity: 0.69, Fig. 1a). Interestingly, ROC analyses for the DFS showed that the same cut-off value of the LCR (7842) could discriminate EC patients with recurrence from those without is, with an AUC of 0.65 (sensitivity: 0.58, specificity: 0.70, Fig. 1b).

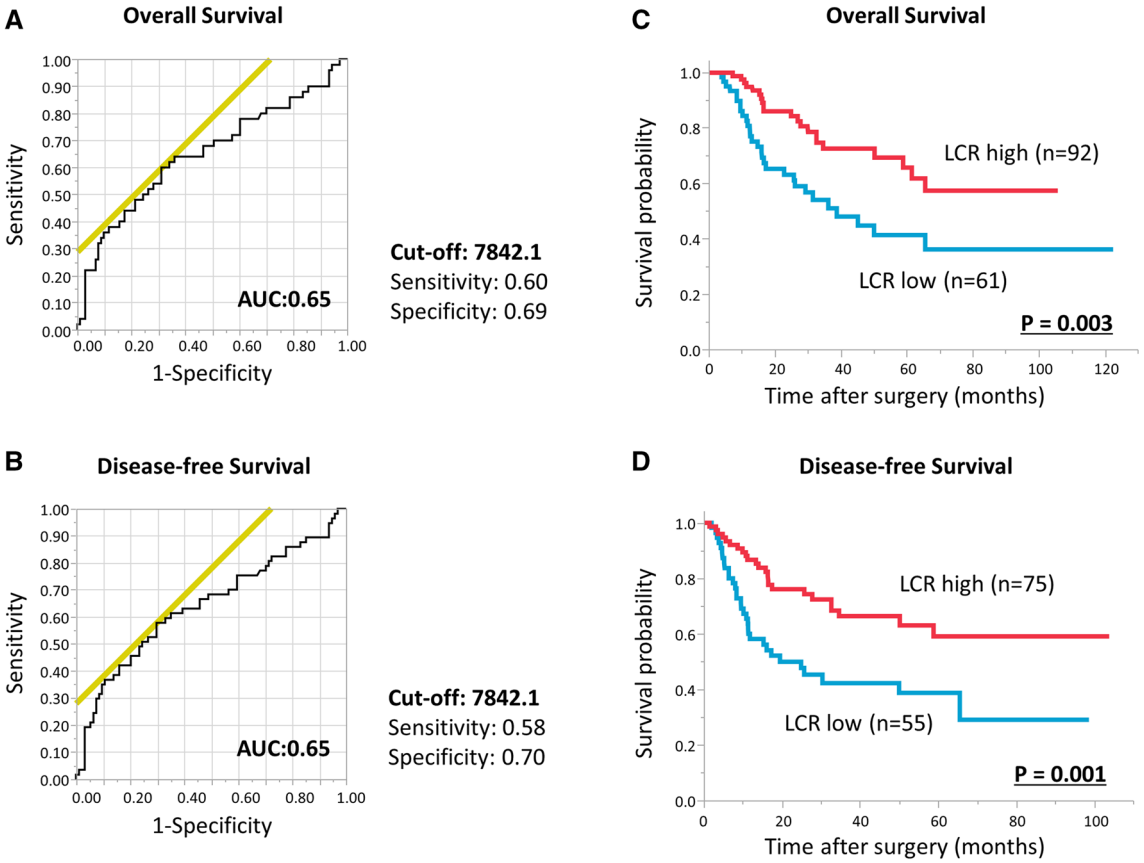

Fig. 1 A receiver-operating characteristic (ROC) analysis for the overall survival (OS) showed that 7842 as the cut-off value of the lymphocyte C-reactive protein ratio (LCR) discriminated esophageal cancer (EC) patients with a poor prognosis from those with a good prognosis, with an area under the curve (AUC) of 0.65 (**a**). An ROC analysis for the disease-free survival (DFS) showed that 7842 as the cut-off value of the LCR discriminated EC patients with early recurrence from those without early recurrence, with an AUC of 0.65 (**b**). A time-to-event analysis showed that patients with a low LCR were significantly correlated with poor outcomes compared to those with a high LCR in terms of the OS (**c**). EC patients with a low LCR were correlated with early recurrence compared with those with a high LCR in terms of the DFS (**d**)

Subsequent time-to-event analyses showed that EC patients with a low LCR (< 7842; $N = 61$) were significantly more likely to have a poor outcome than those with a high LCR (≥ 7842; $N = 92$) in terms of the OS (log-rank test, $P = 0.003$, Fig. 1c). In addition, EC patients with a low LCR (< 7842; $N = 55$) were significantly more likely to have a poor DFS than those with a high LCR (≥ 7842; $N = 75$; log-rank test, $P = 0.001$, Fig. 1d).

A decreased preoperative LCR was an independent prognostic factor for both the OS and DFS

To clarify the potential utility of the preoperative LCR as a prognostic predictor for the survival and recurrence, we conducted a Cox proportional hazard regression analysis for the OS and DFS in EC patients. A multivariate analysis showed that an advanced pathological T stage (HR: 3.02, 95% CI: 1.35–6.74, $P = 0.007$), presence of lymph-node metastasis (HR: 2.24 95% CI: 1.12–4.67, $P = 0.02$), presence of distant metastasis (HR: 4.79, 95% CI: 1.54–13.6, $P = 0.009$), high serum CEA level (HR: 4.17, 95% CI: 2.17–8.08, $P < 0.0001$), and decreased preoperative LCR (HR: 2.76, 95% CI: 1.33–5.86, $P = 0.006$) were independent prognostic factors for a poor OS in EC patients (Table 2a). Furthermore, a multivariate analysis revealed that a low preoperative LCR was also an independent prognostic factor for a poor DFS in EC patients (HR: 1.98, 95% CI: 1.06–3.72, $P = 0.03$, Table 2b).

The preoperative LCR was an independent predictive factor for postoperative SSI

We observed a significant association between the preoperative LCR and postoperative SSI in EC patients (Table 1). One clinically necessary biomarker for the perioperative period is a predictive biomarker for identifying patients at risk of infectious complications, especially SSI. We, therefore, analyzed the predictive factors of SSI in EC patients

Table 2 Univariate and multivariate analyses for predictors of the overall survival

Variables	Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Sex (male vs. female)	1.16	0.57–2.67	0.69			
Age (> 69 vs. ≤ 69 years old)[#]	1.18	0.68–2.07	0.55			
Neoadjuvant therapy (yes vs. no)	2.76	1.54–5.14	0.0006*	0.78	0.35–1.78	0.55
Histological type (others vs. SCC)	3.40	1.05–20.8	0.04*	2.25	0.66–14.2	0.22
T classification (pT3/4 vs. pT0/1/2)	2.69	1.51–4.73	0.0009*	3.02	1.35–6.74	0.007*
Node involvement (present vs. absent)	3.57	1.98–6.76	< 0.0001*	2.24	1.12–4.67	0.02*
Distant metastasis (present vs. absent)	6.09	2.31–13.4	0.0009*	4.79	1.54–13.6	0.009*
LCR levels (≤ 7842 vs. > 7842)[##]	2.31	1.32–4.11	0.003*	2.76	1.33–5.86	0.006*
NLR (≤ 2.5 vs. > 2.5)	1.71	0.98–3.00	0.06			
mGPS (2 vs. 0,1)	2.84	1.17–5.93	0.02*	1.45	0.52–4.69	0.49
CEA levels (> 5.0 vs. ≤ 5.0 ng/mL)	3.97	2.16–7.28	< 0.0001*	4.17	2.17–8.08	< 0.0001*
SCC levels (> 1.5 vs. ≤ 1.5 ng/mL)	0.99	0.45–1.96	0.99			
Variables	Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Sex (male vs. female)	1.22	0.61–2.79	0.59			
Age (> 69 vs. ≤ 69 years old)[#]	0.99	0.59–1.68	0.99			
Neoadjuvant therapy (yes vs. no)	2.91	1.70–5.13	< 0.0001*	1.27	0.66–2.55	0.48
Histological type (others vs. SCC)	1.83	0.75–6.06	0.20			
T classification (pT3/4 vs. pT0/1/2)	2.46	1.44–4.16	0.001*	2.04	1.01–4.03	0.05*
Node involvement (present vs. absent)	4.07	2.31–7.45	< 0.0001*	2.55	1.35–5.05	0.004*
LCR levels (≤ 7842 vs. > 7842)[##]	2.37	1.40–4.07	0.001*	1.98	1.06–3.72	0.03*
NLR (≤ 2.5 vs. > 2.5)	1.61	0.95–2.73	0.08			
mGPS score (2 vs. 0,1)	3.19	1.39–6.40	0.008*	1.25	0.48–3.61	0.66
CEA levels (> 5.0 vs. ≤ 5.0 ng/mL)	2.96	1.67–5.19	0.0003*	2.91	1.57–5.37	0.0008*
SCC levels (> 1.5 vs. ≤ 1.5 ng/mL)	1.15	0.58–2.12	0.67			

HR hazard ratio, *CI* confidence interval, *SCC* squamous cell carcinoma, *T* tumor, *LCR* lymphocyte C-reactive protein ratio, *NLR* neutrophil–lymphocyte ratio, *mGPS* modified Glasgow prognostic score, *CEA* carcinoembryonic antigen

[#]The median age was 69 years (range = 35–90 years) in this cohort

[##]The cut-off value of the LCR was determined by an ROC analysis with Youden's index for the overall survival in this cohort

by a logistic regression analysis. A multivariate analysis showed that a low LCR (≤ 7842) was the only independent factor for predicting SSI in EC patients [odds ratio (OR): 2.62, 95% CI: 1.12–6.12, $P = 0.03$, Table 3].

The preoperative LCR reflects the nutritional or inflammatory status of the host

Several lines of evidence demonstrated that preoperative nutritional or inflammatory status predicted postoperative SSI in various malignancies [21]. Furthermore, recent evidence from our group first showed that the preoperative LCR reflected the nutritional status of patients with gastric cancer [22]. Based on this evidence, we further assessed the direct correlation between the preoperative LCR and nutritional or inflammatory indicators in EC patients. As nutritional factors, although the BMI did not correlate with the LCR (Fig. 2a), serum ALB and Ch-E showed positive correlations with the LCR (ALB: $R = 0.30$, $P = 0.0002$; Ch-E: $R = 0.23$, $P = 0.005$, Fig. 2b, c). In addition, as inflammatory indicators, the NLR and mGPS demonstrated negative correlations with the LCR (NLR: $R = -0.27$, $P = 0.001$; mGPS: $R = -0.35$, $P < 0.0001$, Fig. 2d, e).

The preoperative LCR identified EC patients with a poor OS and DFS among those who did and did not receive NAC

Although the prognostic impact of the LCR was revealed in the total cohort, some of the EC patients received NAC before surgery in our cohort. This adjuvant therapy may have affected their laboratory data. Indeed, EC patients who received NAC might have had a reduced preoperative LCR compared with those who did not (6385 ± 14,205 vs.

Table 3 Univariate and multivariate analyses of factors that were predictive of SSI in EC patients

Variables	Univariate			Multivariate		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Sex (male vs. female)	1.14	0.36–3.64	0.83			
Age (> 69 vs. ≤ 69 years)[#]	1.04	0.45–2.38	0.93			
Neoadjuvant therapy (yes vs. no)	1.52	0.66–3.51	0.33			
Histological type (others vs. SCC)	3.75	0.48–29.5	0.21			
T classification (pT3/4 vs. pT0/1/2)	1.00	0.41–2.42	1.00			
Node involvement (present vs. absent)	1.00	0.44–2.31	0.99			
Distant metastasis (present vs. absent)	3.84	0.81–18.3	0.09			
BMI (≤ 19.4 [median], > 19.4)	1.76	0.62–5.03	0.29			
ALB (≤ 3.5 vs. > 3.5 g/dL)	0.76	0.21–2.78	0.67			
Ch-E (≤ 240 vs. > 240 U/L)	0.84	0.35–2.04	0.70			
LCR levels (≤ 7842 vs. > 7842)[##]	2.62	1.12–6.12	0.03*	2.62	1.12–6.12	**0.03***
NLR levels (≤ 2.5 vs. > 2.5)	1.79	0.77–4.15	0.18			
mGPS (2 vs. 0/1)	2.22	0.27–18.1	0.46			
CEA levels (> 5.0 vs. ≤ 5.0 ng/mL)	1.01	0.37–2.80	0.98			
SCC levels (> 1.5 vs. ≤ 1.5 ng/mL)	1.27	0.48–3.32	0.63			
Operation time (> median vs. ≤ median)	1.26	0.54–2.93	0.59			
Blood loss (> median vs. ≤ median)	1.02	0.44–2.39	0.96			

SSI surgical site infection, *EC* esophageal cancer, *OR* odds ratio, *CI* confidence interval, *SCC* squamous cell carcinoma, *T* tumor, *LCR* LYMPHOCYTE C-reactive protein ratio, *NLR* neutrophil–lymphocyte ratio, *mGPS* modified Glasgow prognostic score, *CEA* carcinoembryonic antigen

[#]The median age was 69 years (range = 35–90 years) in this cohort

[##]The cut-off value of the LCR was determined by an ROC analysis with Youden's index for the

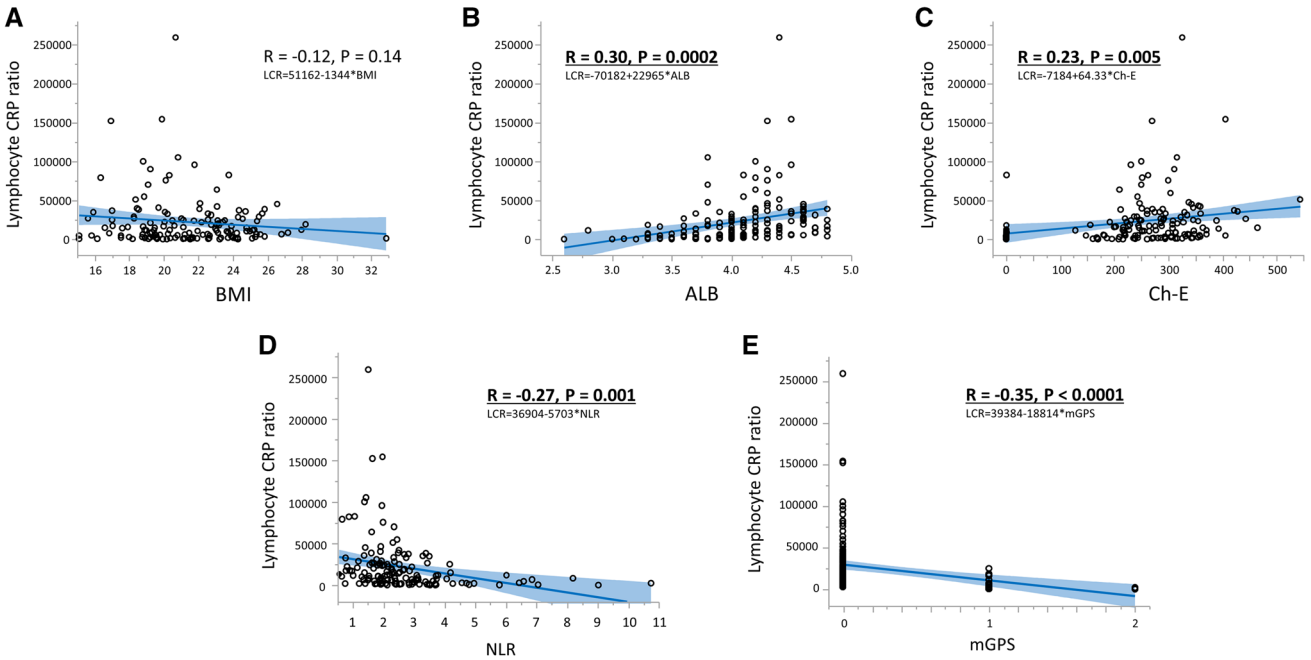

Fig. 2 The evaluation of the correlation between nutritional or inflammatory markers and the lymphocyte C-reactive protein ratio (LCR). As a nutritional marker, the BMI did not have a significant correlation with the LCR (**a**), while the serum albumin (ALB) and choline esterase (Ch-E) showed positive correlations with the LCR (**b**, **c**). As inflammatory indicators, the neutrophil-to-lymphocyte ratio (NLR) and modified Glasgow prognostic score (mGPS) showed negative correlations with the LCR (**d**, **e**)

19,125 ± 28,789, $P < 0.0001$, Fig. 3a). Therefore, we next investigated whether or not the LCR was a predictor of a poor OS and DFS in EC patients divided by whether or not they were receiving NAC (NAC[−] group: $N = 89$; NAC[+] group: $N = 64$). Although adjusting the cut-off threshold in each cohort was necessary due to the effect of NAC, a survival curve analysis based on the NAC(−) group showed a clear stratification for assessing the prognosis using the LCR for both the OS and DFS (Fig. 3b, c). Furthermore, the preoperative LCR status identified EC patients with a poor OS and DFS in the NAC(+) group (Fig. 3d, e). In addition, a multivariate Cox regression analysis revealed very consistent findings for the total cohort and showed that a low LCR was an independent prognostic factor, especially for the DFS, in both groups (NAC[−] EC patients: DFS, HR = 9.53, 95% CI: 1.76–44.4, $P = 0.01$, Table 4a, b; NAC[+] EC patients: DFS, HR = 2.27, 95% CI: 1.11–4.98, $P = 0.02$, Table 5a, b).

Discussion

The systemic inflammatory response may contribute to tumor development, and emerging evidence has suggested the potential utility of several parameters for assessing the systemic inflammation status, including neutrophils, lymphocytes, albumin, and CRP, to predict the prognosis of the oncological outcome in EC patients [4, 23–26]. In addition, several combination markers, such as the NLR and mGPS, have been described as feasible prognostic biomarkers for malignancies [27, 28].

Our recently developed parameter of the LCR is calculated using the lymphocyte count and serum CRP level and mainly assesses the systemic inflammation and nutritional status [20, 22]. The LCR can be a more reliable indicator of a poor oncological outcome than other combinations of inflammatory markers as well as a reliable indicator of perioperative complications, as previously described [20]. Furthermore, a recent study from another group also validated these findings in other types of cancer [29]. However, the predictive potential of the preoperative LCR for the short-term (perioperative risk) and long-term outcomes (prognosis) in EC patients have never been elucidated. Thus, this study explored whether or not the preoperative LCR can be used as a predictive biomarker for the perioperative risk and prognosis in EC patients.

Several novel findings were demonstrated regarding the clinical relevance of the preoperative LCR during the course of this study. First, we showed that a low preoperative LCR was significantly associated with clinicopathological factors for disease development and that EC patients with a low preoperative LCR showed a poorer prognosis for both the OS and DFS than those with a high preoperative LCR. Second, a low preoperative LCR was an independent prognostic factor for both OS and DFS. Third, we showed that a low

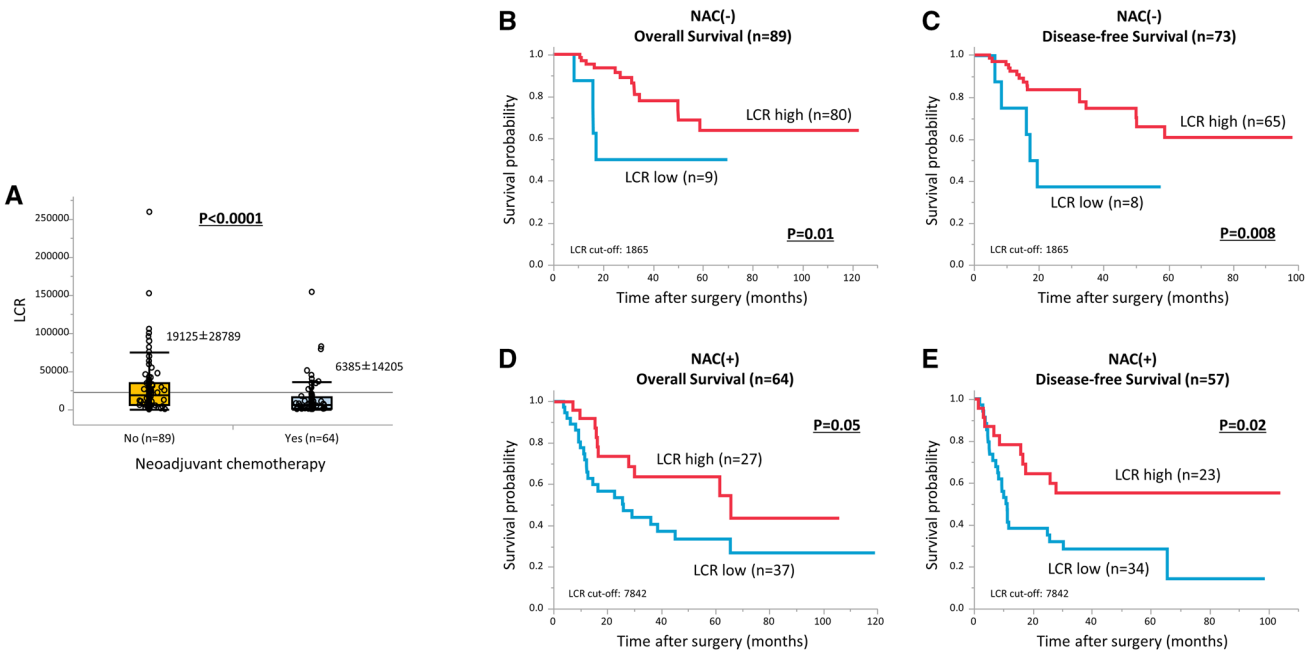

Fig. 3 The lymphocyte C-reactive protein ratio (LCR) was decreased among esophageal cancer (EC) patients who did and did not receive neoadjuvant chemotherapy (NAC) (**a**). Survival curve analyses based on the NAC(−) group showed clear stratification for assessing the prognosis for both the overall survival (OS) and disease-free survival (DFS), with an LCR cut-off value of 1865 (**b**, **c**). The LCR also identified EC patients with a poor OS and DFS in the NAC(+) group with an LCR cut-off value of 7842 (**d**, **e**)

Table 4 Univariate and multivariate analyses for predictors of the overall survival in EC patients not receiving NAC

Variables	Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Sex (male vs. female)	1.52	0.43–9.64	0.56			
Age (> 68 vs. ≤ 68 years)[#]	1.10	0.42–2.91	0.86			
Histological type (others vs. SCC)	3.18	0.65–57.3	0.18			
T classification (pT3/4 vs. pT0/1/2)	1.08	0.25–3.32	0.90			
Node involvement (present vs. absent)	2.72	1.05–7.51	0.04*	3.12	1.00–9.98	0.05*
LCR levels (≤ 1865 vs. > 1865)[##]	3.40	0.96–9.63	0.06			
NLR (≤ 2.5 vs. > 2.5)	1.24	0.46–3.91	0.68			
mGPS (2 vs. 0,1)	2.37	0.13–11.6	0.46			
CEA levels (> 5.0 vs. ≤ 5.0 ng/mL)	8.54	2.83–28.4	0.0002*	11.00	3.53–37.7	< 0.0001*
SCC levels (> 1.5 vs. ≤ 1.5 ng/mL)	0.83	0.19–2.56	0.76			
Variables	Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Sex (male vs. female)	1.83	0.53–11.5	0.38			
Age (> 68vs. ≤ 68)[#]	0.79	0.33–1.88	0.59			
Histological type (others vs. SCC)	2.20	0.63–13.8	0.24			
T classification (pT3/4 vs. pT0/1/2)	2.59	0.84–6.71	0.09			
Node involvement (present vs. absent)	5.43	2.23–14.5	0.0002*	5.90	2.09–18.5	0.0008*
LCR levels (≤ 1865 vs. > 1865)[##]	3.61	1.16–9.46	0.03*	9.53	1.76–44.4	0.01*
NLR (≤ 2.5 vs. > 2.5)	1.24	0.50–3.48	0.65			
mGPS score (2 vs. 0,1)	7.78	1.21–28.3	0.03*	2.84	0.24–72.2	0.42
CEA levels (> 5.0 vs. ≤ 5.0 ng/mL)	4.90	1.80–13.4	0.003*	4.68	1.55–14.0	0.008*
SCC levels (> 1.5 vs. ≤ 1.5 ng/mL)	1.88	0.61–4.95	0.25			

EC esophageal cancer, *NAC* neoadjuvant chemotherapy, *HR* hazard ratio, *CI* confidence interval, *SCC* squamous cell carcinoma, *T* Tumor, *LCR* lymphocyte C-reactive protein ratio, *NLR* neutrophil–lymphocyte ratio, *mGPS* modified Glasgow prognostic score, *CEA* carcinoembryonic antigen

[#]The median age was 68 years (range = 41–90 years) in this cohort

[##]The cut-off value of the LCR was determined by an ROC analysis with Youden's index for the overall survival in this cohort

preoperative LCR was a potential predictor for postoperative SSI, because it reflects the host's systemic nutrition and inflammation status. Finally, we showed that the preoperative LCR identified EC patients with a poor prognosis, especially with regard to the DFS, among populations who did or did not receive NAC.

Inflammation and the immune response play critical roles in cancer development. Lymphocytes are assigned a major role in immune surveillance, and tumor-infiltrating lymphocytes are widely recognized as key indicators of antitumor effects via the host's cytotoxic immune response [24]. Lymphocytes infiltrating the tumor microenvironment are a trigger for a cell-mediated immunological antitumor reaction, and this cell-mediated immune response is largely dependent on lymphocytes [24]. Therefore, lymphopenia is recognized as a marker of host immunological incompetence for malignant disease and a prognostic marker for the oncological outcome [30–32]. CRP is a well-established serum marker reflecting systemic inflammatory responses in clinical settings. In addition, it has a role as both a marker of cancer development and a prognostic marker [4]. Some studies have shown that an elevated CRP level was associated with an unfavorable prognosis and/or perioperative complications in EC patients [23, 33, 34]. Furthermore, CRP has been combined with other markers of the systemic inflammatory response in prognostic scores, such as mGPS, and has been shown to be a useful prognostic biomarker in several types of tumor [4]. Given the above evidence, the preoperative LCR is expected to be able to assess the combined status of the host immunological response and systemic inflammation, and a decreased LCR might reflect an impaired immunological response and an enhanced systemic inflammatory response in EC patients. Thus, LCR can be a more reliable prognostic marker and predictor of recurrence than the peripheral lymphocyte count or serum CRP alone.

In the present study, we also revealed that the preoperative LCR status is a potential predictor for postoperative SSI. Several lines of evidence have demonstrated a preoperative

Table 5 Univariate and multivariate analyses for predictors of the overall survival in EC patients receiving NAC

Variables	Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Sex (male vs. female)	0.96	0.42–2.57	0.92			
Age (> 69 vs. ≤ 69 years old)[#]	1.27	0.63–2.53	0.49			
Histological type (others vs. SCC)	1.80	0.39–32.1	0.52			
T classification (pT3/4 vs. pT0/1/2)	1.18	0.59–2.40	0.64			
Node involvement (present vs. absent)	1.67	0.79–3.97	0.19			
Distant metastasis (present vs. absent)	3.94	1.45–9.11	0.01*	8.45	2.57–27.4	0.0008*
LCR levels (≤ 7842 vs. > 7842)[##]	2.41	1.18–5.33	0.02*	3.17	1.23–9.41	0.02*
NLR (≤ 2.5 vs. > 2.5)	2.26	1.12–4.79	0.02*	1.04	0.47–2.35	0.63
mGPS (2 vs. 0,1)	2.63	0.97–6.03	0.06			
CEA levels (> 5.0 vs. ≤ 5.0 ng/mL)	2.37	1.11–4.92	0.03*	1.78	0.82–3.82	0.14
SCC levels (> 1.5 vs. ≤ 1.5 ng/mL)	0.55	0.21–1.25	0.16			
Variables	Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Sex (male vs. female)	0.93	0.41–2.51	0.87			
Age (> 69 vs. ≤ 69 years old)[#]	1.34	0.68–2.62	0.39			
Histological type (others vs. SCC)	1.63	0.26–5.50	0.54			
T classification (pT3/4 vs. pT0/1/2)	1.52	0.78–3.00	0.22			
Node involvement (present vs. absent)	2.31	1.12–5.24	0.02*	2.32	1.08–5.05	0.03*
LCR levels (≤ 7842 vs. > 7842)[##]	2.35	1.15–5.15	0.02*	2.27	1.11–4.98	0.02*
NLR (≤ 2.5 vs. > 2.5)	1.94	0.99–3.97	0.06			
mGPS score (2 vs. 0,1)	1.72	0.64–3.90	0.26			
CEA levels (> 5.0 vs. ≤ 5.0 ng/mL)	2.00	0.97–4.04	0.06			
SCC levels (> 1.5 vs. ≤ 1.5 ng/mL)	0.84	0.34–1.82	0.68			

EC esophageal cancer, *NAC* neoadjuvant chemotherapy, *HR* hazard ratio, *CI* confidence interval, *SCC* squamous cell carcinoma, *T* Tumor, *LCR* lymphocyte C-reactive protein ratio, *NLR* neutrophil–lymphocyte ratio, *mGPS* modified Glasgow prognostic score, *CEA* Carcinoembryonic antigen

[#]The median age was 69 years (range = 35–90 years) in this cohort

[##]The cut-off value of the LCR was determined by an ROC analysis with Youden's index for the overall survival in this cohort

systemic inflammatory reaction via host–tumor interactions, including immune disorders and malnutrition, as a potential predictive marker for postoperative complications in cancer patients. The LCR had a positive correlation with other serum biomarkers that reflect immune and nutritional conditions, such as ALB and Ch-E. ALB reflects inflammation and nutrition, and a low ALB status is associated with postoperative complications [25]. A low Ch-E concentration is also thought to be indicative of immune disorders and malnutrition, and therefore, it is closely associated with postoperative complications [35, 36]. However, the LCR has a negative correlation with the NLR and mGPS as relevant combination biomarkers reflecting the immune and nutritional status. Although the preoperative status of the inflammatory markers in this study was not found to be an independent factor for predicting postoperative SSI, the preoperative LCR, which was correlated with all of these inflammatory markers, was extracted as an independent predictor for postoperative SSI in RC patients. Considering our findings alongside previous evidence concerning lymphocytes and the CRP level, the LCR might represent not only an immunological response and systemic inflammatory response but also the nutritional condition of the host. Collectively, the preoperative LCR may be used as a predictive biomarker for postoperative SSI in EC patients.

Another main result of our study was that the preoperative LCR status identified EC patients with a poor oncological outcome among those who were or were not receiving NAC, even though the LCR differed by the treatment course. The theoretical advantages of adding chemotherapy before surgery for EC are the potential for tumor downstaging and for targeting micro-metastasis, which can decrease the risk of distant metastasis [37]. Preoperative chemotherapy with fluorouracil and cisplatin (FP) is currently regarded as standard treatment for EC patients with stage II/III disease in Japan [37]. However, whether preoperative treatment

alone is sufficient or if postoperative chemotherapy should additionally be given after surgery remains controversial. A recent phase III study suggested that perioperative chemotherapy may improve the oncological outcome compared with preoperative chemotherapy alone [38]. Considering this background with significant costs and renal toxicity for NAC, a predictive biomarker would be clinically relevant for identifying populations who could benefit from NAC and who would have a high risk of an oncological outcome despite receiving NAC. Interestingly, our LCR approach identified EC patients with a poor DFS in the NAC(−) and NAC(+) groups. Identifying NAC(−) patients with a high risk for an oncological outcome could allow physicians to change the treatment strategy for EC patients who truly need preoperative chemotherapy. Furthermore, the identification of a high-risk population for oncological outcome among NAC(+) EC patients would also help physicians decide on additional chemotherapy treatment options after surgery. Despite the differing cut-off thresholds of the preoperative LCR in patients who do or do not receive NAC, stratifying the outcome using the preoperative LCR is directly linked to decision-making concerning perioperative treatment strategies in EC patients.

Several limitations associated with the present study warrant mention. First, this study was a retrospective and relatively small cohort study. Second, all of the enrolled patients were from a single institution in Japan. Third, whether or not the cut-off threshold of the LCR was optimal is unclear. Although we determined the cut-off threshold of the LCR using ROC curves with Youden's index and clearly demonstrated the predictive value of the preoperative LCR for the OS and DFS, a further validation study will be needed to confirm the prognostic value of the preoperative LCR with a cut-off value of 7842. To overcome these limitations, larger multicenter prospective controlled trials are needed to confirm the prognostic value of the preoperative LCR and its cut-off value and investigate the prognostic and predictive potential of the LCR for identifying EC patients at a high risk of poor outcomes.

In conclusion, our study highlights the clinical utility of the preoperative LCR as a predictive biomarker for the perioperative risk and oncological outcome in EC patients. Assessing the preoperative LCR might help physicians determine individualized perioperative therapeutic strategies.

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Compliance with ethical standards

Conflict of interest We declare no conflicts of interest in this study.

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