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Prognostic Significance of Sarcopenia and Systemic Inflammatory Response in Patients With Esophageal Cancer

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Abstract. *Background/Aim: The association between the presence of sarcopenia and systemic inflammatory response is unclear in patients with esophageal cancer. This study was performed to investigate the relationship between sarcopenia and systemic inflammatory response and clarify the effect of these factors on the prognosis in patients with esophageal cancer. Patients and Methods: This study included 163 patients with esophageal cancer. The patients' body composition was assessed before esophagectomy using multifrequency bioelectrical impedance. The relationship between sarcopenia and inflammatory factors were investigated before surgery. Results: Sarcopenia was significantly associated with a high C-reactive protein-to-albumin (CRP/Alb) ratio (p=0.046). Patients with sarcopenia significantly associated with worse overall survival (OS) (p=0.025) and tended to show a worse recurrence-free survival (RFS) (p=0.065). A high CRP/Alb ratio was significantly associated with worse OS and RFS. Multivariate analysis revealed that among all inflammatory factors, only a high CRP/Alb ratio was an independent prognostic factor for RFS (p=0.022). Conclusion: Sarcopenia is associated with systemic inflammatory response such as high CRP/Alb ratio, while the latter is an independent prognostic marker in patients with esophageal cancer.*

Esophageal cancer is a highly aggressive malignant disease and has a high metastatic potential (1). Despite the development of multimodal therapies such as surgery, chemotherapy, and chemoradiation therapy, postoperative recurrence is observed in more than half of patients who have undergone transthoracic esophagectomy, and the prognosis of patients with esophageal cancer remains poor (2-4). In addition to various clinicopathological factors and the tumor stage, some other prognostic indicators have been discovered in previous studies of esophageal cancer because of the poor prognosis (5-7). Inflammatory factors are reportedly prognostic factors of cancer, and the close correlation between cancer and inflammation was first discovered by Virchow in 1863 (8). Many inflammatory markers that can be used to predict prognosis have been reported, 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). These markers reportedly associated with the prognosis of various types of cancer, including esophageal cancer (9-14).

Sarcopenia, which is characterized by loss of skeletal muscle mass (SMM), has been mainly studied in older people and is known to impair physical performance and survival in this population (15-17). Sarcopenia has recently received great attention in the oncology field and is recognized as an important factor in predicting long-term prognosis in patients undergoing surgery for various types of cancer (18-21). The reason for the relationship between sarcopenia and poor cancer prognosis remains unclear, but inflammation may play a role (22). Previous evidence has supported the association of the systemic inflammatory response with sarcopenia. More specifically, proinflammatory cytokines, including interleukin-1 (IL-1), IL-6, and tumor necrosis factor-α (TNF-α), were found to be mediators of anorexia and skeletal muscle proteolysis, the key components of cancer cachexia (23, 24). Proinflammatory cytokines and growth factors are released as part of the systemic inflammatory response to tumors and have profound catabolic effects on host metabolism, leading to muscle breakdown (25). This inflammatory cycle can, in turn, enhance tumor aggressiveness or reduce treatment response, impairing the transition into survivorship (26, 27).

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Key Words: Esophageal cancer, sarcopenia, C-reactive protein-to-albumin ratio.

To the best of our knowledge, this is the first study to investigate the association between sarcopenia and systemic inflammatory markers and clarify the effect of these factors on the prognosis in patients with esophageal cancer.

Patients and Methods

Patients and perioperative treatment. 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, 21 patients did not undergo a preoperative assessment of body composition and 7 underwent noncurative esophagectomy. After excluding these 28 patients, 163 patients were enrolled in this study. Ninety-five patients were treated with neoadjuvant chemotherapy and 11 were treated with neoadjuvant chemoradiotherapy.

Our treatment strategy for esophageal cancer was as follows: patients with ≥T2, non-T4, or node-positive tumors (Stage ≥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 (28).

Patients were carefully followed up from the initial treatment until March 2018. 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.

Definition of inflammation-based factors. The nutrition- and inflammation- based prognostic scores used in this study were: the CRP/Alb ratio (CRP measured in mg/l and albumin measured in g/l (29)); the mGPS, which was a combination of CRP and albumin (patients with a normal albumin level (≥3.5 g/l) and normal CRP level (≤10 mg/l) were allocated a score of 0, patients with an elevated CRP level (>10 mg/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 (30)); the NLR (13); the PLR (31); and the prognostic nutritional index (PNI), which was calculated by the formula 10 × albumin (g/dl) + 0.005 × lymphocyte count/μl (32). All indicators involved in the calculation of the nutrition- and inflammation-based prognostic scores were evaluated preoperatively.

The Youden index was calculated using the receiver operating characteristic (ROC) curve to determine an optimal cut-off value for the recurrent status of esophageal cancer in association with each inflammatory factor (CRP/Alb ratio, NLR, PNI, and PLR).

Assessment of body composition. Body composition was assessed before esophagectomy using multifrequency bioelectrical impedance with eight electrodes (InBody 720; Biospace, Tokyo, Japan). Various parameters of body composition (SMM, body weight, and body mass index) were automatically measured by the InBody 720. The normal range of SMM in each patient was shown by the InBody 720 and ranged from 90% to 110% of the standard SMM, which was calculated according to the age, sex, and height of each patient. In this study, sarcopenia was defined as an SMM below the lower limit of the standard SMM (<90% of the standard) (33, 34).

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 (HR) and 95% confidence interval (CI) were computed with the Cox proportional hazards model. We used univariate and multivariate analyses of factors considered prognostic for recurrence-free survival (RFS). All calculations were performed using the JMP v9.0.1 software (SAS Institute, Inc., Cary, NC, USA), and *p*-values of <0.05 were considered significant.

Results

Clinical features of patients. The clinicopathological characteristics of patients with and without sarcopenia are shown in Table I. The sarcopenia group comprised 82 patients (50.3%), and the non-sarcopenia group comprised 81 patients (49.7%). The body mass index and SMM were significantly lower in patients with sarcopenia than without ($p<0.001$). However, no significant differences were observed in age, sex, smoking, tumor location, neoadjuvant therapy, histology, depth of tumor invasion, lymph node metastasis, pathological stage, or incidence of complication between the two groups.

Inflammatory factors related to sarcopenia. The association of sarcopenia with various measures of the systemic inflammatory response in patients with esophageal cancer is shown in Table II. Receiver operating characteristic analysis revealed the optimal cut-off value of each inflammatory factor (CRP/Alb ratio, NLR, PNI, and PLR) (Table III). A high CRP/Alb ratio (≥0.00375) was significantly more frequent in the sarcopenia than non-sarcopenia group ($p=0.046$). Furthermore, the mGPS was significantly higher in the sarcopenia group ($p=0.041$). The platelet count was also significantly higher in the sarcopenia group ($p=0.016$). However, no significant differences were observed between the two groups regarding the white blood cell, neutrophil, or lymphocyte counts, albumin, CRP, PNI, NLR, or PLR.

Relationship of sarcopenia and inflammatory factors with long-term prognosis. In this study, 37 patients died of esophageal cancer recurrence, and 3 patients died of other diseases (pneumonia, n=2; multiple organ failure after a traffic accident, n=1). The overall survival (OS) rate was significantly poorer in patients with sarcopenia than in those without (2-year survival rate, 73.1% *vs*. 85.1%, respectively; $p=0.025$) (Figure 1A). The RFS rate tended to be poorer in patients with than without sarcopenia (2-year RFS, 62.8% *vs*. 76.3%, respectively; $p=0.065$) (Figure 1B).

Table I. *Clinical features of esophageal cancer patients with and without sarcopenia*

	Total patients (n=163)	Patients with sarcopenia (n=82)	Patients without sarcopenia (n=81)	*p*-Value
Age, years[a]	64.7±8.0	66.2±7.2	63.7±8.8	0.132
Gender[b]				1.000
Male	128 (79)	64 (78)	64 (79)	
Female	35 (21)	18 (22)	17 (21)	
BMI[a] (kg/m^2)	21.6±3.3	19.6±2.2	23.5±3.1	<0.001
SMMa	24.4±4.6	22.2±3.3	26.6±4.6	<0.001
Brinkman index[a]	716±612	758±512	683±660	0.063
Smoking[b]				0.534
Present	139 (85)	71 (87)	68 (84)	
Absent	24 (15)	11 (13)	13 (16)	
Tumor location[b]				0.341
Upper	32 (20)	16 (19)	16 (20)	
Middle	86 (53)	49 (60)	37 (46)	
Lower	45 (27)	18 (21)	27 (34)	
Neoadjuvant therapy[b]				0.635
None	57 (35)	28 (34)	29 (36)	
Chemotherapy	95 (58)	46 (56)	49 (60)	
Chemoradiotherapy	11 (7)	8 (10)	3 (4)	
Histology[b]				0.535
Squamous cell carcinoma	154 (95)	76 (93)	78 (96)	
Adenocarcinoma	9 (5)	6 (7)	3 (4)	
Lymphadenectomy[b]				0.177
Two fields	50 (31)	21 (26)	29 (36)	
Three fields	113 (69)	61 (74)	52 (64)	
Depth of tumor invasion[b]				0.563
T0	22 (13)	10 (12)	12 (15)	
T1	58 (36)	30 (37)	28 (34)	
T2	21 (13)	8 (10)	13 (16)	
T3	60 (37)	33 (40)	27 (34)	
T4	2 (1)	1 (1)	1 (1)	
Lymph node metastasis[b]				0.270
N0	71 (44)	30 (37)	41 (51)	
N1	59 (3)	37 (45)	22 (27)	
N2	17 (10)	7 (8)	10 (12)	
N3	16 (10)	8 (10)	8 (10)	
Pathological stage[b]				0.175
0	12 (7)	4 (5)	8 (10)	
I	48 (29)	21 (26)	27 (33)	
II	45 (28)	26 (32)	19 (23)	
III	54 (33)	29 (35)	25 (31)	
IV	4 (3)	2 (2)	2 (3)	
Postoperative complications[b]				
Pneumonia	19 (11.7)	11 (13.4)	8 (9.9)	0.480
Anastomotic leakage	9 (5.5)	5 (6.1)	4 (4.9)	0.751

[a]Data are presented as mean±standard deviation. [b]Data are presented as n (%). BMI, Body mass index; SMM, skeletal muscle mass

OS and RFS rates were significantly poorer in patients with a high than low CRP/Alb ratio ($p<0.001$ and $p<0.001$, respectively) (Figure 1C, D). OS was significantly poorer in patients with a mGPS of 1 or 2, compared to those with a mGPS of 0 (2-year survival rate, 75.5% *vs*. 85.2%, respectively; $p=0.049$) (Figure 2A), and the same tendency was observed in the RFS rate, although it was not significant ($p=0.073$) (Figure 2B). OS and RFS rates were significantly poorer in patients with a high than in those with a low NLR ($p<0.001$ and $p=0.003$, respectively) (Figure 2C, D). However, other inflammatory markers such as the PNI and PLR were not associated with prognosis (Figure 3A-D).

Factors related to prognosis. The association of the preoperative clinicopathological parameters, including inflammatory factors, with the RFS after esophagectomy for

Table II. *Relationships between sarcopenia and measures of systemic inflammatory response in patients with esophageal cancer.*

	Total patients (n=163)	Patients with sarcopenia (n=82)	Patients without sarcopenia (n=81)	*p*-Value
WBCs[a]	5757±1813	5939±1868	5719±1902	0.374
Neutrophils[a]	3309±1378	3328±1389	3291±1384	0.821
Lymphocytes[a]	1661±632	1683±685	1651±583	0.754
Platelets[a]	250±72	267±77	237±65	0.016
CRP[a]	0.39±0.92	0.48±1.09	0.29±0.67	0.202
Albumin[a]	3.8±0.4	3.75±0.48	3.88±0.32	0.051
mGPS[b]				0.041
0	69	29	40	
1	73	36	37	
2	21	17	4	
CRP/Alb ratio[b]				0.046
≥0.0375	69	41	28	
<0.0375	94	41	53	
PNI[b]				0.836
≥51.02	28	15	13	
<51.02	125	67	58	
NLR[b]				0.052
≥3.211	32	21	11	
<3.211	131	61	70	
PLR[b]				0.471
≥111.3	123	64	59	
<111.3	40	18	22	

[a]Data are presented as mean±standard deviation. [b]Data are presented as number of patients. WBCs, White blood cells; CRP, C-reactive protein; mGPS, modified Glasgow prognostic score; CRP/Alb ratio, C-reactive protein-to-albumin ratio; PNI, prognostic nutritional index, NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

esophageal cancer are presented in Table IV. In the univariate analysis, RFS was significantly worse in patients with T2 or deeper tumor invasion, positive lymph node metastasis, a high CRP/Alb ratio, and a high NLR. The multivariate analysis revealed that a high CRP/Alb ratio was an independent prognostic factor, together with positive lymph node metastasis.

Table III. *Receiver operating characteristic analysis to determine the optimal cut-off value for the recurrent status of esophageal cancer in each inflammatory factor.*

Variable	Cut-off value	AUC	*p*-Value
CRP/Alb ratio	0.0375	0.642	0.013
NLR	3.211	0.566	0.006
PNI	51.02	0.526	0.416
PLR	111.3	0.553	0.053

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

Discussion

In this study, we investigated the relationship between sarcopenia and systemic inflammatory response. Results showed that sarcopenia is associated with systemic inflammatory response such as high CRP/Alb ratio, while the latter is an independent prognostic marker for RFS in patients with esophageal cancer.

Several studies have investigated the association of the presence of sarcopenia and the systemic inflammatory response in patients with various cancer type (22, 31, 35, 36). However, to the best of our knowledge, this is the first study to demonstrate the relationship between the preoperative CRP/Alb ratio and sarcopenia in esophageal cancer patients.

In the studied cohort of patients with thoracic esophageal cancer, sarcopenia was significantly correlated with the mGPS. This result is similar to that of a recent study by Richards *et al*., who demonstrated a significant association between low skeletal muscle index and elevated systemic inflammatory response, as measured by the mGPS in patients with primary operable colorectal cancer (35). Similarly, Kim *et al*. reported that the mGPS correlated with height-adjusted muscle mass, as calculated by CT imaging, in patients with small cell lung cancer (36).

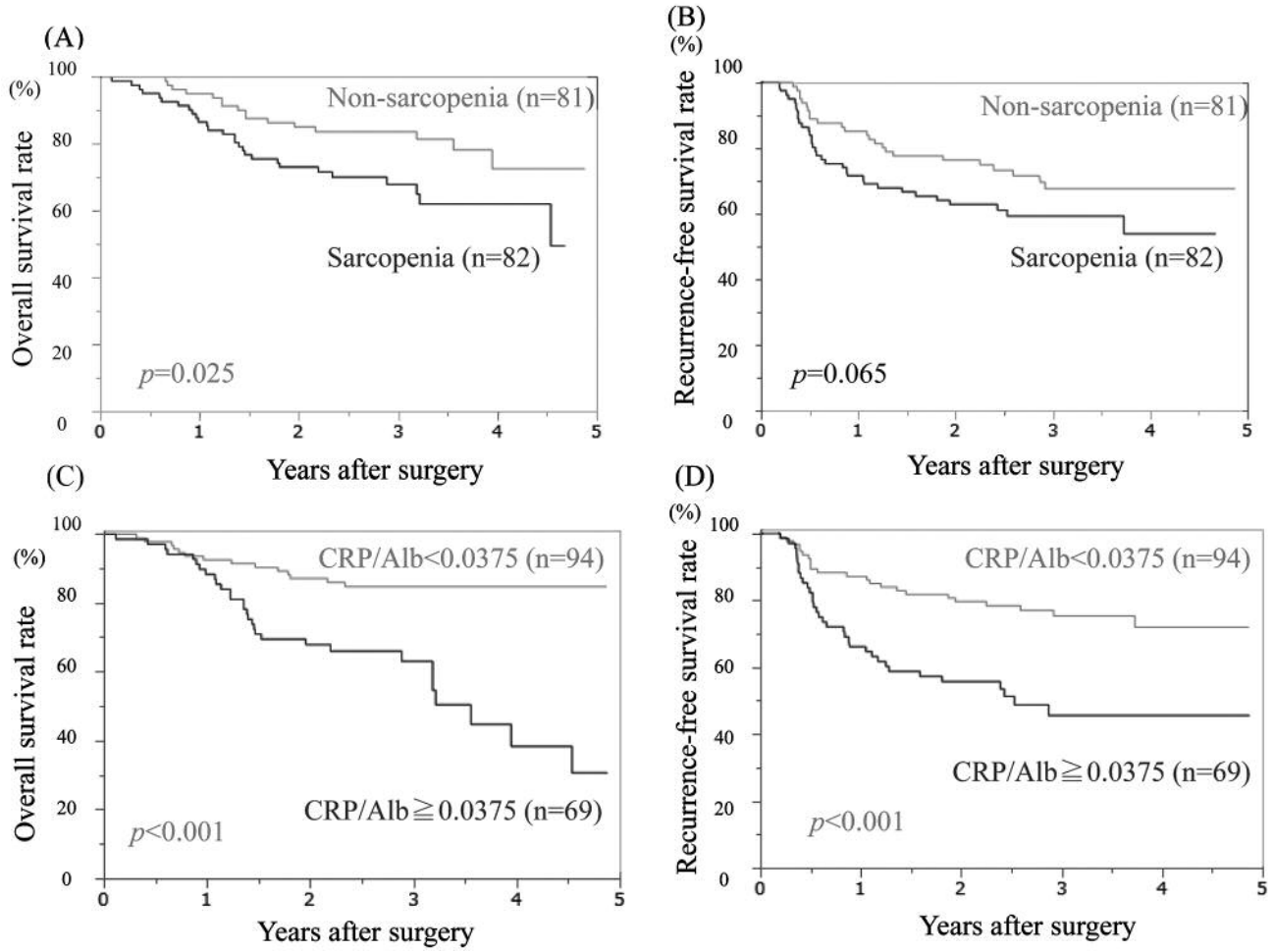

Figure 1. *Overall survival (A) and recurrence-free survival (B) rates following esophagectomy in esophageal cancer patients with or without sarcopenia. Overall survival (C) and recurrence-free survival (D) rates following esophagectomy, in esophageal cancer patients with a low or a high C-reactive protein-to-albumin (CRP/Alb) ratio.*

Further analysis of the relationships between inflammatory markers and the survival rate revealed that CRP/Alb ratio, mGPS, and NLR had a significant impact on OS in the esophageal cancer patients. However, the multivariate analysis showed that only the CRP/Alb ratio was an independent prognostic factor for survival. This result is similar to that of a recent study by Xu *et al*., who showed that CRP/Alb ratio is a prognostic factor in patients with primary operable esophageal squamous cell carcinoma (37). Specifically, they compared the mGPS, NLR, PLR, and CRP/Alb ratio with established prognostic factors and found that the CRP/Alb ratio may be superior to other inflammation-based prognostic scores in terms of its prognostic ability. Furthermore, Haruki *et al*. compared the mGPS and CRP/Alb ratio with established prognostic factors in pancreatic cancer patients with pancreatic resection. This study reported that the CRP/Alb ratio may be an independent and significant indicator of poor long-term outcomes in the studied population, and that it may be superior to the mGPS in terms of its prognostic ability (38). Kinoshita *et al*. also explored the prognostic value of the CRP/Alb ratio in patients with hepatocellular carcinoma (39). They found that it had comparable performance with the mGPS and better performance than the NLR, similar to the findings of the present study. These results suggest that the predictive value of the CRP/Alb ratio may be superior to that of the mGPS.

Sarcopenia has recently received great attention as a negative factor for long-term outcomes in patients with solid cancers (40-42). However, only a few studies have investigated the effect of sarcopenia on the prognosis of patients with esophageal cancer. Nakashima *et al*. retrospectively reviewed the surgical outcomes in 341 patients with esophageal cancer assigned to 2 age groups (<65 and >65 years). They showed that the survival rate was

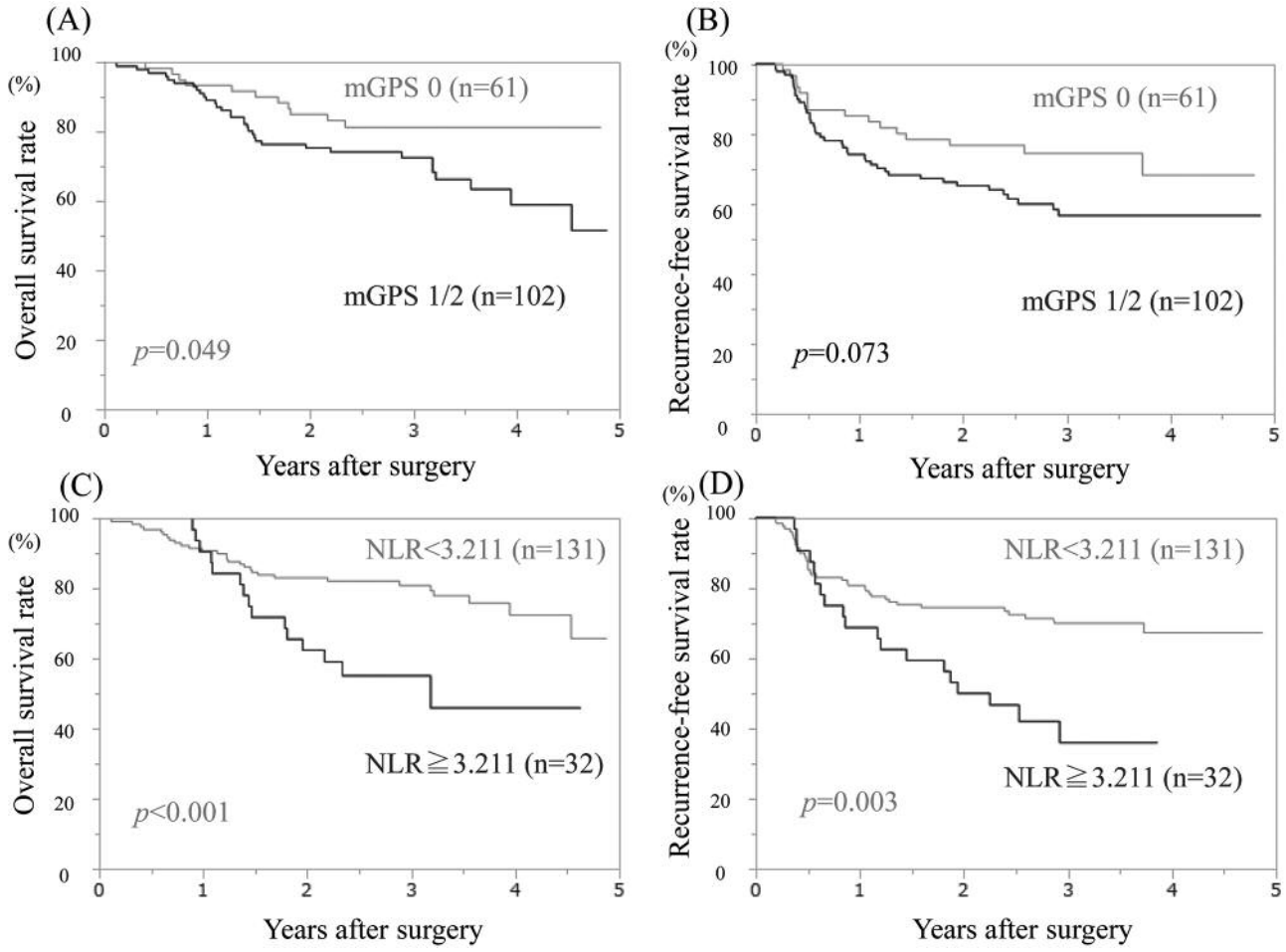

Figure 2. *Overall survival (A) and recurrence-free survival (B) rates following esophagectomy, according to the modified Glasgow prognostic score (mGPS), in patients with esophageal cancer. Overall survival (C) and recurrence-free survival (D) rates following esophagectomy, according to the neutrophil-to-lymphocyte ratio NLR), in patients with esophageal cancer.*

significantly different between patients with and without sarcopenia in the older group (20). Elliot *et al*. retrospectively reviewed the surgical outcomes in 252 patients with locally advanced esophageal cancer who underwent neoadjuvant chemotherapy or chemoradiothreapy. They showed that sarcopenia increased during neoadjuvant therapy, and moreover it was associated with a higher risk of major postoperative complications, resulting in poor survival (43). These reports suggest that sarcopenia is a negative prognostic factor in patients with esophageal cancer. In the current study, the survival rate was significantly poorer in patients with than without sarcopenia, in accordance with these previous studies.

The reason for the poor prognosis in patients with concurrent cancer and sarcopenia has not been sufficiently elucidated. One potential explanation is that preoperative sarcopenia is related to the likelihood of postoperative complications (21, 43) leading to systemic inflammation and resulting in a poor prognosis (44). Indeed, many studies have shown that postoperative complications have a negative impact on the prognosis of patients (45, 46). However, in this study, no significant relationship between the presence of sarcopenia and the occurrence of postoperative complications was found. Another potential explanation is that sarcopenia may be associated with immunosuppression. Myokines, which are proteins secreted from skeletal muscles, have recently gained attention in anticancer research since they mediate exercise-induced metabolic improvement and anti-inflammatory effects (47). In particular, specific myokines have been associated with anticancer immune function (47, 48). Thus, reduction of skeletal muscle may cause weakened immune function against cancer. Further research is needed to clarify the mechanism through which sarcopenia negatively

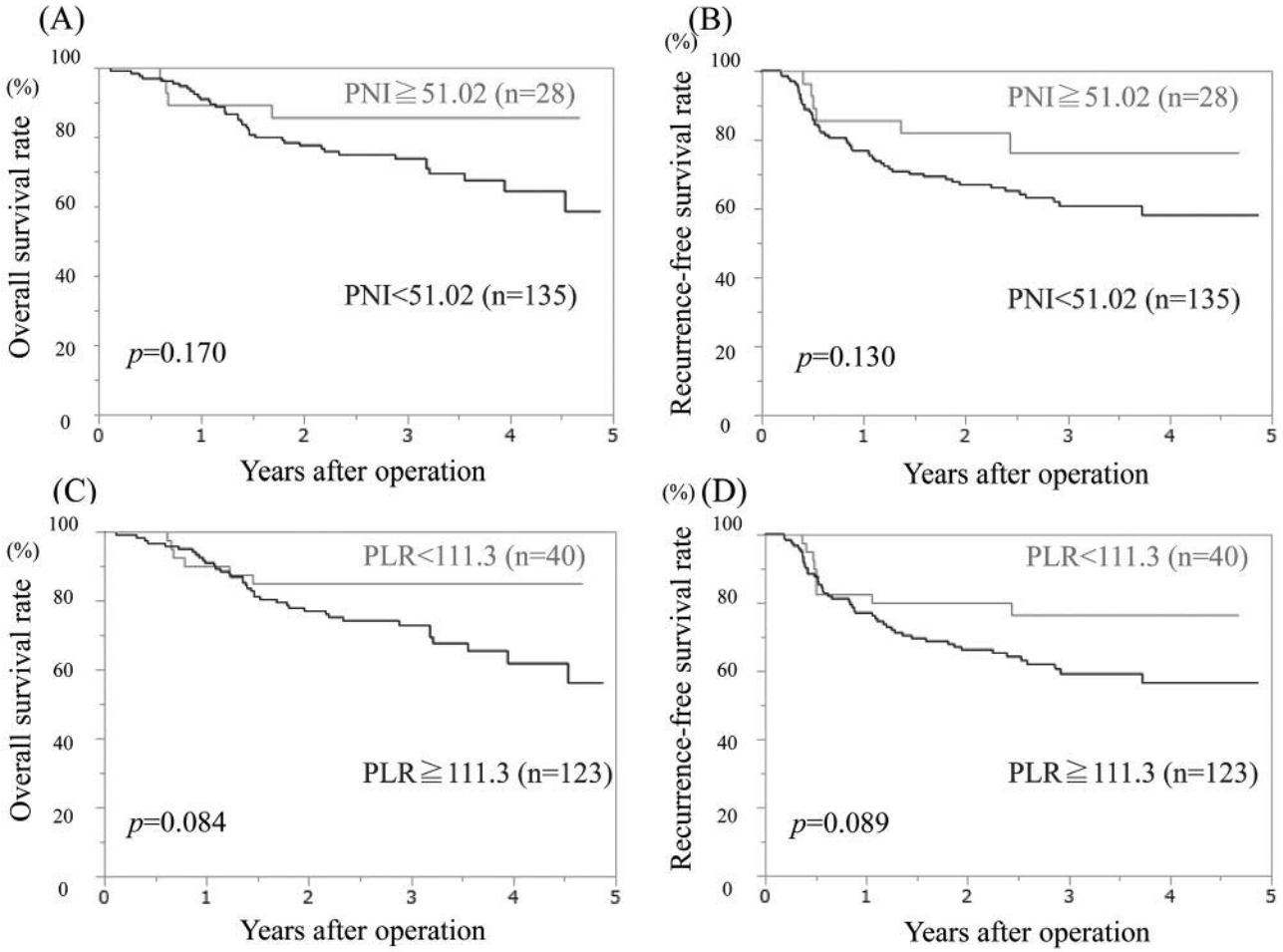

Figure 3. *Overall survival (A) and recurrence-free survival (B) rates following esophagectomy, in patients with esophageal cancer stratified by the prognostic nutritional index (PNI). Overall survival (C) and recurrence-free survival (D) following esophagectomy, in patients with esophageal cancer stratified by the platelet-to-lymphocyte ratio (PLR).*

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

	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*p*-Value	Hazard ratio	95% CI	*p*-Value
Age (<70 *vs*. ≥70 years)	1.179	0.666-2.019	0.561			
Gender (male *vs*. female)	1.549	0.798-3.379	0.206			
pT (0/1 *vs*. 2/3/4)	2.233	1.360-4.126	0.002	1.282	0.691-2.450	0.354
pN (absent *vs*. present)	3.349	1.8550-6.479	<0.001	2.475	1.278-5.070	0.006
Sarcopenia (absent *vs*. present)	1.569	0.931-2.685	0.065	1.240	0.715-2.170	0.445
mGPS (0 *vs*. 1/2)	1.693	0.969-3.107	0.064	1.568	0.659-4.134	0.318
CRP/Alb ratio (<0.00375 *vs*. ≥0.00375)	2.608	1.540-4.497	<0.001	2.462	1.128-6.179	0.022
PNI (<51.02 *vs*. ≥51.02)	1.181	0.691-1.991	0.106			
NLR (<3.211 *vs*. ≥3.211)	2.280	1.285-3.913	0.006	1.672	0.899-3.037	0.102
PLR (<111 *vs*. ≥111)	1.836	0.947-4.002	0.074	1.167	0.565-2.658	0.688

CI, Confidence interval; mGPS, modified Glasgow prognostic score; CRP/Alb ratio, C-reactive protein-to-albumin ratio; PNI, prognostic nutritional index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

affects the prognosis of patients with cancer. Further research is needed to clarify the mechanism through which sarcopenia negatively affects the prognosis of patients with cancer.

This study has several limitations. First, we conducted this retrospective study in a single institution, and the number of patients was small. Second, information regarding proinflammatory cytokines such as TNF-α, IL-1, and IL-6 was not obtained because of the retrospective design. Further *in vitro* and *in vivo* studies are needed to verify the relationship between SMM and proinflammatory cytokines in patients with esophageal cancer. Third, the median follow-up was relatively short because body composition before surgery was not assessed before January 2013. However, because recurrence mainly occurs within 2 years postoperatively (49, 50), the RFS rate was used to investigate independent prognostic factors.

In conclusion, sarcopenia is associated with systemic inflammatory response such as high CRP/Alb ratio and mGPS, and high CRP/Alb ratio is an independent prognostic marker for RFS in patients with esophageal cancer. Modulating systemic inflammation may be a promising treatment for sarcopenia and potentially lead to improved prognosis of esophageal cancer patients.

Conflicts of Interest

All authors declare that they have no conflict of interest.

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