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Platelet-to-Lymphocyte Ratio Multiplied by the Cytokeratin-19 Fragment Level as a Predictor of Pathological Response to Neoadjuvant Chemotherapy in Esophageal Squamous Cell Carcinoma

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ABSTRACT

Background The standard treatment for resectable advanced esophageal squamous cell carcinoma in Japan is surgery followed by neoadjuvant chemotherapy, and it is important to predict the effect of neoadjuvant chemotherapy before treatment. Therefore, this study aims to extract conventional blood examination data, such as tumor markers and/or inflammatory/nutritional index levels, that can predict the pathological response of patients with esophageal squamous cell carcinoma to neoadjuvant chemotherapy.

Methods We retrospectively analyzed the medical records of 66 patients with thoracic esophageal squamous cell carcinoma who received neoadjuvant chemotherapy, followed by curative esophagectomy at Tottori University Hospital between June 2009 and December 2019.

Results We demonstrated that the product of the platelet-to-lymphocyte ratio (PLR) multiplied by the cytokeratin-19 fragment (CYFRA) level, which was termed "PLR-CYFRA," is the most accurate indicator that predicts the pathological response to neoadjuvant chemotherapy, with the highest area under the curve [0.795 (95% confidence interval: 0.665–0.925), $P < 0.001$] in receiver operating characteristic analyses. Therefore, we divided patients into the PLR-CYFRA^{Low} (< 237.6, $n = 21$) and PLR-CYFRA^{High} (≥ 237.6, $n = 45$) groups and found that the percentage of PLR-CYFRA^{Low} was significantly higher in patients with a better pathological response ($P < 0.001$). Furthermore, patients with good pathological response had significantly better prognoses in terms of disease-specific survival ($P = 0.014$), recurrence-free survival ($P = 0.014$), and overall survival ($P = 0.032$). In the multivariate analysis, PLR-CYFRA was an independent predictor of the pathological response of patients with esophageal squamous cell carcinoma to neoadjuvant chemotherapy ($P = 0.002$).

Conclusion Pretreatment PLR-CYFRA might be a useful and simple tool that predicts the pathological effect of neoadjuvant chemotherapy in esophageal squamous cell carcinoma.

Key words cytokeratin; esophageal cancer; lymphocyte; neoadjuvant chemotherapy; platelet

Esophageal cancer is the sixth leading cause of cancer-related deaths worldwide,[1] and in Japan, the most common histological type of esophageal cancer is squamous cell carcinoma (more than 90%).[2] According to the results of the JCOG9907 trial, the standard treatment for locally advanced and resectable esophageal squamous cell carcinoma (ESCC) is esophagectomy with two- or three-field lymphadenectomy after neoadjuvant chemotherapy (NAC).[3] Despite this intensive combination therapy, we often find cases with a poor prognosis because of postoperative recurrence, and the 5-year survival rate after esophagectomy is only 59.3%.[2] One reason for this poor prognosis is the inadequate effect of NAC, as it has been reported that pathological responders to NAC exhibited better prognosis and that the postoperative recurrence pattern often confined to the regional field is predominantly a solitary lesion without distant recurrence.[4] Therefore, although the prediction of the NAC effect before treatment is important as it determines the treatment strategy, no predictive method has been established.

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Abbreviations: 5-FU, 5-fluorouracil; AUC, area under the curve; CRP, C-reactive protein; CYFRA, cytokeratin-19 fragment; DSS, disease-specific survival; ESCC, esophageal squamous cell carcinoma; mGPS, modified Glasgow prognostic score; NAC, neoadjuvant chemotherapy; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; pCR, pathological complete response; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; RFS, recurrence-free survival; ROC, receiver operating characteristic; SCC Ag, squamous cell carcinoma antigen

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In recent years, several studies have reported that pretherapeutic values of tumor markers might be useful in predicting prognosis and NAC efficacy in ESCC.[5] Furthermore, various inflammatory/nutritional biomarkers, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and prognostic nutritional index (PNI), have been reported to be associated significantly with prognosis and to be useful in predicting the chemotherapeutic effects in ESCC.[6–10] However, it is unknown whether each indicator alone or in combination can predict the effects of NAC in ESCC with the highest accuracy.

Therefore, this study aims to evaluate the predictive value of a single indicator or a combination of indicators, including tumor markers and inflammatory/nutritional biomarkers, in predicting NAC efficacy. This study also aims to establish the best predictor of NAC efficacy in ESCC.

MATERIALS AND METHODS

Patients and NAC regimens

This study was based on a retrospective analysis of 66 patients with locally advanced thoracic ESCC who received NAC, followed by curative esophagectomy at Tottori University Hospital between June 2009 and December 2019. The clinicopathological findings were determined according to the Japanese Classification of Esophageal Cancer (11th edition).[11, 12] The criteria for NAC administration were clinical stage II, III, or IVa disease. As standard chemotherapeutic drugs, 5-fluorouracil (5-FU) and cisplatin (FP regimen) were used for all eligible patients, except those with impaired renal function and those treated with 5-FU and nedaplatin (FN regimen). The FP regimen consisted of 80 mg/m^2 cisplatin on day 1 and 800 mg/m^2 5-FU infusions on days 1–5, whereas the FN regimen consisted of 90 mg/m^2 nedaplatin on day 1 and 800 mg/m^2 5-FU infusions on days 1–5. The length of one chemotherapy cycle of each regimen ranged from 21 to 28 days. Surgery was performed 6–8 weeks after the last NAC cycle. The standard surgical approach was thoracoscopic subtotal esophagectomy and reconstruction with a gastric tube, and lymphadenectomies, including two- or three-field procedures, were performed.

Criteria of pathological response to NAC

The pathological response was evaluated by pathologists using the primary tumor of the surgical specimens according to the Japanese Classification of Esophageal Cancer (11th edition),[11, 12] as follows: grade 0, no recognizable cytological or histological therapeutic effect is observed; grade 1a, viable cancer cells account for two-thirds or more of the tumor tissue; grade 1b, viable cancer cells account for between one-third and two-thirds of the tumor tissue; grade 2, viable cancer cells account for less than one-third of the tumor tissue; and grade 3, no viable cancer cells are apparent (pathological complete response; pCR).

Serum biomarkers

The results of peripheral blood tests, including the detection of serum albumin (g/dL), C-reactive protein (CRP) (mg/dL), squamous cell carcinoma antigen (SCC Ag) (ng/mL) and cytokeratin-19 fragment (CYFRA) (ng/mL) levels, and total platelet, lymphocyte, and neutrophil counts (/μL), were obtained from the patients' medical records. Blood test data were obtained within 1 month of NAC. The NLR and PLR were obtained by dividing the peripheral neutrophil count and platelet count, respectively, by the peripheral lymphocyte count. The PNI was calculated as follows: 10 × peripheral serum albumin + 0.005 × peripheral lymphocyte count, as reported by Onodera et al.[13] The modified Glasgow prognostic score (mGPS) was scored as 0, 1, or 2 based on CRP (> 1.0 mg/dL) and hypoalbuminemia (<3.5 g/dL), as described previously.[14] The PLR-CYFRA was first defined as the PLR value × the serum CYFRA level. Our institutional review board approved this study (20A234). The need for informed consent was waived.

Statistical analyses

The Youden index was calculated using receiver operating characteristic (ROC) curve analysis and was defined as the maximum value of "sensitivity + specificity –1".[15, 16] The Youden index value was used as an optimal cut-off for the PLR-CYRFA in the pathological response, which was used to divide patients into the PLR-CYFRA^{High} and PLR-CYFRA^{Low} groups. Survival curves were calculated according to the Kaplan–Meier method, and differences between the curves were identified using the log-rank test. Univariate and multivariate analyses using Cox proportional hazards models were performed to evaluate prognostic factors for disease-specific survival (DSS). Moreover, to evaluate the effects of clinical variables on the pathological response, a univariate analysis was performed using χ^2 tests, followed by a multivariate logistic analysis. P values < 0.05 were considered significant. GraphPad Prism (GraphPad Software, Inc., La Jolla, CA) and IBM SPSS Statistics 25 (IBM SPSS, Chicago, IL) software were used for the statistical analyses.

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RESULTS

Clinicopathological characteristics

The clinicopathological characteristics of the 66 patients with ESCC in this study are shown in Table 1. Of these, 8 (12.1%) patients were female and 58 (87.9%) were male, with a median age of 65 years. The clinical stage of ESCC before NAC was II in 29 patients (43.9%), III in 36 patients (54.5%), and IVa in 1 patient (1.5%). Fifty-three patients (80.3%) received the FP regimen and 13 patients (19.7%) received the FN regimen as NAC. The pathological response of the resected tumors after NAC was grade 0 in 3 patients (4.5%), grade 1a in 38 patients (57.6%), grade 1b in 9 patients (13.6%), grade 2 in 13 patients (19.7%), and grade 3 (pCR) in 3 patients (4.5%). We then divided the 66 patients into the responder (16 patients with grades 2 or 3) and nonresponder groups (50 patients with grades 0 or 1).

PLR-CYFRA was valuable in predicting the pathological response to NAC

ROC curves were constructed to evaluate the pathological response, and the area under the curve (AUC) values were compared to assess the discriminatory ability of SCC Ag, CYFRA, PNI, mGPS, NLR, and PLR (Table 2). In this analysis, the AUC values of CYFRA, NLR and PLR were particularly higher than those of the other indicators. Therefore, we defined NLR-CYFRA and PLR-CYFRA as the product of NLR and PLR multiplied by CYFRA, respectively. ROC analysis showed that PLR-CYFRA was most accurate in predicting the pathological response with an AUC = 0.795 [95% confidence interval (CI): 0.665–0.925, $P < 0.001$] (Table 2); the optimal cut-off PLR-CYFRA value was 237.6. Based on this cut-off, the sensitivity, specificity, positive predictive value, and negative predictive value of PLR-CYFRA for pathological response grade ≥ 2 were 0.81, 0.84, 0.62, and 0.93, respectively. Then, we divided the patients into the PLR-CYFRA^{Low} (PLR-CYFRA < 237.6, $n = 21$) and PLR-CYFRA^{High} groups (PLR-CYFRA ≥ 237.6, $n = 45$). Figure 1 shows the percentage of PLR-CYFRA^{Low} or PLR-CYFRA^{High} according to the pathological response grade, and the percentage of PLR-CYFRA^{Low} was found to be significantly higher when the pathological response grade was higher ($P < 0.001$). Then, Table 3 shows the correlations between the PLR-CYFRA and the clinicopathological variables in all patients included in this study. The value of PLR-CYFRA was significantly higher in younger patients (< 70 years) than in older patients (≥ 70 years: $P < 0.001$), in those with low body mass index (< 18.5) than those with high body mass index (≥ 18.5: $P = 0.014$), and in those treated with FN regimen than in those treated with FP regimen ($P = 0.028$).

Pathological response to NAC and pretreatment factors had a prognostic impact

We next examined the prognostic impact of the pathological response to NAC and pretreatment factors, including PLR-CYFRA. When the pathological response was compared between the 2 groups [grade ≥ 2 ($n = 16$) or grade < 2 ($n = 50$)] using Kaplan–Meier analyses, the grade ≥ 2 group had a significantly better prognosis in terms of DSS ($P = 0.014$) (Fig. 2a), recurrence-free survival (RFS) ($P = 0.014$) (Fig. 2b), and overall survival (OS) ($P = 0.032$) (Fig. 2c). Similarly, the prognostic comparison between the 2 groups of PLR-CYFRA^{High} ($n = 45$) and PLR-CYFRA^{Low} ($n = 21$) showed a significantly better prognosis for PLR-CYFRA^{Low} in terms of DSS ($P = 0.014$) (Fig. 2d) and RFS ($P = 0.001$) (Fig. 2e). However, no significant difference was observed in OS ($P = 0.111$) (Fig. 2f), although there was a trend toward a better prognosis. Then, prognostic factor analyses of pretreatment factors for DSS showed that clinical stage III/IVa ($P = 0.016$), PNI < 50 ($P = 0.024$), and PLR-CYFRA ≥ 237.6 ($P = 0.023$) were significant factors for a poor prognosis according to a univariate analysis (Table 4). In the multivariate analysis, clinical stage III/IVa ($P = 0.032$) and PLR-CYFRA ≥ 237.6 ($P = 0.030$) were extracted as independent poor prognostic factors (Table 4).

PLR-CYFRA was an independent predictor of pathological response to NAC

Finally, we evaluated the effects of clinical variables on the pathological response to NAC. The univariate analysis indicated that NLR ($P = 0.009$) and PLR-CYFRA ($P < 0.001$) were associated significantly with the pathological response (Table 5). In the multivariate analysis, PLR-CYFRA ($P = 0.002$) was an independent predictor of pathological response in patients with ESCC who received NAC (Table 5).

DISCUSSION

The purpose of the present study was to extract valuable predictors of NAC efficacy in ESCC using various factors, including inflammatory/nutritional biomarkers and tumor markers. We then demonstrated that pretreatment PLR-CYFRA was an independent predictor of pathological response and an independent prognostic factor for patients with ESCC treated with NAC. Furthermore, the pathological response to NAC was also correlated with patient prognosis. In this study, we demonstrated that the inflammatory biomarker PLR and the tumor marker CYFRA were useful predictors of NAC effects in ESCC. It is well known that the systemic inflammatory response plays an important role in tumorigenesis and predicts the survival of patients

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Table 1. Clinicophathological characteristics

	No. of patients = 66
Age (years), median (range)	65 (51–79)
Sex, *n* (%)	
Female	8 (12.1%)
Male	58 (87.9%)
Body mass index (kg/m^2), median (range)	20.2 (14.6–26.9)
Tumor location, *n* (%)	
Upper	11 (16.7%)
Middle	29 (43.9%)
Lower	26 (39.3%)
Clinical invasion depth, *n* (%)	
cT1	6 (9.1%)
cT2	22 (33.3%)
cT3	38 (57.6%)
Clinical lymph node metastasis, *n* (%)	
cN0	15 (22.7%)
cN1	25 (37.9%)
cN2	23 (34.8%)
cN3	2 (3.0%)
cN4	1 (1.5%)
Clinical stage, *n* (%)	
cStage II	29 (43.9%)
cStage III	36 (54.5%)
cStage IVa	1 (1.5%)
Chemotherapy, *n* (%)	
5-FU + cisplatin	53 (80.3%)
5-FU + nedaplatin	13 (19.7%)
Differentiation, *n* (%)	
Moderately differntiated	55 (83.3%)
Poorly differntiated	9 (13.6%)
No tumor (pCR)	2 (3.0%)
Lymphatic involvement, *n* (%)	
ly0	11 (16.7%)
ly1	32 (48.5%9
ly2	18 (27.3%)
ly3	5 (7.6%)
Venous involvement, *n* (%)	
v0	16 (24.2%)
v1	30 (45.5%)
v2	18 (27.3%)
v3	2 (3.0%)

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Table 1. (continued)

	No. of patients = 66
Pathological invasion depth, *n* (%)	
pT0	2 (3.0%)
pT1	13 (19.7%)
pT2	17 (25.8%)
pT3	33 (50.0%)
pT4a	1 (1.5%)
Pathological lymph node metastasis, *n* (%)	
pN0	20 (30.3%)
pN1	17 (25.8%)
pN2	24 (36.4%)
pN3	4 (6.1%)
pN4	1 (1.5%)
Pathological stage, *n* (%)	
pStage 0	3 (4.5%)
pStage I	4 (6.1%)
pStage II	26 (39.4%)
pStage III	31 (47.0%)
pStage IVa	2 (3.0%)
Pathological response, *n* (%)	
Grade 0	3 (4.5%)
Grade 1a	38 (57.6%)
Grade 1b	9 (13.6%)
Grade 2	13 (19.7%)
Grade 3	3 (4.5%)

Table 2. Receiver operating characteristic curve analysis for the predictive value of tumor markers and serum-based inflammatory indicators of pathological response

	AUC	95% CI	*P*
SCC Ag	0.542	0.395–0.689	0.616
CYFRA	0.723	0.577–0.869	0.008
PNI	0.641	0.484–0.798	0.091
mGPS	0.528	0.364–0.691	0.742
NLR	0.683	0.554–0.812	0.028
PLR	0.701	0.553–0.849	0.016
NLR-CYFRA	0.763	0.633–0.893	0.002
PLR-CYFRA	0.795	0.665–0.925	< 0.001

CI, confidence interval.

with cancer, and inflammation can be assessed easily by counting neutrophils, lymphocytes, monocytes, and platelets in peripheral blood.[17] Specifically, it has been reported that PLR can predict the efficacy of chemotherapy in non-small cell lung cancer, colorectal cancer, and breast cancer.[18–20] The mechanism of PLR in tumorigenesis may stem from the role of platelets in promoting angiogenesis, adhesion, and invasion by increasing the production of vascular epidermal growth factor and transforming growth factor-β in the tumor

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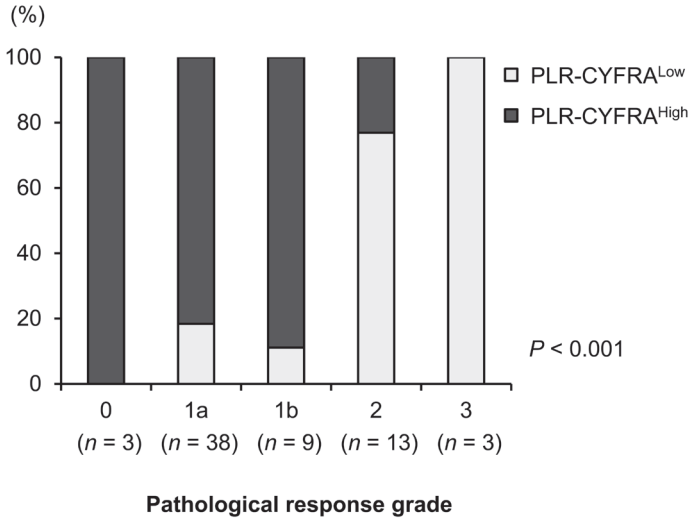

Fig. 1. The percentage of PLR-CYFRA high and low cases according to the pathological response grade. CYFRA, cytokeratin-19 fragment; PLR, platelet-to-lymphocyte ratio.

Table 3. Relationships between PLR-CYFRA and clinicopathological variables in patients with ESCC treated with NAC

	PLR-CYFRA (mean ± standard deviation)	*P*
Age (years)		< 0.001
< 70 (*n* = 46)	525.0 ± 519.4	
≥ 70 (*n* = 20)	233.9 ± 144.3	
Sex		0.409
Female (*n* = 8)	746.1 ± 1079.0	
Male (*n* = 58)	394.1 ± 287.1	
Body mass index (kg/m^2)		0.014
< 18.5 (*n* = 18)	656.6 ± 734.7	
≥ 18.5 (*n* = 48)	354.3 ± 266.8	
Tumor location		0.753
Upper, middle (*n* = 40)	393.8 ± 293.8	
Lower (*n* = 26)	502.8 ± 637.7	
Invasion depth		0.092
cT1, 2 (*n* = 28)	347.8 ± 252.6	
cT3 (*n* = 38)	502.3 ± 560.2	
Lymph node metastasis		0.496
Absent (*n* = 15)	368.5 ± 255.6	
Present (*n* = 51)	456.9 ± 504.3	
Clinical stage		0.408
cStage II (*n* = 23)	373.5 ± 260.9	
cStage III, IVa (*n* = 43)	470.6 ± 536.3	
Chemotherapy		0.028
5-FU + cisplatin (*n* = 53)	368.3 ± 277.0	
5-FU + nedaplatin (*n* = 13)	716.1 ± 839.9	

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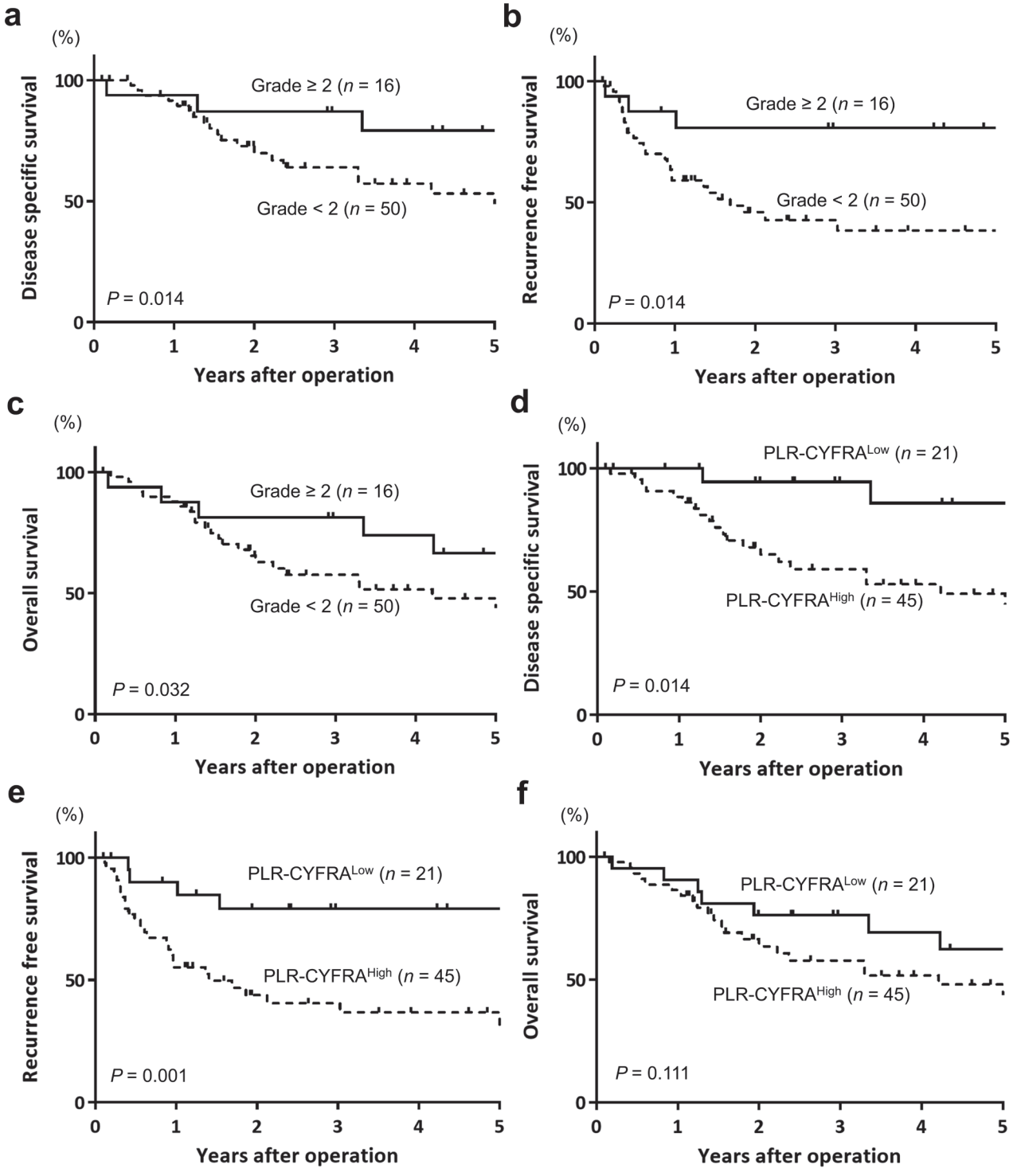

Fig. 2. (**a**) Disease-specific survival, (**b**) recurrence-free survival, and (c) overall survival rates of patients with esophageal squamous cell carcinoma with pathological response grade ≥ 2 (n = 16) and grade < 2 (n = 50). (**d**) Disease-specific survival, (**e**) recurrence-free survival, and (**f**) overall survival rates of patients with esophageal squamous cell carcinoma with PLR-CYFRA^{High} (n = 45) and PLR-CYFRA^{Low} (n = 21).

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Table 4. Univariate and multivariate analyses of factors that might affect the disease-specific survival of patients with ESCC treated with NAC

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Age (years)			0.137			
< 70	1					
≥ 70	0.447	0.154–1.294				
Sex			0.744			
Female	1					
Male	1.222	0.367–4.069				
Body mass index (kg/m^2)			0.239			
< 18.5	1					
≥ 18.5	0.617	0.276–1.379				
Tumor location			0.266			
Upper, middle	1					
Lower	1.553	0.715–3.373				
Invasion depth			0.160			
cT1, 2	1					
cT3	1.809	0.791–4.138				
Lymph node metastasis			0.056			
Absent	1					
Present	7.027	0.953–51.841				
Clinical stage			0.016			0.032
cStage II	1			1		
cStage III, IVa	4.365	1.314–14.506		3.781	1.119–12.774	
Chemotherapy			0.949			
5-FU + cisplatin	1					
5-FU + nedaplatin	1.014	0.658–1.564				
SCC Ag			0.261			
< 1.5	1					
≥ 1.5	1.246	0.849–1.829				
CYFRA			0.407			
< 3.5	1					
≥ 3.5	1.192	0.787–1.807				
PNI			0.024			0.528
≥ 50	1			1		
< 50	2.411	1.124–5.168		1.298	0.578–2.916	
mGPS			0.960			
0	1					
1, 2	1.023	0.411–2.547				
NLR			0.124			
< 2.5	1					
≥ 2.5	1.829	0.847–3.950				
PLR			0.291			
< 150	1					
≥ 150	1.509	0.703–3.239				
PLR-CYFRA			0.023			0.030
< 237.6	1			1		
≥ 237.6	4.057	1.212–13.580		4.037	1.142–14.270	

CI, confidence interval; HR, hazard ratio.

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Table 5. Univariate and multivariate analyses of factors that might affect the pathological response in patients with ESCC treated with NAC

	Univariate analysis			Multivariate analysis		
	Pathological response, *n*					
	Grade < 2	Grade ≥ 2	*P*	OR	95% CI	*P*
Age (years)			0.064			
< 70	38	8				
≥ 70	12	8				
Sex			1.000			
Female	6	2				
Male	44	14				
Body mass index (kg/m^2)			0.524			
< 18.5	15	3				
≥ 18.5	35	13				
Tumor location			0.859			
Upper, middle	30	10				
Lower	20	6				
Invasion depth			0.199			
cT1, 2	19	9				
cT3	31	7				
Lymph node metastasis			0.167			
Absent	9	6				
Present	41	10				
Clinical stage			0.391			
cStage II	16	7				
cStage III, IVa	34	9				
Chemotherapy			0.496			
5-FU + cisplatin	39	14				
5-FU + nedaplatin	11	2				
SCC Ag			0.417			
< 1.5	32	12				
≥ 1.5	18	4				
CYFRA			0.162			
< 3.5	38	15				
≥ 3.5	12	1				
PNI			0.155			
≥ 50	31	13				
< 50	19	3				
mGPS			0.719			
0	41	12				
1, 2	9	4				
NLR			0.009			0.681
< 2.5	22	13		1		
≥ 2.5	28	3		1.627	0.159–16.642	
PLR			0.059			
< 150	24	12				
≥ 150	26	4				
PLR-CYFRA			< 0.001			0.002
< 237.6	8	13		1		
≥ 237.6	42	3		31.481	3.438–288.303	

CI, confidence interval; OR, odds ratio.

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environment.[21] Additionally, cytokines and chemokines released from platelets promote the infiltration of other immune cells, including neutrophils and lymphocytes, into the tumor stroma, which induces the progression of inflammation.[22] On the contrary, tumor markers are substances produced by tumor cells or by non-tumor cells in response to tumor cells that reflect the presence of tumors, tumor cell types, and tumor quantity.[23] Therefore, tumor markers directly reflect the disease activity of the tumor itself, and CYFRA is known to be a useful tumor marker in ESCC.[24, 25] Furthermore, CYFRA has been reported to predict the response to chemotherapy in patients with non-small cell lung cancer.[26, 27] On the other hand, it has been reported that other tumor markers such as SCC Ag and serum p53 antibody, as well as PET-CT scan after NAC are useful in predicting the effect of NAC in ESCC patients.[5, 28, 29] Consistent with PLR-CYFRA in our results, these markers were shown to be independent predictors for pathological response to NAC in surgical specimens. The reason why different markers became independent predictors between these studies and our study may be due to the differences in patient backgrounds and the NAC regimens used. Here, we showed that the value of PLR multiplied by CYFRA is a highly accurate predictor of chemotherapy efficacy and that pretreatment PLR-CYFRA might be an important biomarker for patients with ESCC who receive NAC. To our knowledge, this is the first report that demonstrates the utility of PLR in predicting the effects of NAC in ESCC. Several meta-analyses have reported the impact of PLR on the prognosis of patients with ESCC,[30–32] and therefore, PLR is an important indicator during ESCC treatment. However, these reports included patients with various treatment strategies, and consequently, the clinical impact of PLR on NAC (the standard treatment for patients with locally advanced resectable ESCC in Japan) response was unclear. Yang et al. reported that PLR was more useful than NLR and PNI in predicting prognosis and treatment responses in patients with nonmetastatic ESCC who received postoperative chemotherapy[10]; however, the inflammatory status of patients who received postoperative chemotherapy should differ from that of patients who received NAC because of the effects of surgery. Therefore, this study, which revealed the ability of PLR to predict the effects of NAC, presents a novel finding that is useful for ESCC treatment. We also showed that PLR-CYFRA was a useful prognostic factor for ESCC, and this was especially significant for DSS and RFS, but not for OS (Figs. 2d, e and f). This suggests that PLR-CYFRA may be more closely related to ESCC death, but it is not clear because there were only 7 patients who died of other diseases in this study. We acknowledge that this study has several limitations. First, this was a retrospective study with a small sample size, and therefore, a prospective study with a larger cohort is needed to validate the utility of PLR-CYFRA. Second, we did not evaluate the effect of NAC on metastatic lymph nodes, because the outcome of this study was a pathological response of the primary tumor, according to the Japanese Classification of Esophageal Cancer (11th edition).[11, 12] However, approximately 20% of the patients in this study had no clinical lymph node metastasis, and the pathological response was correlated significantly with prognosis, as shown in Fig. 2; thus, we regard the results of this study as reliable. In conclusion, pretreatment PLR-CYFRA was an independent predictor of the pathological response of patients with ESCC to NAC. According to these findings, we should consider more intensive NAC regimens for patients with ESCC with high pretreatment PLR-CYFRA, because patients with poor NAC responses also exhibit a poorer prognosis. We believe that a further prospective study of pretreatment PLR-CYFRA will lead to a novel and valuable biomarker for ESCC treatment.

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The authors declare no conflict of interest.

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