Prognostic Significance of C-reactive Protein-to-prealbumin Ratio in Patients with Esophageal Cancer

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ABSTRACT

Background   The prognostic value of combination of C-reactive protein and prealbumin (CRP/PAlb) in esophageal cancer remains unclear.

Methods   We enrolled 167 esophageal cancer patients who underwent curative esophagectomy. Univariate and multivariate analyses were performed to determine the prognostic significance of various markers, including CRP-to-albumin (CRP/Alb) ratio, modified Glasgow prognostic score, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and prognostic nutritional index.

Results   Receiver operating characteristic analysis revealed the optimal cut-off value of each inflammatory factor, and CRP/PAlb ratio had the greatest discriminative power in predicting recurrence-free survival (RFS) among the examined measures (AUC 0.668). The 5-year overall survival and RFS rates were significantly lower in patients with high CRP/PAlb ratio than in those with low CRP/PAlb ratio ($P < 0.001$, $P = 0.001$, respectively). In the univariate analysis, RFS was significantly worse in patients with low BMI, T2 or deeper tumor invasion, positive lymph node metastasis, positive venous invasion, high CRP/PAlb ratio, high CRP/Alb ratio, high NLR, and high LMR. Multivariate analysis revealed that CRP/PAlb, but not CRP/Alb, was an independent prognostic factor along with lymph node metastasis.

Conclusion   CRP/PAlb ratio was useful for predicting the prognosis of esophageal cancer patients.

Key words   C-reactive protein-to-prealbumin ratio; esophageal cancer; esophagectomy; inflammatory marker; prognosis

Esophageal cancer is the eighth most frequently diagnosed cancer worldwide and a highly aggressive malignant disease with high metastatic potential.[1] Surgery is the mainstay treatment for esophageal cancer, but the majority of patients who undergo curative resection subsequently develop local or systemic recurrence. Despite the development of multimodal therapies, the prognosis of patients with esophageal cancer remains poor.[2–4] Therefore, accurate prognosis predictors are needed to improve patient survival and to provide appropriate preoperative patient counseling.

Host-related factors, such as age, performance status, and comorbidity, as well as the biological properties of individual tumors, play an important role in cancer outcome.[5] In addition to various clinicopathologic factors and tumor stage, other prognostic indicators for esophageal cancer have been identified.[6–8] The close correlation between cancer and inflammation was first discovered by Virchow in 1863, and increasing evidence has shown that the systemic inflammatory response and nutritional status are associated with the long-term survival outcome in patients with various types of cancers.[9–11] Therefore, a variety of inflammatory indicators, such as the C-reactive protein (CRP)-to-albumin ratio (CRP/Alb ratio), modified Glasgow prognostic score (mGPS), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR), have been explored as prognostic predictors in various cancers. These inflammatory markers have been associated with the prognosis of various types of cancers, including esophageal cancer.[12–17] However, the best predictor of long-term outcome after potentially curative esophagectomy has remained unclear.

Low serum albumin concentration is another predictor of poor prognosis in patients with esophageal cancer. Several studies have shown that prealbumin has

a short half-life and can be used as a parameter in nutritional status evaluation with demonstrated superiority to albumin.[18–21] Prealbumin is also associated with postoperative recovery and is an independent predictor of prognosis in patients with malignancies.[22, 23] Recently, the preoperative CRP/prealbumin ratio (CRP/PAlb ratio) was reported to have a better predictive value for the recurrence of gastric cancer than traditional inflammatory indices.[24] However, the prognostic significance of CRP/PAlb ratio in esophageal cancer is unclear.

This study was performed to investigate the prognostic ability of various inflammatory markers including CRP/prealbumin ratio in patients with esophageal cancer.

MATERIALS AND METHODS
Patients
From January 2013 to December 2015, 191 consecutive patients with thoracic esophageal cancer underwent esophagectomy with radical lymph node dissection at the Osaka International Cancer Institute in Japan. Among them, 17 patients did not undergo a preoperative assessment of prealbumin and 7 underwent non-curative esophagectomy, and these 24 patients were excluded. A total of 167 patients were enrolled in this study. Ninety-four patients were treated with neoadjuvant chemotherapy and 15 patients were treated with neoadjuvant chemoradiotherapy.

The treatment strategy for esophageal cancer was as follows: patients with $\geq$ T2, non-T4, or node-positive tumors (Stage $\geq$ 1B) received neoadjuvant chemotherapy followed by esophagectomy, and patients with T4 tumors suspected to have invaded other organs (T4b) received neoadjuvant chemoradiation therapy. Tumor staging was based on the 7th edition of the Union for International Cancer Control TNM staging system.[25] Patients were carefully followed up from the initial treatment until April 2019. Physical examinations and blood tests were performed every 3 months after discharge from the hospital. Abdominal ultrasonography and/or computed tomography were performed at least every 6 months to check for recurrence. Institutional review board approval was obtained (No.18033), and informed consent requirements were waived for this study.

Inflammation markers
The nutrition- and inflammation-based prognostic scores examined in this study were the following: CRP/Alb ratio (CRP measured in mg/L and albumin measured in g/L[26]); CRP/PAlb ratio (prealbumin measured in g/L); mGPS, which is a combination of CRP and albumin (patients with a normal albumin level ($\geq$ 3.5 g/L) and normal CRP level ($\leq$ 10 mg/L) were allocated a score of 0, patients with an elevated CRP level (> 10 mg/L) and a low albumin level (< 3.5 g/L) were allocated a score of 1, and patients with both a low albumin level (< 3.5 g/L) and elevated CRP level (> 10 mg/L) were allocated a score of 2[27]); NLR[16]; PLR[28]; LMR,[29] and prognostic nutritional index (PNI), which was calculated by the formula 10 × albumin (g/dL) + 0.005 × lymphocyte count/μL.[30] All indicators involved in the calculation of the nutrition- and inflammation-based prognostic scores were derived within the 5 days prior to surgery.

The Youden index was calculated using the receiver operating characteristic analysis to determine an optimal cutoff value for the recurrent status of esophageal cancer in association with each inflammatory factor (CRP/Alb ratio, CRP/PAlb ratio NLR, LMR, PNI, and PLR).[31, 32]

Statistical analysis
Continuous variables are expressed as mean ± standard deviation. The χ^2 test or Fisher's exact test was used to compare categorical variables. Student's t-test was used to compare continuous variables. The Mann-Whitney U test was used to compare sequential variables. The Wilcoxon test was used to compare continuous variables. Survival curves were calculated using the Kaplan-Meier method, and differences between survival curves were examined with the log-rank test. Cox regression was used for univariate and multivariate analyses. The hazard ratio and 95% confidence interval were computed with the Cox proportional hazards model. The recurrence-free survival (RFS) period was defined as the period from the date of surgery to the date of recurrence or last follow up without recurrence. For RFS, patients who died without known tumor recurrence were censored at the last documented evaluation. We used univariate and multivariate analyses of factors considered prognostic for RFS. All calculations were performed using JMP v9.0.1 (SAS Institute, Inc., Cary, NC), and P values of < 0.05 were considered significant.

RESULTS
Patients characteristics
The clinicopathological characteristics of patients are shown in Table 1. Based on the optimal cutoff, patients were divided into the high CRP/PAlb group (CP^{High}; CRP/PAlb $\geq$ 5.517; n = 71) and low CRP/PAlb group (CP^{Low}; CRP/PAlb < 5.517; n = 96). Neoadjuvant therapy was performed more frequently in the CP^{High} group than in the CP^{Low} group (P = 0.030). The CP^{High} group

Table 1. Clinicopathologic features of patients with low or high CP

	All ($n = 167$)	CP^{Low} ($n = 96$)	CP^{High} ($n = 71$)	P value
Age (years)				1.000
< 65	67 (40.1)	39 (40.6)	28 (39.4)	
≥ 65	100 (59.9)	57 (59.4)	43 (60.6)	
Gender				0.057
Male	131 (78.4)	70 (72.9)	61 (85.9)	
Female	36 (21.6)	26 (27.1)	10 (14.1)	
BMI				0.756
< 21.0	80 (47.9)	46 (47.1)	34 (47.9)	
≥ 21.0	87 (52.1)	50 (52.9)	37 (52.1)	
Smoking				0.129
Present	142 (85.0)	78 (81.3)	64 (90.1)	
Absent	25 (15.0)	18 (18.7)	7 (9.9)	
Tumor location, n (%)				0.355
Upper	35 (21.0)	21 (21.9)	14 (19.7)	
Middle	83 (49.7)	51 (53.1)	32 (45.1)	
Lower	49 (29.3)	24 (25.0)	25 (35.2)	
Neoadjuvant therapy				0.030
None	58 (34.7)	41 (42.7)	17 (23.9)	
Chemotherapy	94 (56.3)	46 (47.9)	48 (67.6)	
Chemoradiotherapy	15 (9.0)	9 (9.4)	6 (8.5)	
Histology				0.172
Squamous cell carcinoma	159 (95.2)	94 (97.9)	65 (91.5)	
Adenocarcinoma	8 (4.8)	2 (2.1)	6 (8.5)	
Lymphadenectomy				0.869
Two field	55 (32.9)	31 (32.3)	24 (33.8)	
Three field	112 (67.1)	65 (67.7)	47 (66.2)	
Depth of tumor invasion				0.004
T0	24 (14.4)	15 (15.6)	9 (12.7)	
T1	58 (34.7)	44 (45.8)	14 (19.7)	
T2	21 (12.6)	10 (10.5)	11 (15.5)	
T3	62 (37.1)	26 (27.1)	36 (50.7)	
T4	2 (1.2)	1 (1.0)	1 (1.4)	
Lymph node metastasis				< 0.001
N0	75 (44.9)	56 (58.3)	19 (26.7)	
N1	58 (34.7)	26 (27.1)	32 (45.1)	
N2	19 (11.4)	9 (9.4)	10 (14.1)	
N3	15 (9.0)	5 (5.2)	10 (14.1)	
Pathological stage				< 0.001
0	12 (7.3)	7 (7.3)	5 (7.0)	
I	52 (31.1)	40 (41.7)	12 (16.9)	
II	45 (26.9)	27 (28.1)	18 (25.4)	
III	58 (34.7)	22 (22.9)	36 (50.7)	
IV	0	0	0	

Data are presented as n (%). BMI, body mass index; CP, C-reactive protein-to-prealbumin ratio.

Table 2. Receiver operating characteristic analysis for each inflammatory factor

Variable	Cut off	AUC	*P* value
CRP/Alb ratio	0.036	0.666	0.002
CRP/PAlb ratio	5.517	0.668	0.004
LMR	3.356	0.639	0.001
NLR	3.110	0.577	0.008
PLR	172.2	0.590	0.008
PNI	42.09	0.582	0.046

AUC, area under the curve; CRP/Alb, C-reactive protein-to-albumin ratio; CRP/PAlb, C-reactive protein-to-prealbumin ratio; LMR, lymphocyte to monocyte ratio; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; PNI, prognostic nutritional index.

was closely associated with poor clinical characteristics, including T stage ($P = 0.004$), N stage ($P < 0.001$) and pathological stage ($P < 0.001$). No correlations were found among age, gender, body mass index, histology and lymphadenectomy.

Predictive values of CRP/PAlb ratio

The Receiver operating characteristic analysis revealed the optimal cut-off value of each inflammatory factor (Table 2). CRP/PAlb ratio had the greatest discriminative power in predicting RFS among the examined measures (AUC 0.668). The relationships between CRP/PAlb ratio and various measures of the systemic inflammatory response in patients with esophageal cancer are shown in Table 3. High white blood cell count ($P = 0.010$), CRP ($P < 0.001$), platelet ($P = 0.002$) and CRP/Alb ratio ($P < 0.001$) were significantly more frequent in the CP^{High} group than in the CP^{Low} group. Low albumin ($P = 0.019$), prealbumin ($P < 0.001$) and PNI ($P = 0.026$) were significantly more frequent in CP^{High} patients than CP^{Low} patients. Furthermore, the mGPS was significantly higher in the CP^{High} group than in the CP^{Low} group ($P < 0.001$). However, there was no significant relationship between CRP/PAlb ratio and LMR, NLR and PLR. A statistically significant correlation was observed between CRP/PAlb ratio and CRP/Alb ratio ($r = 0.989$, $P < 0.001$, Fig. 1a), although there was only a weak correlation between prealbumin level and albumin level ($r = 0.223$, $P < 0.001$, Fig. 1b).

Prognosis of esophageal cancer patients

In the study group, 37 patients died of esophageal cancer recurrence and 6 patients died of other diseases (pneumonia, $n = 3$; other cancer, $n = 2$; multiple organ failure after a traffic accident, $n = 1$). The overall survival (OS) and RFS rates were significantly poorer in CP^{High} patients than in CP^{Low} patients ($P < 0.001$ and $P = 0.001$, respectively) (Figs. 2a and b). Subgroup analyses based

on TNM stage revealed that CRP/PAlb ratio was significantly associated with RFS in Stage I and Stage II (Figs. 3a–d). The OS and RFS rates were significantly poorer in patients with a high CRP/Alb ratio than in those with low CRP/Alb ratio ($P < 0.001$ and $P = 0.007$, respectively) (Figs. 2c and d). Patients with higher LMR and NLR values had significantly poorer OS and RFS compared with those with lower LMR and NLR values (Figs. 4a–d). Patients with lower PNI values had significantly poorer OS compared with those with higher PNI values, although there was no statistical difference between PNI and RFS (Figs. 5a and b). However, there was no statistical difference between other inflammatory markers such as PLR and mGPS and prognosis of patients (Figs. 5c and d, Figs. 6a and b).

In the univariate analysis, RFS was significantly worse in patients with low BMI, T2 or deeper tumor invasion, positive lymph node metastasis, positive venous invasion, high CRP/PAlb ratio, high CRP/Alb ratio, high NLR and high LMR (Table 4). In multivariate analysis in which CRP/PAlb ratio and CRP/Alb ratio were included as covariates separately because a statistically significant correlation was observed between the two factors (Fig. 1a), CRP/PAlb ratio, but not CRP/Alb ratio, was an independent prognostic factor along with lymph node metastasis (Table 4).

DISCUSSION

In this study, several inflammatory markers were explored as potential prognosis predictors in esophageal cancer. The survival rate was significantly poorer in patients with a high CRP/PAlb ratio, a high CRP/Alb ratio, high LMR and high NLR. Multivariate analysis revealed that only a high CRP/PAlb ratio was an independent prognostic factor.

Our results demonstrated that CRP/PAlb ratio was the best prognostic factor among various systemic inflammation markers for esophageal cancer patients.

Table 3. The relationships between CP and various measures of the systemic inflammatory response

	All (n = 167)	CP^{Low} (n = 96)	CP^{High} (n = 71)	P value
WBC				0.010
< 7970	149 (89.2)	91 (94.8)	58 (81.7)	
≥ 7970	18 (10.8)	5 (5.2)	13 (18.3)	
CRP				< 0.001
< 0.15	96 (57.5)	93 (96.9)	3 (4.2)	
≥ 0.15	71 (42.5)	3 (3.1)	68 (95.8)	
Albumin				0.019
< 3.8	80 (47.9)	38 (39.6)	42 (43.8)	
≥ 3.8	87 (52.1)	58 (60.4)	29 (56.2)	
Prealbumin				< 0.001
< 24.6	74 (44.3)	28 (29.2)	46 (64.8)	
≥ 24.6	93 (55.7)	68 (70.8)	25 (35.2)	
Platelet				0.002
< 245	80 (47.9)	56 (58.3)	24 (33.8)	
≥ 245	87 (52.1)	40 (41.7)	47 (66.2)	
CRP/Alb ratio				< 0.001
< 0.036	95 (56.9)	93 (96.9)	2 (2.8)	
≥ 0.036	72 (43.1)	3 (3.1)	69 (97.2)	
LMR				0.137
< 3.356	112 (67.1)	69 (71.9)	43 (60.6)	
≥ 3.356	45 (32.9)	27 (28.1)	18 (39.4)	
NLR				0.570
< 3.110	131 (78.4)	77 (80.2)	54 (76.1)	
≥ 3.110	36 (21.6)	19 (19.8)	17 (23.9)	
PLR				0.082
< 172.2	98 (58.7)	62 (64.6)	36 (50.7)	
≥ 172.2	69 (41.3)	34 (35.4)	35 (49.3)	
PNI				0.026
< 42.09	39 (23.4)	16 (16.7)	23 (32.4)	
≥ 42.09	128 (76.6)	80 (83.3)	48 (67.6)	
mGPS				< 0.001
0	66 (39.5)	61 (63.5)	5 (7.0)	
1, 2	101 (60.5)	35 (36.5)	66 (93.0)	

CRP, C-reactive protein; CRP/Alb, C-reactive protein-to-albumin ratio; CRP/PAlb, C-reactive protein-to-prealbumin ratio; LMR, lymphocyte to monocyte ratio; mGPS, modified Glasgow prognostic score; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; pT, pathological depth of invasion; pN, pathological lymph node metastasis; PNI, prognostic nutritional index.

This result is similar to that of a recent study by Jun et al., where the prognostic value of the CRP/PAlb ratio in patients with gastric cancer was explored.[24] They retrospectively reviewed various inflammation markers for prognosis ability in 401 patients with gastric cancer and found that the predictive value of preoperative CRP/PAlb for the recurrence of gastric cancer was significantly better than other inflammatory markers. Furthermore, multivariate analysis showed that CRP/PAlb ratio, not CRP/Alb ratio, was an independent factor associated with RFS. Except for our study, there has been only one study showing the prognostic impact of the CRP/PAlb ratio in patients with esophageal cancer. Feng et al. retrospectively reviewed preoperative
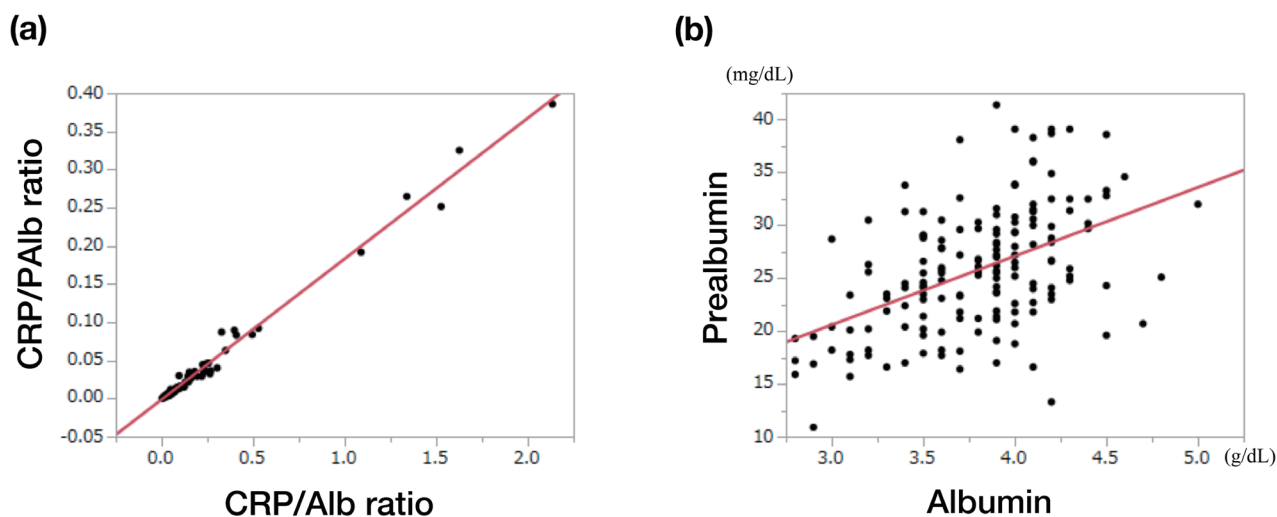
(a)

(b)

Fig. 1. The correlation between each inflammatory factor. The correlation between CRP/PAlb and CRP/Alb (**a**) and prealbumin and albumin (**b**). CRP/Alb, C-reactive protein-to-albumin ratio; CRP/PAlb, C-reactive protein-to-prealbumin ratio.
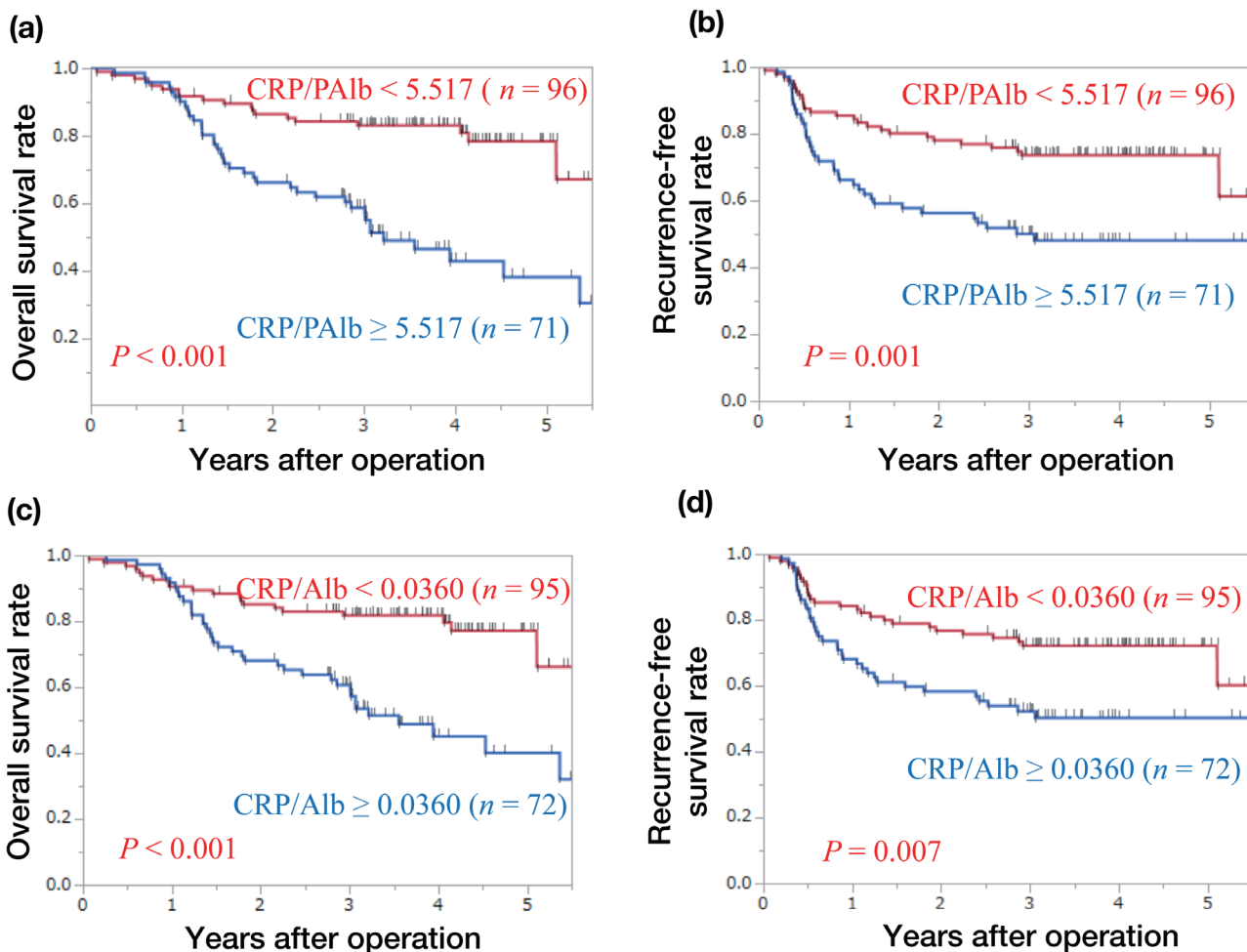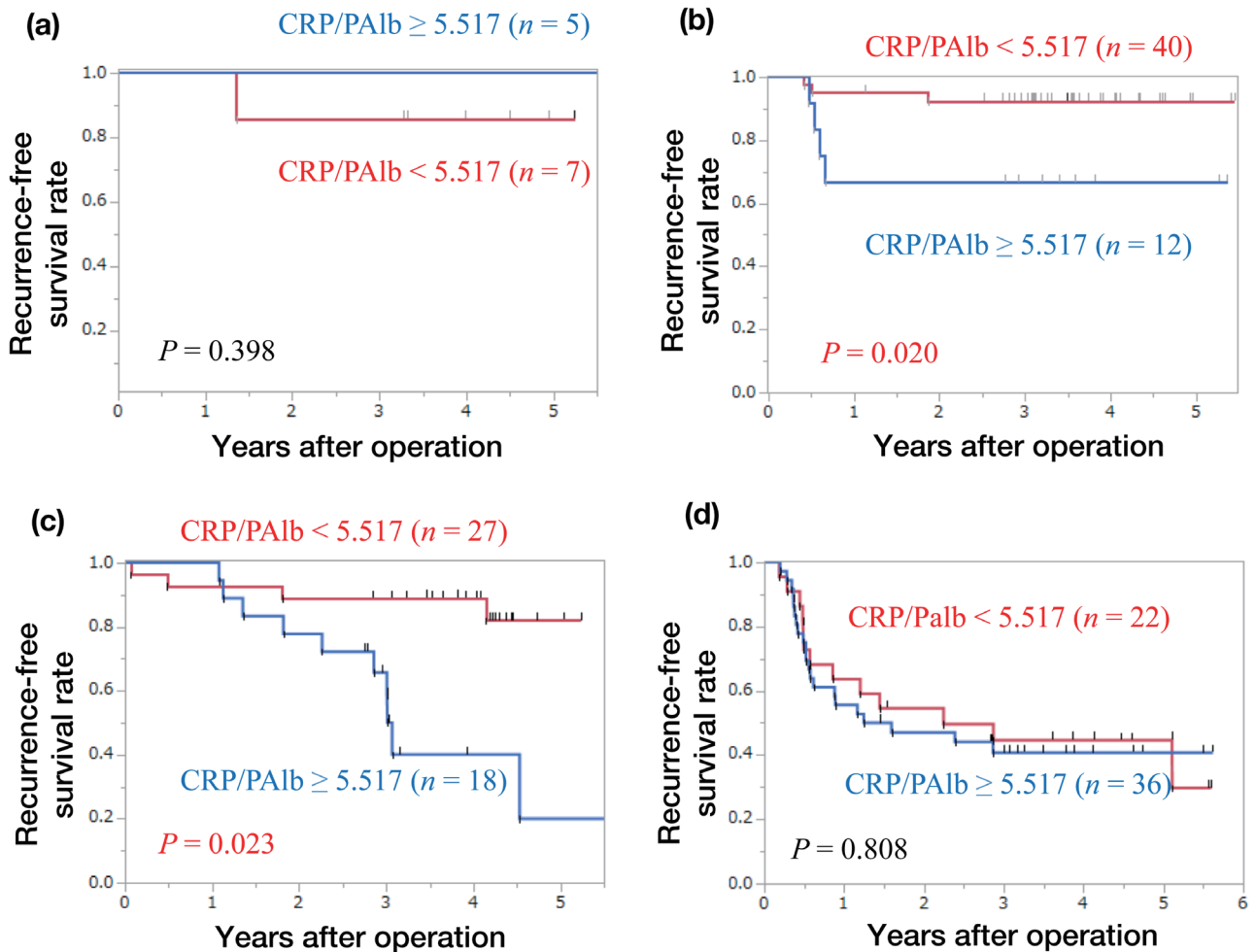
(a)

(b)

(c)

(d)

Fig. 2. Relationship of CRP/PAlb ratio and CRP/Alb ratio with long-term prognosis. Overall (**a**) and recurrence-free (**b**) survival curves according to the CRP/PAlb ratio in patients with esophageal cancer. Overall (**c**) and recurrence-free (**d**) survival curves according to the CRP/Alb ratio in patients with esophageal cancer. CRP/Alb, C-reactive protein-to-albumin ratio; CRP/PAlb, C-reactive protein-to-prealbumin ratio.

Fig. 3. Relationship of CRP/PAlb ratio with long-term prognosis according to pathological stage. (**a**) Recurrence-free survival curve in esophageal cancer patients with Stage 0. (**b**) Stage I, (**c**) Stage II, (**d**) Stage III, CRP/PAlb, C-reactive protein-to-prealbumin ratio.

CRP/PAlb ratio and CRP/Alb ratio for prognosis ability in 346 patients with resectable esophageal cancer and found that the predictive value of CRP/PAlb ratio for OS was better than CRP/Alb ratio. Furthermore, multivariate analysis showed that CRP/PAlb ratio, not CRP/Alb ratio, was an independent factor associated with OS.[33] These results suggest that CRP/PAlb ratio is superior to CRP/Alb ratio in terms of the prognostic value of patients with gastric or esophageal cancer.

Elevated CRP level, which is a marker of systemic inflammation, was found to be a predictor of low survival in patients with various cancers.[34] CRP/Alb ratio is a superior prognostic measure involving inflammatory and nutritional factors in various cancers, including esophageal cancer.[35] In our study, CRP/Alb ratio, CRP/PAlb ratio, LMR and NLR were suitable indicators of an unfavorable prognosis in patients with esophageal cancer, and the P values of CRP/Alb ratio and CRP/PAlb ratio were lower than other those of

other inflammation markers in multivariate analyses. This result is similar to those of Ishibashi et al., who reported CRP/Alb ratio as the most significant indicator of poor long-term outcome in patients with esophageal cancer.[34] The authors compared the systemic immune-inflammatory index, NLR, PLR, and CRP/Alb ratio with established prognostic factors and found that the CRP/Alb ratio was superior to other inflammation-based prognostic scores in terms of prognostic ability. Wei et al. also retrospectively tested the mGPS, NLR, PLR and CRP/Alb ratio together with established prognostic factors in univariate and multivariate Cox regression analyses of OS in 423 esophageal cancer patients.[36] The authors demonstrated that the CRP/Alb ratio showed a superior discriminatory ability compared with the NLR and PLR. These results suggest that the predictive value of the CRP/Alb ratio is superior to that of other inflammatory markers in esophageal cancer patients.

Previous studies showed that prealbumin has a
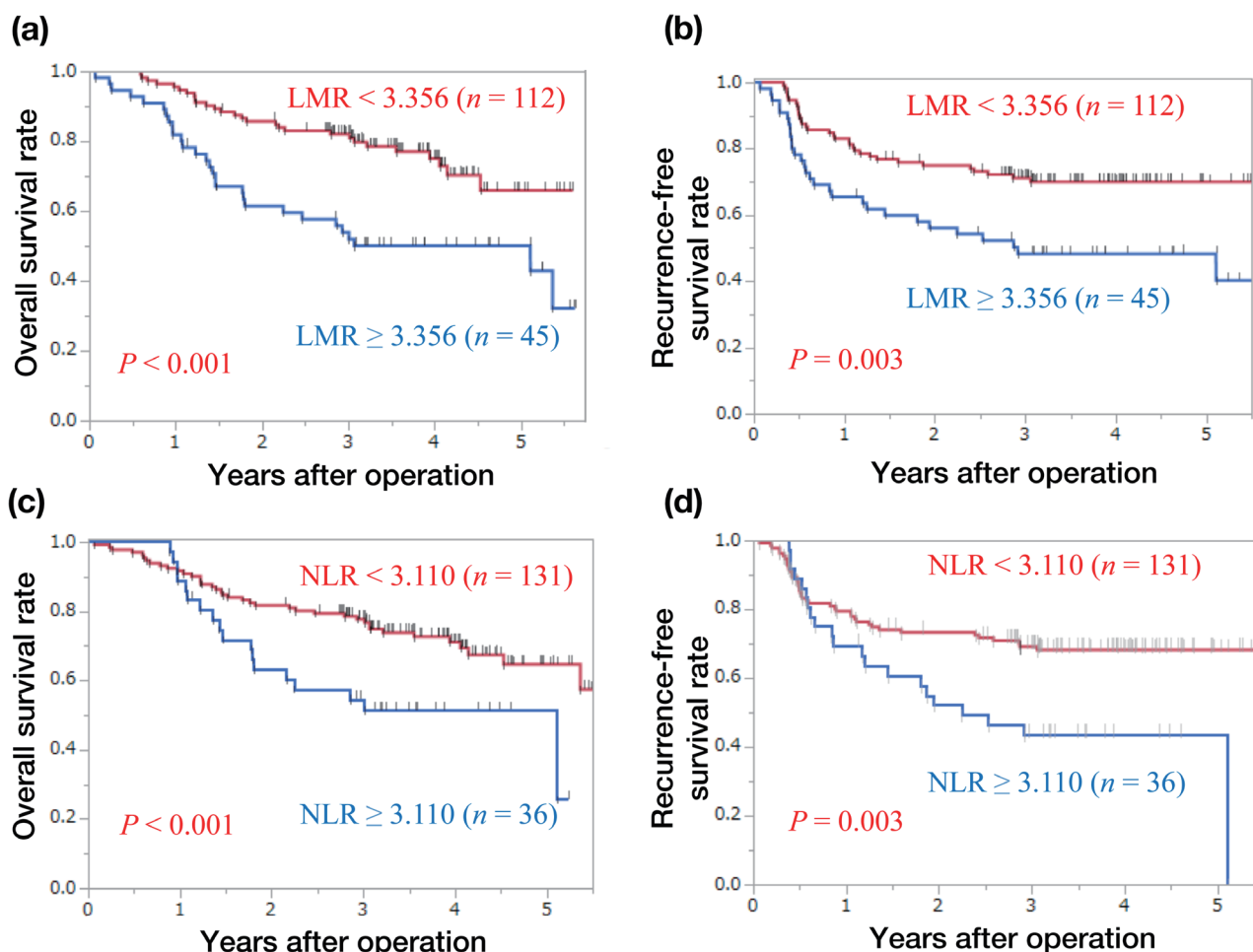
Fig. 4. Relationship of LMR and NLR with long-term prognosis. Overall (**a**) and recurrence-free (**b**) survival curves according to the LMR in patients with esophageal cancer. Overall (**c**) and recurrence-free (**d**) survival curves according to the NLR in patients with esophageal cancer. LMR, lymphocyte -to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio.

shorter half-life of 2–3 days and its amount in the body is low.[21] Therefore, measurement of prealbumin is a good marker of visceral protein status and prealbumin is affected earlier by acute variations in protein balance.[37, 38] Serum albumin is commonly used as a surrogate marker of nutrition; however, its half-life of 21 days and its steady state level of 100 days limit its utility and value.[37] Therefore, prealbumin is considered superior to albumin in nutritional assessment.[21] Furthermore, prealbumin has recently been identified as an independent prognostic factor in various cancers.[39, 40] Based on this theoretical advantage, CRP/PAlb may be more sensitive and superior to CRP/Alb for tumor prognosis. In this study, we found that CRP/PAlb ratio was more useful for predicting the prognosis of patients with esophageal cancer compared with CRP/Alb ratio.

Our results showed that high CRP/PAlb ratio was significantly associated with deeper depth of

tumor invasion, positive lymph node metastasis and advanced pathological stage. This result was similar to the report of Jun et al. in patients with gastric cancer.[24] The authors retrospectively reviewed the association between CRP/PAlb and clinical features in 401 patients with gastric cancer and found that the CRP/PAlb ratio was significantly associated with deeper depth of tumor invasion, positive lymph node metastasis and advanced pathological stage. Furthermore, the CRP/PAlb ratio was significantly associated to inflammation markers including mGPS, NLR, PLR, and CRP/Alb ratio. In our study, CRP/PAlb ratio was significantly associated with mGPS, CRP/Alb ratio, and PNI. In cancer tissues, oncoproteins activate inflammatory transcriptional programs to produce various inflammatory mediators such as cytokines, which can trigger the proliferation and differentiation of inflammation markers, suggesting that the systemic immune inflammatory responses are
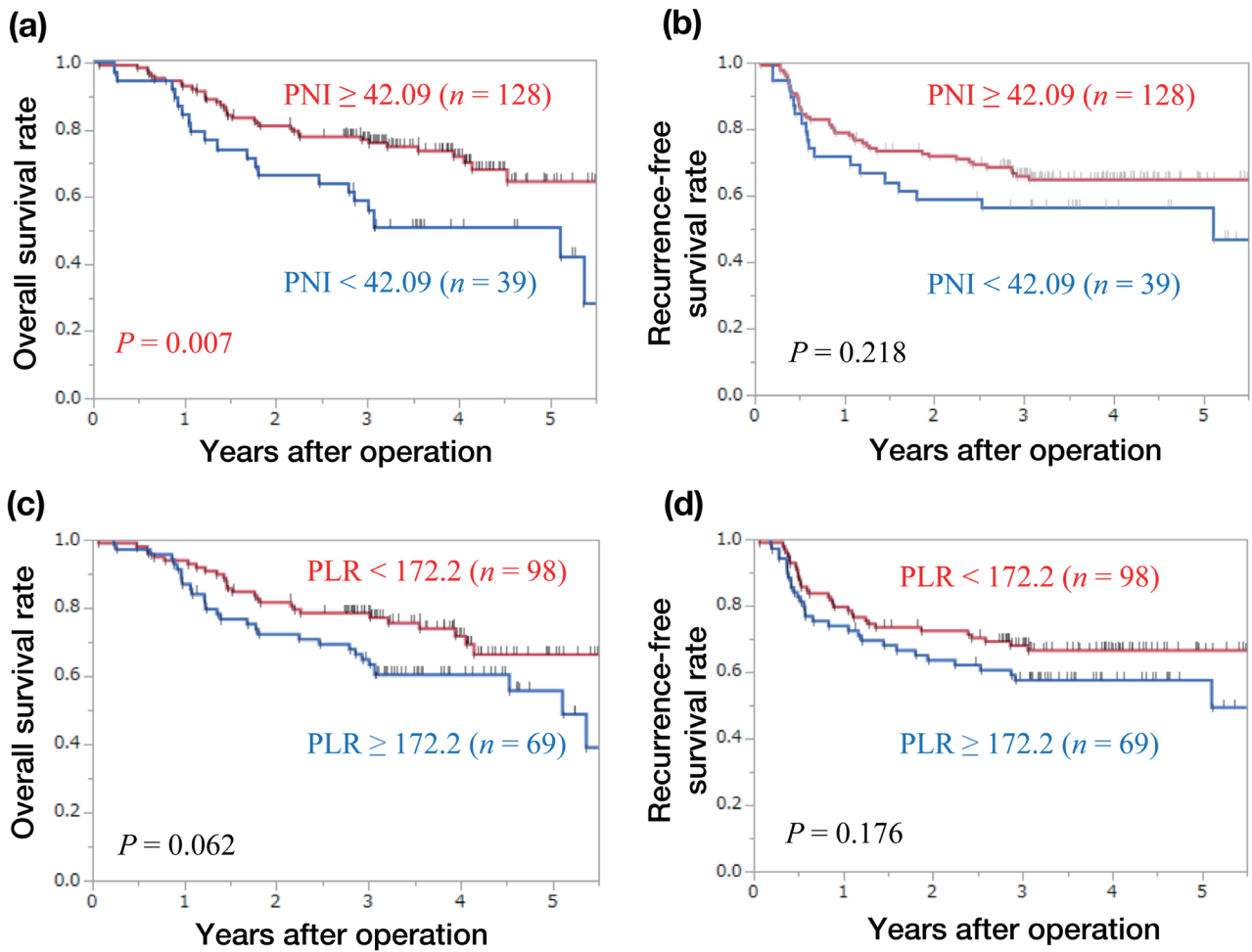
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(a)

(b)

(c)

(d)

Fig. 5. Relationship of PLR and PNI with long-term prognosis. Overall (**a**) and recurrence-free (**b**) survival curves according to the PLR in patients with esophageal cancer. Overall (**c**) and recurrence-free (**d**) survival curves according to the PNI in patients with esophageal cancer. PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index.
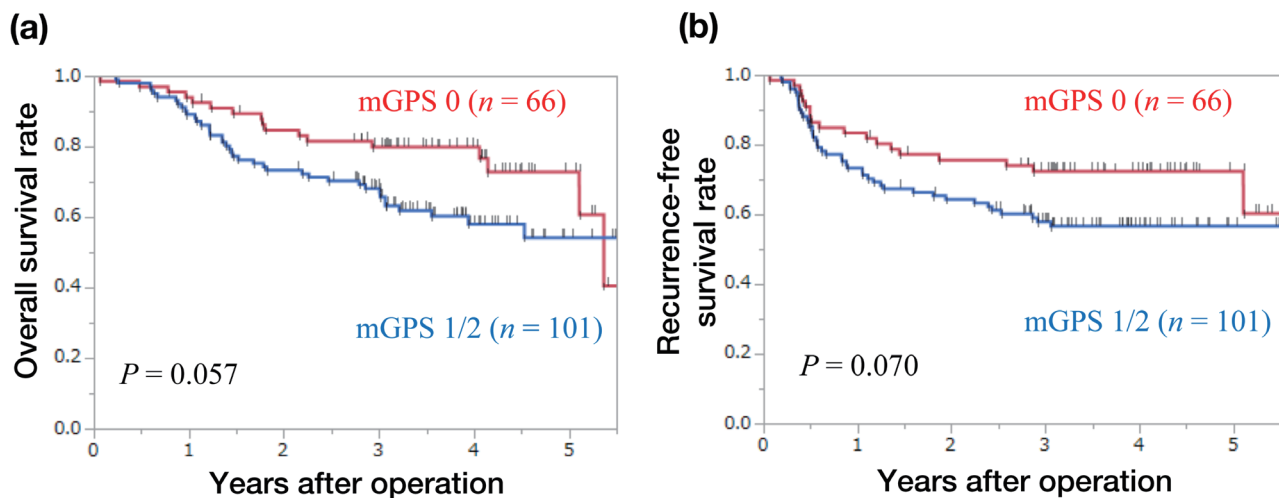
(a)

(b)

Fig. 6. Relationship of mGPS with long-term prognosis. Overall (**a**) and recurrence-free (**b**) survival curves according to the mGPS in patients with esophageal cancer. mGPS, modified Glasgow prognostic score.

Table 4. Univariate and multivariate analyses of prognostic factors for recurrence-free survival in patients with esophageal cancer

Variable	Univariate analysis			Multivariate analysis (Model A)			Multivariate analysis (Model B)		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Age ($\geq$ 65 vs < 65)	1.232	0.738–2.111	0.429						
Gender (Female vs Male)	0.629	0.301–1.185	0.159						
BMI (< 21.0 vs $\geq$ 21.0)	1.694	1.025–2.839	0.040	1.592	0.939–2.697	0.084	1.637	0.965–2.775	0.067
Smoking (Present vs Absent)	1.526	0.744–3.677	0.267						
Lymphatic invasion (Present vs Absent)	1.698	0.993–2.830	0.053						
Venous invasion (Present vs Absent)	2.069	1.249–3.410	0.005	1.758	0.998–3.101	0.051	1.700	0.969–2.983	0.064
pT (2, 3, 4 vs 0, 1)	2.262	1.352–3.899	0.002	1.020	0.559–1.908	0.949	1.068	0.589–1.988	0.830
pN (Present vs Absent)	3.931	2.197–7.564	< 0.001	2.638	1.371–5.371	0.003	2.742	1.427–5.572	0.002
Postoperative pneumonia (Present vs Absent)	1.221	0.506–2.504	0.628						
Anastomosis leakage (Present vs Absent)	1.924	0.670–4.360	0.200						
CRP/PAlb ($\geq$ 5.517 vs < 5.517)	2.234	1.352–3.740	0.002	1.771	1.037–3.067	0.036			
CRP/Alb ($\geq$ 0.0360 vs < 0.0360)	1.979	1.200–3.300	0.008				1.625	0.964–2.766	0.068
NLR ($\geq$ 3.11 vs < 3.11)	2.066	1.197–3.461	0.010	1.377	0.743–2.502	0.304	1.316	0.712–2.385	0.375
LMR ($\geq$ 3.37 vs < 3.37)	2.111	1.274–3.480	0.004	1.571	0.879–2.773	0.126	1.614	0.903–2.849	0.105
PLR ($\geq$ 172 vs < 172)	1.406	0.850–2.318	0.183						
PNI (< 42.1 vs $\geq$ 42.1)	1.411	0.794–2.404	0.232						
mGPS	1.640	0.970–2.878	0.065						

BMI, body mass index; CI, confidence interval; CRP/Alb, C-reactive protein-to-albumin ratio; CRP/PAlb, C-reactive protein-to-prealbumin ratio; LMR, lymphocyte to monocyte ratio; mGPS, modified Glasgow prognostic score; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; pT, pathological depth of invasion; pN, pathological lymph node metastasis; PNI, prognostic nutritional index.

significantly associated with tumor progression.[41]

This study has several limitations. First, we conducted this retrospective study in a single institution, and the number of patients was not sufficiently large. Second, we included both patients with or without neoadjuvant therapy and we performed peripheral blood test only after neoadjuvant therapy. Previous studies showed that systemic immunoinflammatory measures are easily affected by chemotherapy and radiation.[42] However, Otowa et.al reported that CRP/Alb ratio after neoadjuvant therapy, but not CRP/Alb ratio before neoadjuvant therapy, was an independent prognostic factor in patients with Stage II/III esophageal squamous cell carcinoma.[43] In this study, preoperative data were obtained within 5 days before surgery to reduce the impact of preoperative treatment in patients with neoadjuvant

chemotherapy or neoadjuvant chemoradiotherapy.

In summary, our study showed that CRP/PAlb ratio was superior to other systemic inflammation markers as a predictor of prognosis in esophageal cancer patients. A prospective study with a larger number of patients is needed to clarify the utility of CRP/PAlb ratio as a prognostic marker in patients with esophageal cancer.

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