Absolute lymphocyte count and C-reactive protein-albumin ratio can predict prognosis and adverse events in patients with recurrent esophageal cancer treated with nivolumab therapy

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Abstract. Predicting the prognosis and adverse events (AEs) of nivolumab therapy for recurrent esophageal cancer is very important. The present study investigated whether a simple blood biochemical examination could be used to predict prognosis and AEs following nivolumab treatment for relapse of esophageal cancer. A total of 41 patients who received nivolumab treatment for recurrent esophageal cancer after esophagectomy were analyzed. The absolute lymphocyte count (ALC), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), monocyte-lymphocyte ratio (MLR) and C-reactive protein-albumin ratio (CAR) were assessed at the time of nivolumab induction as indices that can be calculated by blood biochemical examinations alone. Median values were 1,015 for ALC, 3.401 for NLR, 242.6 for PLR, 0.458 for MLR and 0.119 for CAR, and patients were divided into two groups according to values. A high ALC, low NLR, low PLR, low MLR and low CAR were associated with a better response to nivolumab. In addition, patients with the aforementioned indices, with the exception of low PLR, or better response were more likely to develop AEs in univariate analysis. In multivariate analysis, a high ALC [odds ratio (OR): 4.857, P=0.043] and low CAR (OR: 9.099, P=0.004) were identified as independent risk factors for AEs. Survival analysis revealed that overall survival and progression-free survival (PFS) rates after nivolumab treatment differed significantly between the high and low groups of ALC, NLR, PLR, MLR and CAR. The multivariate analysis identified a low ALC [hazard ratio (HR): 3.710, P=0.003] and high CAR (HR: 2.953, P=0.007) as independent poor prognostic factors of PFS. In conclusion, ALC and CAR have potential as biomarkers for outcomes of recurrent esophageal cancer following nivolumab treatment.

Introduction

Esophageal cancer is the eighth most common malignancy and the sixth leading cause of death worldwide. Esophageal cancer is a common cancer with a yearly worldwide incidence of approximately 57,0000 new cases and 51,0000 deaths (1). In Japan, the 5-year overall survival (OS) rate for esophageal cancer after esophagectomy is 59.3% and the recurrence rate after radical resection is approximately 40% (2-4). In Western countries, the recurrence rate has been reported to exceed 50%, indicating a poor prognosis for esophageal cancer (5). Therefore, it is important to provide appropriate anticancer therapy to patients with recurrent esophageal cancer in order to improve their survival rate.

Recently, chemotherapy has made remarkable progress, and immune checkpoint inhibitors in particular are attracting attention as a novel cancer treatment because they can be used for multiple types of cancer. The number of cancer types for which nivolumab is indicated has increased, and based on the ATTRACTION-3 trial, nivolumab is now indicated for unresectable or recurrent esophageal cancer (6). The prediction of the therapeutic effects of nivolumab in a simple way can contribute greatly to the treatment of recurrent esophageal cancer using nivolumab.

The aim of the present study was to investigate the clinical background factors, treatment outcomes, and adverse events (AEs) of nivolumab treatment in esophageal cancer patients with recurrence after esophagectomy. In addition, we focused on identifying patients whose prognosis was improved by nivolumab and assessed whether a simple examination, blood biochemical examination, or a simple score, performance status (PS), can be used to predict the prognosis after nivolumab treatment for relapsed esophageal cancer.

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Materials and methods

Patients and data collection. A total of 41 patients who received nivolumab treatment for recurrent esophageal cancer after esophagectomy between February 2020 and April 2022 at our institution were included into this study. Inclusion criteria were as follows: i) Patients pathologically diagnosed with esophageal cancer; ii) patients undergoing esophagectomy; iii) patients diagnosed with esophageal cancer recurrence by imaging examinations by a gastrointestinal surgeon and radiologist. Patients who did not undergo resection or esophagectomy were excluded due to keep the pre-treatment conditions and background factors as same as possible. The clinicopathological data were reviewed from the medical record database of our institution.

The present study was determined to be a retrospective analysis of de-identified data, and written informed consent was waived for the individual participants included in the study in accordance with the standards of the Kyoto Prefectural University of Medicine Institutional Medical Ethics Review Committee. The present study was approved by the ethics committee of the Kyoto Prefectural University of Medicine (approval no. ERB-C-2289).

Surgical procedure, follow-up, and diagnosis of recurrence. Esophagectomy with lymph node dissection was performed based on the Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus (7). Tumor staging was performed according to the 8th edition of the Tumor, Node, Metastasis staging classification (8). After esophagectomy for esophageal cancer, patients were followed up at regular intervals for serum squamous cell carcinoma every 3 months; positron emission tomography (PET) and computed tomography (CT) every 6 months; and upper gastrointestinal endoscopy every 12 months, according to the Guidelines (7). Recurrence of esophageal cancer is assessed by imaging by a gastrointestinal surgeon and radiologist. When recurrence is observed after esophagectomy, surgery or radio-chemotherapy is performed as curative treatment if possible for recurrence in a localized area (9-11). When recurrence is not localized, chemotherapy is the only systemic treatment for esophageal cancer (12). As the use of nivolumab after first-line treatment is allowed in Japan, nivolumab was mainly used as second-line treatment for chemotherapy (6).

Nivolumab treatment, follow-up, and evaluation outcomes. Nivolumab was administered at 240 mg intravenously over 30 min every 2 weeks. Patients underwent blood biochemical examinations at each visit to confirm AEs. In addition, PET or CT was performed every 3 months to evaluate the target lesions. The Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 were used to assess the treatment response composed of complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) (13). AEs were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (14). In the analysis of therapeutic effects, AEs, and survival analysis, we focused on the absolute lymphocyte count (ALC), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), monocyte-lymphocyte ratio (MLR), C-reactive protein-albumin ratio (CAR), and PS, which are expected to be useful in predicting the therapeutic efficacy of nivolumab and can be easily measured based on previous reports of gastric cancer and lung cancer (15-21). The above biomarkers were calculated from the blood biochemical examinations immediately before the first nivolumab treatment.

Statistical analysis. The cut-off values for ALC, NLR, PLR, MLR, and CAR were selected based on median values, and the cut-off value for PS was set at 2. Differences between the two groups for categorial variables were analyzed by the Fisher's exact test. OS and progression-free survival (PFS) were generated using the Kaplan-Meier method, and differences between the two groups were assessed with the log-rank test. Parameters with significant differences in univariate analyses were further assessed using logistic regression analysis and multivariate Cox's models. Only ALC was used for the lymphocyte-related index in order to eliminate confounding factors, and NLR, PLR, and MLR were not used. Hazard ratios (HRs), odds ratios (ORs) and 95% confidence intervals (CIs) were subsequently calculated. $P<0.05$ was considered to indicate a statistically significant difference. Statistical analyses were performed using the software package JMP software version 10 (JMP, Cary, NC, USA).

Results

Patient characteristics. The clinicopathological characteristics of 41 patients are shown in Table I. The median age was 68 years, with 34 male (82.9%) and 7 female patients (17.1%). Among the patients, 31 had curative R0 resections, whereas 10 had R1 or R2 resections. The target lesions of nivolumab (with overlap) were lymph node metastasis in 33 cases, lung metastasis in 12 cases, liver metastasis in 8 cases, bone metastasis in 6 cases, and others in 7 cases. Nivolumab treatment was mainly performed as second-line chemotherapy for postoperative esophageal cancer recurrence, and first-line therapy was often 5-fluorouracil and cisplatin (FP) therapy or docetaxel, cisplatin, and 5-fluorouracil (DCF) therapy. The median number of doses of nivolumab was 9 times (range 1-41) and the median follow-up period after nivolumab treatment was 294 days (range; 35 to 772 days). The median (range) values were 1015 (390-5300) for ALC, 3.401 (0.542-9.641) for NLR, 242.6 (37.74-675.4) for PLR, 0.458 (0.103-1.436) for MLR, and 0.119 (0.002-3.024) for CAR.

Efficacy of nivolumab treatment. The best overall response to nivolumab was as follows: CR, PR or SD was observed in 18 patients, and PD was observed in 23 patients, as shown in Table II. Based on the Fisher's exact test, the high ALC, low NLR, low PLR, low MLR, and low CAR groups had significantly more cases of CR, PR, or SD (P-value=0.002, =0.002, =0.012, <0.001, and =0.002, respectively), whereas the good PS groups tended to have more cases of CR, PR, or SD, but no significant differences were found (Table II).

Safety of nivolumab treatment. Of 41 patients, 24 (58.5%) exhibited AEs of any grade, and 2 (4.9%) had AEs of grade 3 or 4, but no treatment-related deaths were observed

Table I. Clinicopathological characteristics of patients (n=41).

Variable	Value
Median age, years (range)[a]	68 (51-81)
Sex	
Male	34
Female	7
Primary tumor location	
Ce, Ut	12
Mt, Lt, Ae	29
Histopathological type	
Squamous cell carcinoma	38
Basaloid carcinoma	1
Others[b]	2
pStage	
0-II	17
III, IV	24
Residual tumor	
R0	31
R1, R2	10
Neoadjuvant chemotherapy[c]	
5-fluorouracil and cisplatin therapy	7
Docetaxel, cisplatin, and 5-fluorouracil therapy	18
Others	3
None	13
Adjuvant chemotherapy[d]	
5-fluorouracil and cisplatin therapy	3
None	38
Median time to recurrence after surgery, months (range)	7.4 (0-200)
Radio-chemotherapies after recurrence	
Present	17
Absent	24
Prior 1st line	
5-fluorouracil and cisplatin therapy	19
Docetaxel, cisplatin, and 5-fluorouracil therapy	11
Others	11
Number of prior chemotherapies	
1 (Nivolumab as 2nd-line therapy)	32
>2 (Nivolumab as 3rd-line or later therapy)	9
Target lesion[e]	
Lymphatic metastasis	33
Lung metastasis	12
Liver metastasis	8
Bone metastasis	6
Others	7
Median number of doses of nivolumab (range)	9 (1-41)
Performance status[a]	
0	16
1	16
≥2	9
Median ALC[a], cell/mm^3 (range)	1,015 (390-5,300)
Median NLR[a] (range)	3.401 (0.542-9.641)
Median PLR[a] (range)	242.6 (37.74-675.4)
Median MLR[a] (range)	0.458 (0.103-1.436)
Median CAR[a] (range)	0.119 (0.002-3.024)

[a]Before nivolumab therapy; [b]squamous cell carcinoma and adenocarcinoma; [c]before primary tumor surgery; [d]after primary tumor surgery; [e]target lesions include duplications. pStage, pathological stage; Ce, cervical esophagus; Ut, upper thoracic esophagus; Mt, middle thoracic esophagus; Lt, lower thoracic esophagus; Ae, abdominal esophagus; ALR, absolute lymphocyte count; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; MLR, monocyte-lymphocyte ratio; CAR, C-reactive protein-albumin ratio.

(Table III). The most common AEs were skin disorder (29.3%), hypothyroidism (12.2%), and pneumonitis (7.3%). Treatment discontinuation was required for only one patient who developed grade 3 colitis. We also analyzed the relationships of AEs. In univariate analysis, patients with a high ALC, low NLR, low MLR, and low CAR, and better response were more likely to develop AEs (P-value=0.011, =0.001, =0.001, =0.001, and <0.001, respectively), as shown in Table IV. In multivariate analysis, a high ALC (OR 4.857; 95% CI 1.053-26.170; P=0.043) and low CAR (OR 9.099; 95% CI 1.997-53.463; P=0.004) were identified as independent risk factors for AEs.

Survival analysis after nivolumab treatment. As shown in Fig. S1A, the 1-year OS rate after first nivolumab therapy was 52.0%, which was close to the 45.3% in the ATTRACTION-3 trial (6). In this study, the 1-year PFS rate was 32.2% (Fig. S1B). The 41 patients were divided into two groups according to each parameters. The cut-off values were set at the median as follows: ALC, NLR, PLR, MLR, CAR, and PS were 1,015 cell/mm^3, 3.401, 242.6, 0.458, 0.119, and 2, respectively. As shown in Fig. 1, the OS analysis demonstrated that the prognosis was better in the high ALC, low NLR, low PLR, low MLR, low CAR, and good PS groups (P-value =0.002, <0.001, <0.001, <0.001, <0.001, and =0.007, respectively). Using the multivariate Cox's model, a low ALC (HR 4.698; 95% CI 1.462-18.301; P=0.008), high CAR (HR 10.149; 95% CI 2.664-66.729; P<0.001), and poor PS (HR 3.355; 95% CI 1.064-10.664; P=0.039), were identified as independent risk factors for a poor OS (Table VA).

On the other hand, PFS analysis revealed a better prognosis in the high ALC, low NLR, low PLR, low MLR, and low CAR groups (P-value <0.001, <0.001, =0.003, <0.001, and <0.001, respectively), but no significant difference in good and bad PS groups were observed (P-value=0.419), as shown in Fig. 2. The multivariate Cox's model identified a low ALC (HR 3.710; 95% CI 1.546-9.808; P=0.003) and high CAR (HR 2.953; 95% CI 1.344-6.782; P=0.007) as independent predictors of PFS (Table VB).

Table II. Analysis of the effects of nivolumab treatment.

Variable	All patients (n=41)	CR, PR or SD[b] (%)	PD[b] (%)	P-value
Number of patients	41	18	23	NA
Performance status				0.254
0 or 1	32	16 (88.9)	16 (30.4)	
≥2	9	2 (11.1)	7 (69.6)	
ALC[a], cell/mm^3				0.002[c]
High	20	14 (77.8)	6 (26.1)	
Low	21	4 (22.2)	17 (73.9)	
NLR[a]				0.002[c]
Low	20	14 (77.8)	6 (26.1)	
High	21	4 (22.2)	17 (73.9)	
PLR[a]				0.012[c]
Low	20	13 (72.2)	7 (30.4)	
High	21	5 (27.8)	16 (69.6)	
MLR[a]				<0.001[c]
Low	20	15 (83.3)	5 (21.7)	
High	21	3 (16.7)	18 (78.3)	
CAR[a]				0.002[c]
Low	20	14 (77.8)	6 (26.1)	
High	21	4 (22.2)	17 (73.9)	

[a]Before nivolumab therapy; [b]The best overall response was 0 for CR, 18 for CR, PR or SD, and 23 for PD; [c]P<0.05 (Fisher's exact test, significantly different between two groups). ALR, absolute lymphocyte count; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; MLR, monocyte-lymphocyte ratio; CAR, C-reactive protein-albumin ratio; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NA, not applicable.

Table III. Adverse events during nivolumab treatment in patients (n=41).

Variables	Patients
Adverse events[a]	
Overall	24
Skin disorders	12
Rash	11
Bullous dermatitis	1
Hypothyroidism	5
Pneumonitis	3
Anorexia	3
Gastrointestinal disorders	2
Colitis	1
Diarrhea	1
Others	6
Grade of chemotherapy adverse events	
None	17
1	6
2	16
≥3	2
Chemotherapy death	None

[a]Adverse events include duplications, and overall indicates the number of patients who developed the adverse events.

Discussion

In the present study, we investigated the clinical background factors, treatment outcomes, and AEs of nivolumab treatment for recurrent esophageal cancer after esophagectomy. In particular, we focused on identifying patients whose prognosis was improved by nivolumab and examined easily measurable indices that are useful for prognosis prediction in other carcinomas. A high ALC, low NLR, low PLR, low MLR, and low CAR were correlated with a better response to nivolumab. In addition, a high ALC and low CAR were identified as independent risk factors for AEs. Moreover, we revealed that a high ALC and low CAR are independent prognostic factors for better OS and PFS. This study suggests that the prognostic efficacy and AEs of nivolumab may be predicted by a simple method using blood biochemical examinations.

In recent years, immune checkpoint inhibitors, such as nivolumab, have been reported to be effective against a variety of carcinomas, including malignant melanoma, non-small cell lung cancer, and renal cell carcinoma, and are attracting attention as a novel cancer treatment method (22-24). Nivolumab is also expected to be effective in the gastrointestinal field and has become an established treatment for gastric cancer (25). According to several reports, nivolumab improved the prognosis of patients with advanced or recurrent esophageal cancer, and it has been used in clinical practice in Japan since 2020 (6,26,27).

Table IV. Analysis of the adverse events during nivolumab treatment.

		Univariate			Multivariate	
		Adverse events				
Variables	All patients (n=41)	Presence (%)	Absence (%)	P-value	OR (95%CI)	P-value
Performance status				0.128		
0 or 1	32	21 (87.5)	11 (64.7)			
≥2	9	3 (12.5)	6 (35.3)			
ALC[a], cell/mm^3				0.011[b]		0.043[b]
High	20	16 (66.7)	4 (23.5)		4.857 (1.053-26.170)	
Low	21	8 (33.3)	13 (76.5)		1	
NLR[a]				0.001[b]	NA	
Low	20	17 (70.8)	3 (17.6)			
High	21	7 (29.2)	14 (82.4)			
PLR[a]				0.208		
Low	20	14 (58.3)	6 (35.3)			
High	21	10 (41.7)	11 (64.7)			
MLR[a]				0.001[b]	NA	
Low	20	17 (70.8)	3 (17.6)			
High	21	7 (29.2)	14 (82.4)			
CAR[a]				0.001[b]		0.004[b]
Low	20	17 (70.8)	3 (17.6)		9.099 (1.997-53.463)	
High	21	7 (29.2)	14 (82.4)		1	
Best overall response				<0.001[b]	NA	
CR, PR, or SD	18	16 (66.7)	2 (11.8)			
PD	23	8 (33.3)	15 (88.2)			

[a]Before nivolumab therapy; [b]P<0.05 (significantly different). ALR, absolute lymphocyte count; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; MLR, monocyte-lymphocyte ratio; CAR, C-reactive protein-albumin ratio; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NA, not applicable.

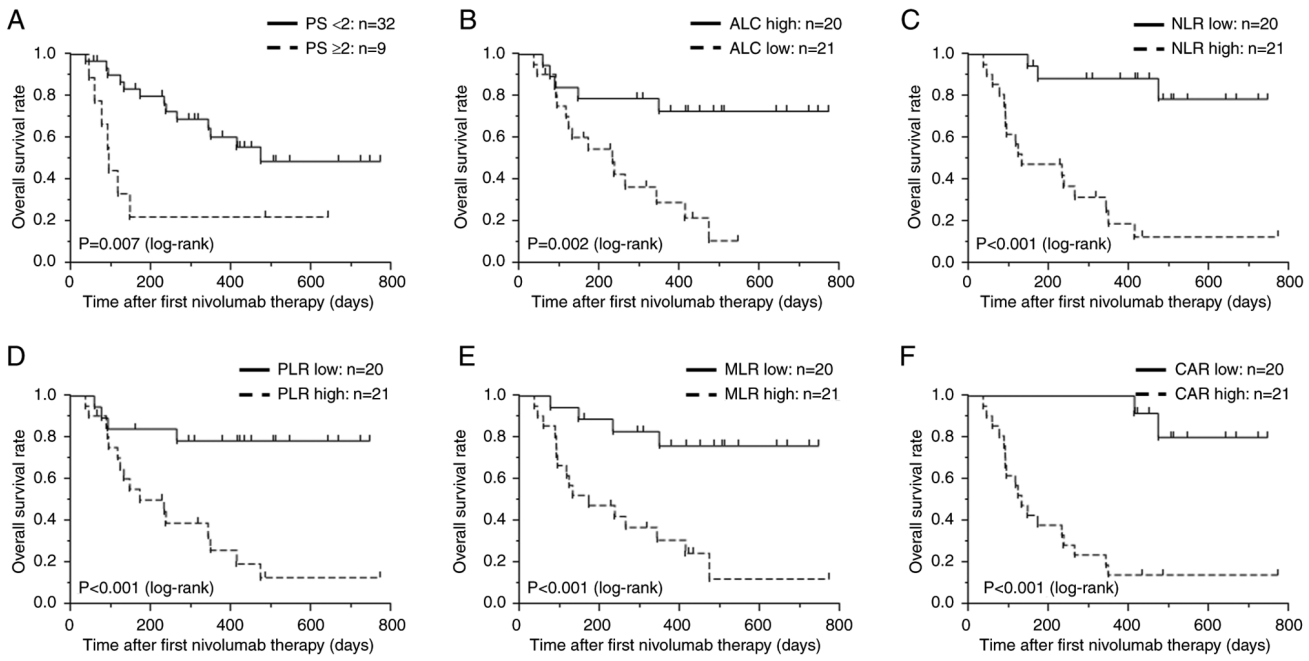

Figure 1. Overall survival after nivolumab treatment stratified by (A) PS, (B) ALC, (C) NLR, (D) PLR, (E) MLR and (F) CAR. PS, performance status; ALC, absolute lymphocyte count; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; MLR, monocyte-lymphocyte ratio; CAR, C-reactive protein-albumin ratio.

Table V. Univariate and multivariate survival analyses.

A, Analysis of overall survival

	Univariate		Multivariate[b]	
Variables	HR (95% CI)	P-value	HR (95% CI)	P-value
Age, years		0.814		
≥65	1			
<65	1.111 (0.448-2.687)			
Sex		0.595		
Male	1			
Female	1.394 (0.466-5.987)			
Performance status[a]		0.007[c]		0.039[c]
0 or 1	1		1	
≥2	3.354 (1.243-8.328)		3.355 (1.064-10.664)	
ALC[a], cell/mm^3		0.002[c]		0.008[c]
High	1		1	
Low	4.507 (1.704-14.129)		4.698 (1.462-18.301)	
NLR[a]		<0.001[c]	NA	
Low	1			
High	10.628 (3.428-46.885)			
PLR[a]		<0.001[c]	NA	
Low	1			
High	5.686 (2.057-20.036)			
MLR[a]		<0.001[c]	NA	
Low	1			
High	5.841 (2.109-20.623)			
CAR[a]	1	<0.001[c]		<0.001[c]
Low	1		1	
High	16.520 (4.669-104.965)		10.149 (2.664-66.729)	

B, Analysis of progression-free survival

	Univariate		Multivariate[b]	
Variables	HR (95% CI)	P-value	HR (95% CI)	P-value
Age, years		0.160		
>65	1			
<65	1.679 (0.799-3.511)			
Sex		0.849		
Male	1.092 (0.471-2.966)			
Female	1			
Performance status[a]		0.419		
0 or 1	1			
>2	1.415 (0.560-3.145)			
ALC[a], cell/mm^3		<0.001[c]		0.003[c]
High	1		1	
Low	4.430 (1.929-11.225)		3.710 (1.546-9.808)	
NLR[a]		<0.001[c]	NA	
Low	1			
High	4.170 (1.923-9.801)			
PLR[a]		0.003[c]	NA	
Low	1			
High	3.028 (1.434-6.816)			

Table V. Continued.

B, Analysis of progression-free survival

	Univariate		Multivariate[b]	
Variables	HR (95% CI)	P-value	HR (95% CI)	P-value
MLR[a]		<0.001[c]	NA	
Low	1			
High	4.632 (2.112-10.987)			
CAR[a]		<0.001[c]		0.007[c]
Low	1		1	
High	3.621 (1.701-8.206)		2.953 (1.344-6.872)	

[a]Before nivolumab therapy; [b]in multivariate analysis, only ALC was used for the lymphocyte-related index in order to eliminate confounding factors, and NLR and MLR were not used; [c]P<0.05 (significantly different). NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; CAR, C-reactive protein-albumin ratio; NA, not applicable.

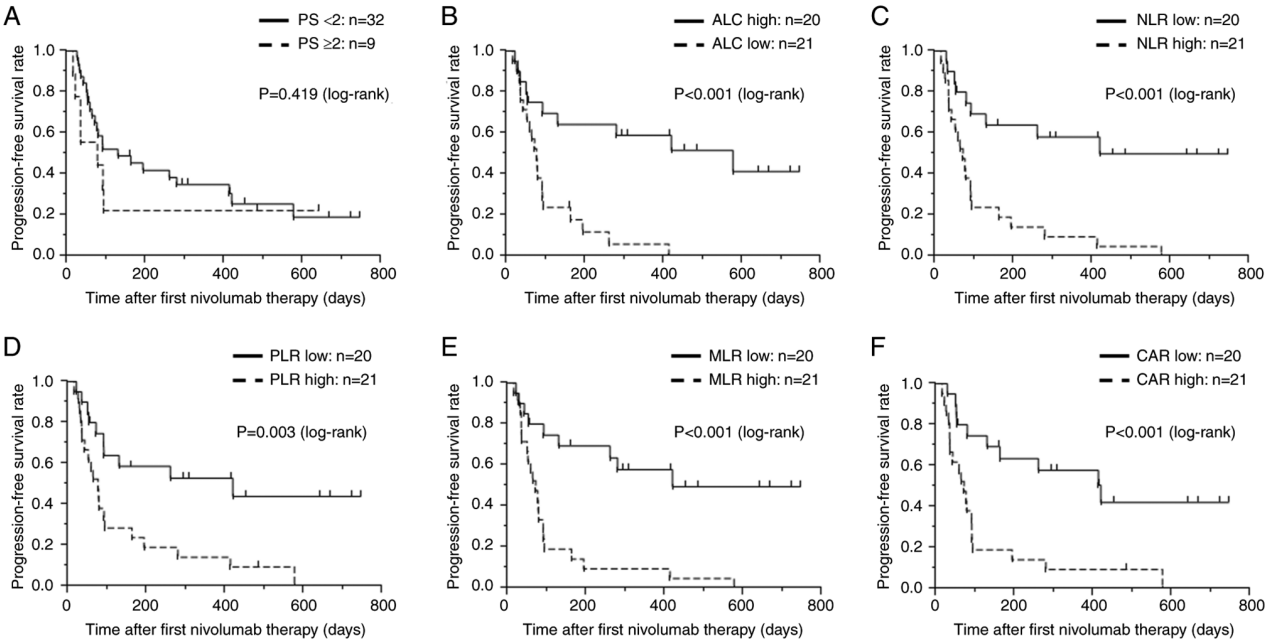

Figure 2. Progression-free survival after nivolumab treatment stratified by (A) PS, (B) ALC, (C) NLR, (D) PLR, (E) MLR and (F) CAR. PS, performance status; ALC, absolute lymphocyte count; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; MLR, monocyte-lymphocyte ratio; CAR, C-reactive protein-albumin ratio.

When using nivolumab, it is very important to predict how effective it will be and how likely AEs are. A few reports suggested that programmed cell death ligand 1 (PD-L1) and tumor infiltrating lymphocytes (TILs) affect the prediction of nivolumab response, but evidence is still lacking and these require additional pathological examinations such as immunohistochemical staining. On the other hand, in gastric and lung cancers, simple indices that can be calculated only by blood biochemical examination, such as ALC, NLR, PLR, MLR, and CAR, in addition to PS that can be calculated without examination, have been reported to be prognostic factors for nivolumab treatment (15-21). These indices are considered to be very simple and easy to use biomarkers that can be measured without a pathologist, different from the TIL and PD-L1 evaluations. In addition, single parameters such as neutrophils, platelets, albumin and C-reactive protein (CRP) were also examined, but no significant differences were found except for CRP (Fig. S2). Also, although there were significant differences in CRP in the current study, more than half of the patients had very low inflammation values of 1 or less. Therefore, CAR was considered more appropriate than CRP because even a small difference could result in different groups. Furthermore, the biomarkers considered in this study, unlike single parameters except for ALC such as neutrophil and platelet counts, albumin, and CRP levels, have been shown to be useful in predicting nivolumab prognosis in other carcinomas and are expected to be effective in esophageal cancer (15-21). For the above reasons, we investigated whether

a simple index such as ALC, NLR, PLR, MLR, CAR, and PS (not neutrophils, platelets, albumin and CRP) can predict the prognosis after nivolumab therapy for recurrent esophageal cancer.

In the present study, two or three explanatory variables were used in the multivariate analysis. The NLR, PLR, and MLR contain ALC as a component and are strongly correlated with ALC. In this study, ALC, a component of the three indicators (NLR, PLR, and MLR) and a simpler indicator, was used in the multivariate analysis to avoid confounding. In addition, both Akaike information criterion and Bayesian information criterion were minimized when only ALC was analyzed as a lymphocyte-related index, not including NLR, PLR or MLR. Whether NLR, PLR, MLR, or ALC is a more effective biomarker needs to be discussed in the future.

As shown in Figs. 1 and 2, ALC, NLR, PLR, MLR, and CAR were useful predictors of OS and PFS after nivolumab treatment for recurrent esophageal cancer. Calculating cut-off values from receiver operating characteristic curves due to the small number of cases makes the results unstable, and bias in the number of cases leads to imbalance in the data. It is also difficult to interpret and cannot be generalized because cut-off values must be set according to the outcome. For this reason, the cut-off values for the above indicators were set to the median in this study. Previous studies demonstrated the negative impact of a low ALC, high NLR, high PLR, high MLR, high CAR, and poor PS on the survival outcomes of various cancers; however, the cut-off values of these indicators differed among studies. Karantanous *et al* reported that lung cancer patients with an ALC ≥1,700/μl have a better OS than for those with <900/μl (16). Ueda *et al* demonstrated that the optimal cut-off value of ALC for predicting PFS was 1,300/μl and that an ALC ≥1,300/μl is an independent prognostic factor in metastatic renal cell carcinoma patients (28). In gastric cancer, Ogata *et al* (18) set the cut-off value for NLR in unresectable or recurrent gastric cancer at 5, whereas Yamada *et al* (17) set it at 2.5; therefore, the cut-off value differs among studies. The cut-off values determined in this study were all within the range of previous reports and we believe that setting the cut-off value at the median is not inappropriate. However, as the previously reported cut-off values have a wide range, further large-scale studies are necessary to calculate the exact optimal cut-off values.

The AEs of nivolumab for recurrent esophageal cancer were more frequent in the groups with a high therapeutic efficacy, as shown in Table IV. The mechanisms underlying the association of AEs with the outcome of nivolumab treatment remains unclear. It is possible that esophageal cancer cells share antigens with tissues affected by AEs in patients with esophageal cancer, but these have not been elucidated. Further basic studies are expected to clarify this mechanism. Although the mechanism remains unknown, many reports of an association between AEs and treatment effects have been reported in other cancers (29). This study also suggests an association between AEs and treatment effects in recurrent esophageal cancer. The high ALC, low NLR, low MLR, and low CAR groups are expected to benefit from nivolumab treatment, but close follow-up is needed to reduce AEs to enable nivolumab to be continued for a longer period of time.

We want to discuss which is more affective to prognosis or AEs, systemic factors such as ALC or CAR, or local factors such as the percent of PD-L1 positive cells and TILs. Although PD-L1-positive cells and TILs have been reported to play a role in the prognosis of nivolumab therapy, in esophageal cancer, the results of the ATTRACTION-3 trial suggest that PD-L1 positivity is not a prognostic factor for nivolumab therapy (6,30,31). Similarly, for AEs, PD-L1 is not a prognostic factor, so ALC or CAR may be more useful than PD-L1 expression (32). On the other hand, many reports showed that TILs were a prognostic factor for nivolumab therapy, and a few reports indicated that ALC and TILs were correlated (33,34). Therefore, it is difficult to determine the superiority between ALC and TILs. However, one problem with local factors is that PD-L1 and TILs are evaluated in specimens at the time of primary tumor resection (35-38). Therefore, they may not accurately reflect the status at the time of nivolumab induction, as they cannot be evaluated at metastases and may be affected by 1st line therapy such as chemotherapy. On the other hand, systemic factors such as ALC and CAR may reflect the status at the time of nivolumab induction, but they are still few reports and need to be further studied and validated.

To the best of our knowledge, this is the first report to predict the outcome and side effects of nivolumab therapy for recurrent esophageal cancer using only blood biochemical examination, such as ACL, NLR, PLR, MLR, and CAR values, or a simple score, PS. As nivolumab therapy for recurrent esophageal cancer is expected to become increasingly widespread, prediction of the prognosis and side effects is essential (15-21,28). The more accurate and predictable a measure is using a simple method, the more frequently it will be used; therefore, ALC and CAR as predictors of the outcome and side effects of nivolumab therapy for recurrent esophageal cancer may be versatile.

The present study had several limitations. Firstly, this was a retrospective study with a small sample size from one institution, which may have limited its statistical power and generated statistical biases. In addition, the follow-up period was short because of the short time since nivolumab was approved as a treatment for recurrent esophageal cancer. Furthermore, the prognosis may differ by anticancer treatment lines, but the patients with different treatment lines were included due to the small sample size. Second, as the cut-off value was set as the median, the cut-off value needs to be validated in further studies with a large sample size. Moreover, other prognostic factors for the effects of nivolumab, such as TILs, expression of PD-L1, and tumor mutational burden, which is an indicator of the amounts of genetic mutations in tumor tissue, have been reported and further studies are needed to take these factors into account (27,30,31).

Despite of these limitations, the present study demonstrated that an index calculated using only blood biochemical examinations can predict the prognosis and AEs of nivolumab in recurrent esophageal cancer patients. This will play an important role in the future treatment of recurrent esophageal cancer, and in particular, ALC and CAR may be useful and simple biomarkers to predict survival.

In conclusion, this study revealed the clinical background factors, treatment outcomes, and AEs of nivolumab treatment for esophageal cancer patients with recurrence after esophagectomy. The current study suggested that ALC and CAR have potential as biomarkers for the outcomes of recurrent

esophageal cancer after nivolumab treatment, and further accumulation of cases is considered necessary in the future.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

HIn, AS, HF and EO contributed to the study conception and design. HIn, AS, HF, HK, JK, TO, HS, TA, YY, RM, YK, HIk, TK, KO and EO performed the surgeries, collected the clinical samples, and assessed the clinical data. HIn, AS, HF and HK acquired data. HIn and AS contributed to the analysis, interpretation of data and writing of the manuscript. HF and EO made critical revisions. HIn, AS and HF confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This retrospective study was approved by the Medical Ethics Review Committee of the Kyoto Prefectural University of Medicine (approval no. ERB-C-2289). It was determined to be a retrospective analysis of de-identified data, and written informed consent was waived for the individual participants included in the study in accordance with the standards of the Kyoto Prefectural University of Medicine Institutional Medical Ethics Review Committee.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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