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Combined fibrinogen and neutrophil-lymphocyte ratio as a prognostic marker of advanced esophageal squamous cell carcinoma

Takashi Kijima,[1] Takaaki Arigami,[1,2] Yasuto Uchikado,[1] Yoshikazu Uenosono,[2] Yoshiaki Kita,[1] Tetsuhiro Owaki,[3] Shinichiro Mori,[1] Hiroshi Kurahara,[1] Yuko Kijima,[1] Hiroshi Okumura,[1] Kosei Maemura,[1] Sumiya Ishigami[1] and Shoji Natsugoe[1,2]

[1]Department of Digestive Surgery, Breast and Thyroid Surgery, Field of Oncology; [2]Molecular Frontier Surgery; [3]Education Center for Doctors in Remote Islands and Rural Areas, Course of Advanced Therapeutics, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan

Key words

Drug response, esophageal squamous cell carcinoma, fibrinogen, neutrophils, prognosis

Correspondence

Takashi Kijima, Department of Digestive Surgery, Breast and Thyroid Surgery, Field of Oncology, Kagoshima University Graduate School of Medical and Dental Sciences, 8-35-1 Sakuragaoka, Kagoshima 890-8520, Japan.
Tel: +81-99-275-5361; Fax: +81-99-265-7426;
E-mail: taka_msf73@yahoo.co.jp

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Patients with advanced esophageal squamous cell carcinoma (ESCC) is received chemoradiotherapy or chemotherapy for clinical management. However, it is difficult to predict tumor response and prognosis using blood markers before starting treatments. The purpose of this study was to investigate the pre-treatment plasma fibrinogen and neutrophil–lymphocyte ratio (NLR) in patients with advanced ESCC treated with chemoradiotherapy or chemotherapy, and to assess the clinical utility of a combined score using these blood markers, named as the F-NLR (fibrinogen and NLR) score, as a predictor of tumor response and prognosis. A total of 98 advanced ESCC patients, treated with chemoradiotherapy or chemotherapy, were classified into three groups: F-NLR score of 2, having both hyperfibrinogenemia (>400 mg/dL) and high NLR (>3.0), score of 1, one of these hematological abnormalities, and score of 0, having neither hyperfibrinogenemia nor high NLR. Fibrinogen and NLR were significantly higher in the progressive disease (PD) group than the non-PD group ($P = 0.0419$, and $P = 0.0001$, respectively). A significantly higher F-NLR score was found in the PD group than the non-PD group ($P = 0.0140$). Overall survival was significantly lower in patients with an F-NLR score of 2 than in those with an F-NLR score of 0 or 1 ($P < 0.0001$). Multivariate analysis showed that the F-NLR score was one of the independent prognostic factors ($P = 0.0081$). Our study demonstrates that the F-NLR score is promising as a predictive marker for therapeutic effects and prognosis in patients with advanced ESCC.

Esophageal cancer is one of the most aggressive carcinomas in many gastrointestinal tract cancers. Chemoradiotherapy has been recognized as an effective treatment for patients with esophageal cancer since the 1980s.[1–3] Ishida *et al.*[4] reported that concurrent chemoradiotherapy using 5-fluorouracil and cisplatin along with radiation therapy was suitable for the clinical treatment of patients with unresectable advanced esophageal squamous cell carcinoma (ESCC) in Japan. However, since the recurrence rate of ESCC is high, the prognosis remains unsatisfactory.[5] It is important to predict tumor response to chemoradiotherapy or chemotherapy and prognosis using several indicators before starting these treatments. To date, many investigators have demonstrated several potential blood markers for predicting disease recurrence after surgery, tumor response to chemoradiotherapy or chemotherapy, and prognosis in several malignancies including ESCC.[6–13] The Glasgow Prognostic Score (GPS) consists of C-reactive protein (CRP) and serum albumin. Many investigators have reported the clinical impact of GPS as a predictive marker of prognosis in patients with various malignancies.[14] Recently, the GPS was modified (mGPS) regarding cut-off values of CRP and albumin. The mGPS score has been introduced as a new predictive marker of disease outcomes.[15,16] However, there are few useful predictive markers with the exception of GPS. We focused on the plasma fibrinogen and Neutrophil-lymphocyte ratio (NLR) and reported the clinical usefulness of these combined markers in patients with surgery alone for ESCC.[17] We have never assessed plasma fibrinogen and NLR in patients with advanced ESCC treated with chemoradiotherapy or chemotherapy.

Fibrinogen is a pro-inflammatory protein produced in the liver via stimulation of interleukin (IL)-6 and IL-1β.[18,19] Fibrinogen is transformed to fibrin by activated thrombin in the coagulation cascade, which plays an important role in the malignant process of tumor progression and metastasis.[20,21] Recent studies demonstrate that plasma fibrinogen levels are associated with tumor development in several types of malignancies.[6,22–24] Similarly, NLR has been focused on as a prognostic factor in patients with many malignancies.[9,25–27] Neutrophils promote tumor development and progression by providing an adequate tumor microenvironment via the production of cytokines and chemokines.[28] However, there have been no studies regarding a combined analysis based on plasma fibrinogen and NLR in patients

with advanced ESCC treated with chemoradiotherapy or chemotherapy.

In this study, we investigated plasma fibrinogen, NLR, CRP, and albumin levels between responders and non-responders to chemoradiotherapy or chemotherapy in patients with advanced ESCC. Furthermore, we assessed the clinical utility of a combined score using cut-off values of fibrinogen and NLR (F-NLR score) as a predictor of tumor response and prognosis.

Materials and Methods

Patients. One hundred and nine patients with ESCC treated with chemoradiotherapy or chemotherapy at Kagoshima University Hospital between 2011 and 2014 were retrospectively analyzed. The exclusion criteria of this study were as follows: patients without detailed post-therapeutic information (n = 10) and patients with unknown fibrinogen concentrations (n = 1). Finally, 98 patients (86 men and 12 women; age range, 46–86 years; average, 64.9 years) with ESCC were enrolled in this study (Fig. 1). All patients were evaluated by blood examinations, esophagogastroduodenoscopy, fluoroscopy, endoscopic ultrasonography, and computed tomography (CT) before starting treatment. To date, we have demonstrated the clinical usefulness of endoscopic ultrasonography for predicting lymph node metastasis in patients with ESCC.[29,30] According to these published reports, lymph nodes were classified into three grades (grade 1, grade 2, and grade 3). Lymph nodes with grade 2 or grade 3 were determined as a metastatic status in the present study. Patients were classified and staged based on the 7th International Union Against Cancer (UICC) criteria of tumor-node-metastasis (TNM) classification for esophageal carcinoma.[31] Clinicopathological features are shown in Table 1. In the present study, we defined advanced ESCC as a tumor status of clinical stage III or IV. The number of patients in clinical stage III and IV was 48 and 50, respectively. Among 50 patients with stage IV disease, distant lymph node metastases were identified in 36 patients. Eight and 28 patients had metastatic lesions in para-aortic lymph nodes and supraclavicular lymph nodes, respectively. Liver metastasis was found in seven patients, bone in five patients, and lung in two patients. In this study, resectable ESCC was defined as clinical stage III and T1–3 tumors (n = 31). Two therapeutic strategies were planned in resectable group. From 2011 to 2012, patients with ≥4 metastatic lymph nodes were treated with neoadjuvant chemoradiotherapy. From 2013, neoadjuvant chemotherapy or neoadjuvant chemoradiotherapy were selected based on randomized control trial. On the other hand, unresectable ESCC was defined as clinical stage IV or T4 tumors (n = 67). In the unresectable group, patients with distant metastasis or para-aortic lymph node metastasis were treated with chemotherapy. Patients having cT4 tumors without distant metastasis or para-aortic lymph node metastasis were treated with chemoradiotherapy.

The study received approval from the Ethics Committee of Kagoshima University and all patients provided written informed consent for the use and publication of their information.

Treatment and assessment of therapeutic effect. Seventy-nine of 98 patients received chemoradiotherapy. In chemoradiotherapy, the chemotherapy consisted of two different regimens as follows: a low-dose FP regimen using 5-fluorouracil (350 mg/body over 24 h) and cisplatin (7 mg/body over 2 h) or a DCF regimen using docetaxel (60 mg/m^2 over 2 h), cisplatin (60 mg/m^2 over 2 h), and 5-fluorouracil (350 mg/m^2 over 24 h). Fifty-nine and 20 patients received a low-dose FP regimen and a DCF regimen, respectively. A total dose of concurrent fractionated radiation for neoadjuvant and definitive chemoradiotherapy in the same period was 40 Gy and 60 Gy, respectively.[1] Twenty-eight and 51 patients received neoadjuvant chemoradiotherapy and definitive chemoradiotherapy, respectively. Nineteen patients received chemotherapy alone. Chemotherapy was intravenously performed by a DCF regimen using docetaxel (60 mg/m^2 over 1.5 h), cisplatin (70 mg/m^2 over 3 h), and 5-fluorouracil (700 mg/m^2 over 24 h) or a modified DCF regimen using docetaxel (60 mg/m^2 over 2 h), cisplatin (6 mg/m^2 over 2 h), and 5-fluorouracil (350 mg/m^2 over 24 h).

Clinical responses were evaluated by CT, 1 month after chemoradiotherapy and two cycles of chemotherapy. Tumor response was assessed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).[32] Accordingly, tumor response was classified into four groups as follows; complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD).

Clinical follow-up. All patients were followed-up by routine blood tests including tumor marker studies (carcinoembryonic antigen, SCC antigen, and p53), CT every 3 months, and endoscopy 6–12 months after discharge. The median follow-up period in all patients was 15.4 months (range, 1.5–53.5 months). The median follow-up period in surviving patients was 29.1 months (range, 16.3–53.5 months).

Blood assessment for determination of fibrinogen, NLR, CRP, and albumin. Blood samples were obtained within the 2 weeks before the start of treatment. Plasma fibrinogen concentrations

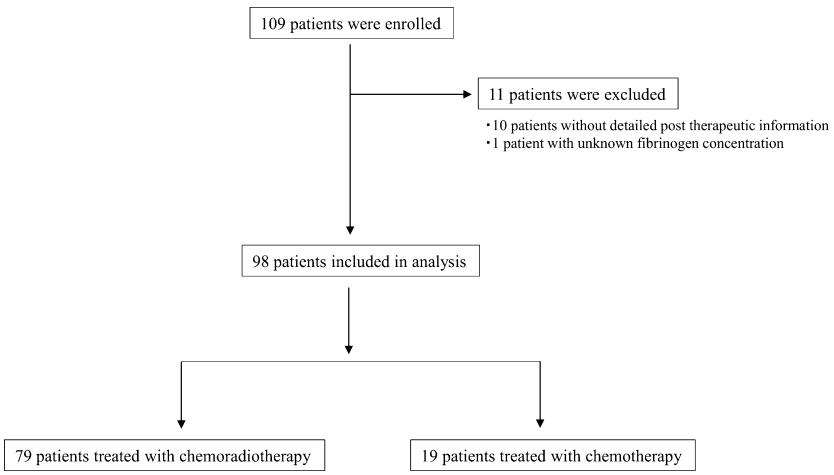

Fig. 1. In total, 109 patients with advanced esophageal squamous cell carcinoma (ESCC) treated with chemoradiotherapy or chemotherapy were enrolled in this study. Eleven patients were excluded from this study: 10 without detailed post-therapeutic information, and one with an unknown fibrinogen concentration. Finally, 79 patients with chemoradiotherapy and 19 patients with chemotherapy were assessed in the analysis.

Table 1. Clinicopathological characteristics of 98 patients with advanced esophageal squamous cell carcinoma (*n* = 98)

Characteristic	*n*
Sex (male/female)	86/12
Age (range)	64.9 (46–86)
Tumor location	
Upper/Middle/Lower	22/59/17
Depth of tumor invasion	
T1/T2/T3/T4	4/2/56/36
Lymph node metastasis	
N1/N2/N3	22/34/42
cStage	
III/IV	48/50
Treatment	
Chemoradiotherapy (+Surgery)	79 (20)
Chemotherapy (+Surgery)	19 (4)
Tumor response	
Non-PD (CR-PR-SD)	60 (7/34/19)
PD	38

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

were assayed by the Clauss method using a STA-R coagulation analyzer (Roche Diagnostics K.K., Tokyo, Japan). Neutrophils and lymphocytes were counted using the XE-2100 automated hematology analyzer (Sysmex Co., Kobe, Japan). Then, the NLR was indicated as the neutrophil count divided by the lymphocyte count. CRP and albumin levels were determined by a JCA-BM automatic analyzer (JEL Ltd., Tokyo, Japan).

Grading system for F-NLR score and GPS. The cut-off value of plasma fibrinogen concentrations was set at 400 mg/dL based on previous published reports.[17,33,34] On the other hand, we set the cut-off value for the NLR at 3.0 based on previous published reports.[26,27,35] The F-NLR score was classified into three groups based on each cut-off value of plasma fibrinogen and NLR as follows; F-NLR score of 2: both hyperfibrinogenemia (>400 mg/dL) and high NLR (>3.0), F-NLR score of 1: one of these hematological abnormalities, and F-NLR score of 0: neither hyperfibrinogenemia nor high NLR. GPS was classified into three groups, as previously described; GPS of 2: both an elevated CRP (>1.0 mg/dL) and hypoalbuminemia (<3.5 g/dL), GPS of 1: one of these hematological abnormalities, and GPS of 0: neither an elevated CRP nor hypoalbuminemia.[14]

Statistical analysis. The Wilcoxon rank sum test was used to evaluate differences in the relationship among fibrinogen, NLR, CRP, or albumin and tumor response. Overall survival curves were calculated using the Kaplan–Meier method and prognostic differences were determined by the log-rank test. Prognostic factors were assessed using univariate and multivariate analyses (Cox proportional hazard regression model). All statistical analyses were done using SAS statistical software (SAS Institute Inc., Cary, NC, USA). A P-value of < 0.05 was considered statistically significant.

Results

Tumor response to chemoradiotherapy or chemotherapy and additional surgery. Seven, 34, 19, and 38 patients had CR, PR, SD, and PD as a tumor response, respectively. Consequently, 60 and 38 patients were grouped as non-PD and PD, respectively. The disease control rate was 61.2% (60/98). Additional esophagectomy with lymphadenectomy was performed in 21 patients with non-PD and three patients with PD. The R0 resection rate was 91.7% (22/24).

Correlation between tumor response and fibrinogen, NLR, CRP, or albumin. Plasma fibrinogen concentrations range from 236 to 789 mg/dL in 98 patients with ESCC. The mean fibrinogen concentration (±SD) was 448.2 ± 122.2 mg/dL in all patients. The mean fibrinogen concentrations (±SD) for patients in the PD and non-PD groups were 481.0 ± 126.5 and 427.5 ± 115.7 mg/dL, respectively (Fig. 2a). Fibrinogen was significantly higher in the PD group than the non-PD group ($P = 0.0419$). The mean NLR (±SD) was 3.3 ± 2.8 in all patients (range, 0.57–22.2). The mean NLR (±SD) in patients in the PD and non-PD groups was 4.4 ± 3.8 and 2.5 ± 1.5, respectively (Fig. 2b). NLR was significantly higher in the PD group than the non-PD group ($P = 0.0001$).

The mean CRP (±SD) values in patients with PD and non-PD were 2.0 ± 3.1 and 1.0 ± 2.7 mg/dL, respectively (Fig. 2c). CRP was significantly higher in PD group than non-PD group ($P = 0.0254$). The mean albumin (±SD) values in patients with PD and non-PD were 3.6 ± 0.5 and 3.9 ± 0.4 mg/dL, respectively (Fig. 2d). Accordingly, albumin was significantly lower in PD group than non-PD group ($P = 0.0305$).

Prognostic analysis based on fibrinogen or NLR levels. Based on the cut-off value of plasma fibrinogen concentration, 63 and 35 patients were classified into two groups at high (>400 mg/dL) and low (≤400 mg/dL) fibrinogen levels, respectively. Furthermore, 38 and 60 patients had high (>3.0) and low (≤3.0) NLR levels, respectively, according to the determined cut-off value for the NLR. Patients with high fibrinogen and NLR levels had a significantly worse prognosis than those with low fibrinogen and NLR levels ($P = 0.0242$ and $P = 0.0019$, respectively; Fig. 3).

Correlation between tumor response and F-NLR score and GPS. According to the grading system of the F-NLR score, 25 (25.5%), 45 (45.9%), and 28 (28.6%) patients had an F-NLR score of 0, 1, and 2 respectively. An F-NLR score of 0, 1, and 2 was identified in six (15.8%), 15 (39.5%), and 17 (44.7%) of the 38 patients with PD, respectively (Table 2). In the 60 patients with non-PD, 19 (31.7%), 30 (50.0%), and 11 (18.3%) had an F-NLR score of 0, 1, 2 respectively (Table 2). A high F-NLR score had a significantly closer relationship in patients with PD, than those with non-PD ($P = 0.0140$).

Next, the GPS classification showed 54 (55%), 30 (31%), and 14 (14%) patients with a GPS of 0, 1, and 2, respectively. A GPS of 0, 1, and 2 was identified in 16 (42.1%), 12 (31.6%), and 10 (26.3%) of the 38 patients with PD, respectively (Table 2). In the 60 patients with non-PD, 38 (63.3%), 18 (30.0%), and four (6.7%) had a GPS of 0, 1, and 2, respectively (Table 2). Patients with PD had a significantly higher GPS than those with non-PD ($P = 0.0165$).

Prognostic analysis based on F-NLR score or GPS. The median survival of patients with F-NLR scores of 0–1 and 2 was 16.9 and 8.7 months, respectively (Fig. 4a). Prognosis was significantly worse in patients with an F-NLR score of 2, than those with an F-NLR score of 0–1 ($P < 0.0001$). Similarly, the median survival of patients at a GPS of 0–1 and 2 was 13.9 and 4.4 months, respectively (Fig. 4b). Survival rate was significantly lower in patients with a GPS of 2 than those with a GPS of 0–1 ($P < 0.0001$).

Univariate analysis demonstrated clinical stage, treatment, F-NLR score, and GPS as independent prognostic factors ($P = 0.0157$, $P = 0.0177$, $P = 0.0001$, and $P = 0.0002$, respectively) (Table 3). F-NLR score, and GPS were selected

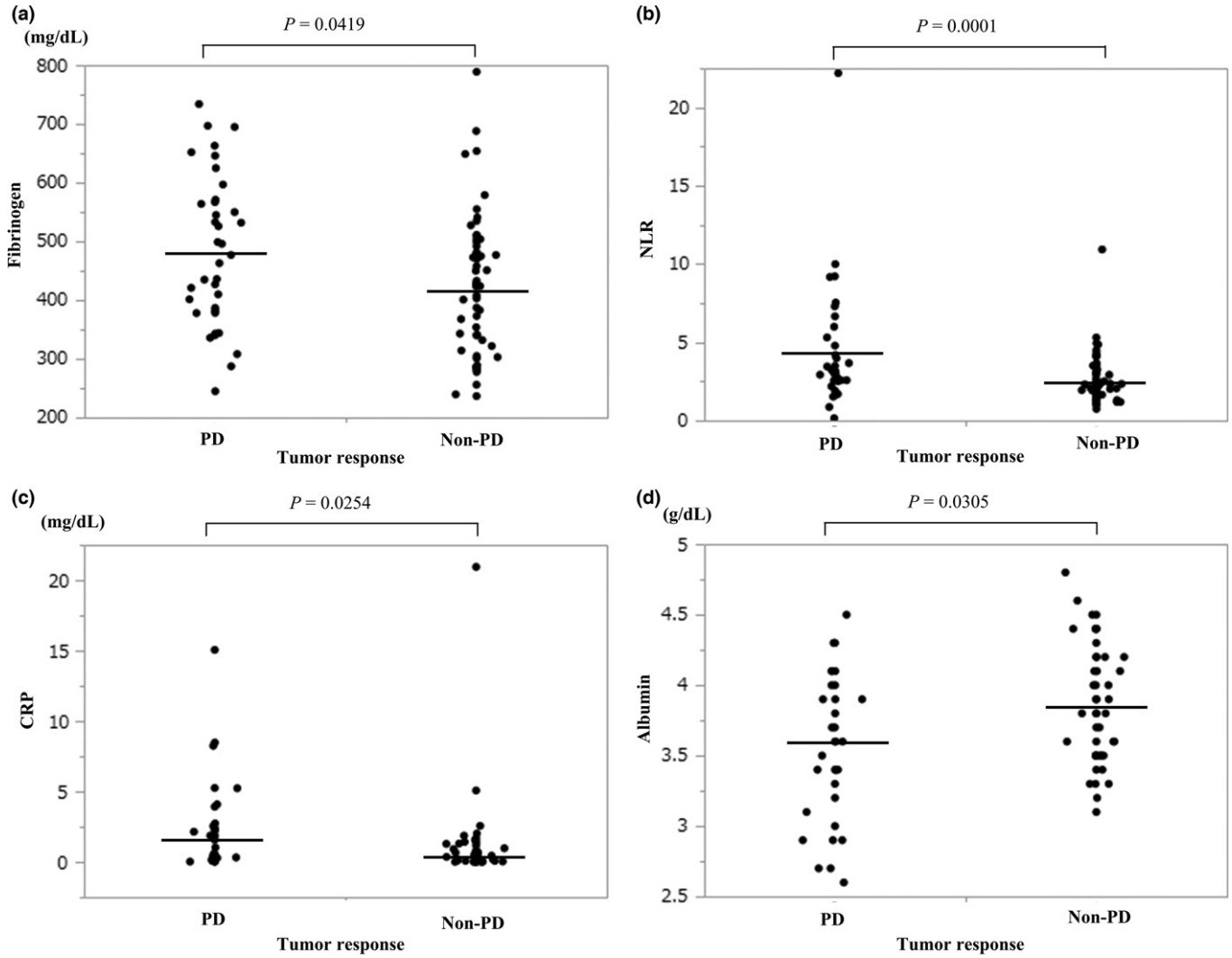

Fig. 2. Relationship between tumor response and value of (a) fibrinogen, (b) neutrophil–lymphocyte ratio (NLR), (c) C-reactive protein (CRP), or (d) albumin. Horizontal bars indicate mean value of each blood marker.

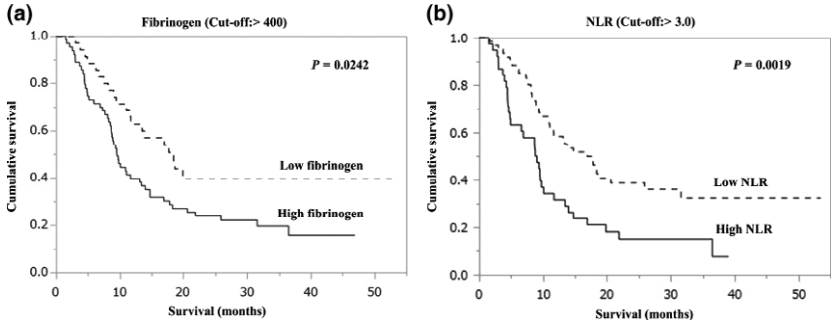

Fig. 3. Kaplan–Meier survival curves according to (a) plasma fibrinogen level and (b) neutrophil–lymphocyte ratio (NLR).

as independent prognostic factors in the multivariate analysis ($P = 0.0081$ and $P = 0.0086$, respectively) (Table 3).

Discussion

In this study, we assessed the clinical significance of pre-treatment fibrinogen and NLR levels in patients with advanced ESCC treated with chemoradiotherapy or chemotherapy. Both fibrinogen and NLR have been known to be associated with tumor progression and metastatic developments in patients with various malignancies including ESCC.[6,10,22–25,36] Interestingly, several investigators have demonstrated hyperfibrinogenemia and elevated NLR as a predictor of poor therapeutic response in blood analysis before starting treatment.[8,9,26,33] In

Table 2. Relationship between clinicopathological characteristics and F-NLR score or GPS (n = 98)

Factors	F-NLR score (%)				GPS (%)			
	0 (n = 25)	1 (n = 45)	2 (n = 28)	P-value	0 (n = 54)	1 (n = 30)	2 (n = 14)	P-value
Sex								
Male	22 (88.0)	39 (86.7)	25 (89.3)	0.9455	48 (88.9)	26 (86.7)	12 (85.6)	0.9268
Female	3 (12.0)	6 (13.3)	3 (10.7)		6 (11.1)	4 (13.3)	2 (14.4)	
Age (year)								
<70	17 (68.0)	32 (71.1)	19 (67.9)	0.9434	42 (77.8)	17 (56.7)	9 (64.3)	0.1196
≥70	8 (32.0)	13 (28.9)	9 (32.1)		12 (22.2)	13 (43.3)	5 (35.7)	
Tumor location								
Upper	3 (12.0)	11 (24.4)	8 (28.6)	0.4042	12 (22.2)	5 (16.7)	5 (35.7)	0.3775
Middle	19 (76.0)	26 (57.8)	14 (50.0)		35 (64.8)	17 (56.7)	7 (50.0)	
Lower	3 (12.0)	8 (17.8)	6 (21.4)		7 (13.0)	8 (26.7)	2 (14.3)	
Depth of tumor invasion								
T1–T3	21 (84.0)	21 (46.7)	20 (71.4)	0.0046	38 (70.4)	19 (63.3)	5 (35.7)	0.0565
T4	4 (16.0)	24 (53.3)	8 (28.6)		16 (29.6)	11 (36.7)	9 (64.3)	
Lymph node metastasis								
N1–N2	16 (64.0)	27 (60.0)	16 (57.1)	0.8778	33 (61.1)	20 (66.7)	6 (42.9)	0.3225
N3	9 (36.0)	18 (40.0)	12 (42.9)		21 (38.9)	10 (33.3)	8 (57.1)	
Stage								
III	14 (56.0)	24 (53.3)	10 (35.7)	0.2419	28 (51.9)	15 (50.0)	5 (35.7)	0.5510
IV	11 (44.0)	21 (46.7)	18 (64.3)		26 (48.1)	15 (50.0)	9 (64.3)	
Treatment								
Chemoradiotherapy	21 (84.0)	37 (82.2)	21 (75.0)	0.6628	47 (87.0)	22 (73.3)	9 (64.3)	0.1010
Chemotherapy	4 (16.0)	8 (17.8)	7 (25.0)		7 (13.0)	8 (26.7)	5 (35.7)	
Tumor response								
Non-PD(CR-PR-SD)	19 (76.0)	30 (66.7)	11 (39.3)	0.0140	38 (70.4)	18 (60.0)	4 (28.6)	0.0165
PD	6 (24.0)	15 (33.3)	17 (60.7)		16 (29.6)	12 (40.0)	10 (71.4)	

F-NLR Score, fibrinogen and neutrophil-lymphocyte ratio score; GPS, Glasgow prognostic score; PD, progressive disease.

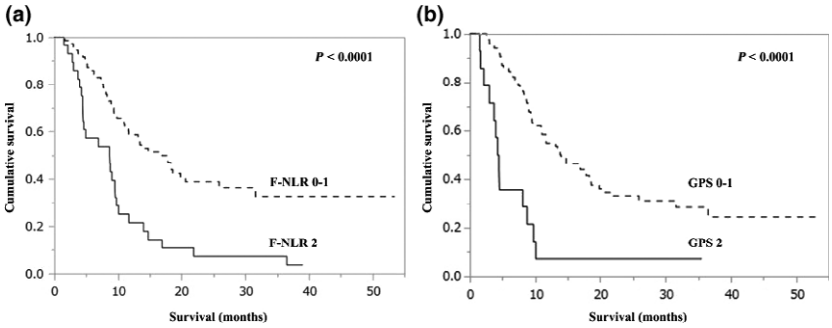

Fig. 4. Kaplan–Meier survival curves according to (a) fibrinogen and neutrophil–lymphocyte ratio (F-NLR) score and (b) Glasgow Prognostic Score (GPS).

the present study, the blood levels of fibrinogen and NLR were significantly higher in patients in the PD group than those in the non-PD group. These findings indicate that fibrinogen and NLR are one of the promising markers for predicting tumor response to the initial chemoradiotherapy or chemotherapy in patients with advanced ESCC. Furthermore, hyperfibrinogenemia (>400 mg/dL) and high NLR (>3.0) significantly correlated with a worse prognosis in this study (P = 0.0242 and P = 0.0019, respectively). According to previous published reports, fibrinogen and NLR are potential predictive markers for prognosis in untreated patients in several resectable cancers, including ESCC.[6,22,24,25,36–38] However, we simultaneously investigated fibrinogen and NLR to assess the relationship between the values of these blood markers and prognosis in patients with advanced ESCC treated with chemoradiotherapy or chemotherapy. To the best of our knowledge, this is the first report to demonstrate the clinical impact of fibrinogen and NLR in patients with ESCC treated with chemoradiotherapy or chemotherapy due to advanced tumor stage.

The most attractive issue of the present study is that we assess the clinical significance of the F-NLR score, which consisted of the plasma fibrinogen level and NLR, in patients with advanced ESCC treated with chemoradiotherapy or chemotherapy. We had already demonstrated that F-NLR score is a useful blood predictor for tumor progression and prognosis in ESCC patients without preoperative treatment.[17] In this study, surprisingly, 17 patients (44.7%) had an F-NLR score of 2 among the 38 patients in the PD group and 11 patients (18.3%) had an F-NLR score of 2 among the 60 patients in the non-PD group (Table 2). These findings indicate a close relationship between F-NLR score and therapeutic effect. Furthermore, this study showed that the median survival times of patients with F-NLR scores of 0–1 and 2 were 16.9 and 8.7 months, respectively. The survival rate was significantly lower in patients with an F-NLR score of 2 than in those with

Table 3. Univariate and multivariate survival analyses

Independent factor	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI	*P*-value
Gender						
Male/Female	1.03	0.52–2.33	0.9419			
Age						
≥70/<70	1.03	0.61–1.70	0.9039			
cStage						
3/4	1.78	1.12–2.89	0.0157	1.29	0.78–2.16	0.3180
Tumor marker						
CEA	0.75	0.36–1.40	0.3872			
SCC	1.09	0.66–1.83	0.7494			
Treatment						
Chemoradiotherapy/ Chemotherapy	2.01	1.14–3.38	0.0177	1.71	0.94–2.97	0.0785
F-NLR score						
0–1/2	2.74	1.66–4.43	0.0001	2.10	1.22–3.54	0.0081
GPS						
0–1/2	3.78	1.96–6.80	0.0002	2.60	1.29–4.92	0.0086

CEA, carcinoembryonic antigen; CI, confidence interval; F-NLR score, fibrinogen and neutrophil-lymphocyte ratio score; GPS, Glasgow prognostic score; SCC, squamous cell carcinoma antigen.

an F-NLR score of 0–1 ($P < 0.0001$). These results suggest that patients with an F-NLR score of 2 exhibit aggressive tumor behavior due to the resistance to chemoradiotherapy or chemotherapy. Here, we assessed the relationship between F-NLR score and tumor response in therapeutic modalities. In chemoradiotherapy group ($n = 79$), F-NLR score was significantly correlated with tumor response ($P = 0.0062$, data not shown). However, tumor response in chemotherapy group was not significantly associated with F-NLR score ($P = 0.9169$, data not shown). These inconsistent results may depend on the small patient sample in chemotherapy group ($n = 19$). It is clinically difficult to discriminate responder from non-responder before starting chemoradiotherapy or chemotherapy. Additionally, few candidate blood markers for predicting tumor response and prognosis are presently available in patients with advanced ESCC. It is important to solve these key issues in clinical management. Consequently, the F-NLR score may be focused on as a promising indicator for considering the therapeutic strategy in patients with unresectable advanced ESCC. Since the F-NLR score, from fibrinogen and the NLR, is determined by conventional blood examinations, a blood approach using the F-NLR score is a simple and cost-effective method.

We investigated not only fibrinogen and NLR but also CRP and albumin in the present study. CRP and albumin, underlying the GPS, have been recognized as a prognostic marker in patients with many malignancies.[14] Kimura *et al.*,[13] in a study of 142 esophageal cancer patients with stage III and IV receiving chemoradiotherapy, reported that GPS may be a good predictor of chemoradiotherapeutic responsiveness and a prognostic indicator for progression-free and disease-specific survival in patients with advanced ESCC. In this study, a high GPS was also significantly associated with a worse tumor response and prognosis. Unfortunately, mGPS was not significantly associated with tumor response ($P = 0.3514$, data not shown). Therefore, we adopted GPS rather than mGPS as a predictor of tumor response in the present study. Here, we compared the F-NLR score with the GPS to assess the clinical significance of these scores. Univariate and multivariate analysis of survival showed that F-NLR score, and GPS were independent prognostic factors in this study. This finding indicates that F-NLR score, as well as GPS, has a clinical utility for predicting prognosis in patients with advanced ESCC treated with chemoradiotherapy or chemotherapy.

There are some limitations in this study. First, this retrospective study was planned by a single institution. Next, 98 patients with ESCC were enrolled in the present study and the sample size may be insufficient to strengthen our results. Accordingly, further, multicenter validation studies are required to confirm our hypothesis. However, the clinical impact of the F-NLR score has shown that it may have a prominent role as a preliminary data.

In conclusion, we demonstrated that F-NLR score, as well as GPS, has clinical potential as a predictive marker for tumor response to chemoradiotherapy or chemotherapy and prognosis in patients with advanced ESCC. The F-NLR score may serve as an economical biomarker for determining the therapeutic plan in patients with advanced ESCC.

Disclosure Statement

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