Ann Surg Oncol (2019) 26:190–199
https://doi.org/10.1245/s10434-018-6944-1

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

The Predictive Value of Pretreatment Neutrophil-To-Lymphocyte Ratio in Esophageal Squamous Cell Carcinoma

Miao-Fen Chen, MD, PhD[1,2], Ping-Tsung Chen, MD[2,3], Feng-Che Kuan, MD[2,3], and Wen-Cheng Chen, MD[1,2]

[1]Department of Radiation Oncology, Chang Gung Memorial Hospital, Chiayi, Taiwan; [2]College of Medicine, Chang Gung University, Taoyuan, Taiwan; [3]Department of Hematology and Oncology, Chang Gung Memorial Hospital, Chiayi, Taiwan

ABSTRACT

Background. The neutrophil-to-lymphocyte ratio (NLR) has been reported to be both a prognostic biomarker for cancer and associated with inflammation, but its predictive role in tumor immunity is not clear. The present study examined the correlations of the NLR and immune suppression with the prognoses in patients with esophageal squamous cell carcinoma (ESCC).

Methods. We performed a retrospective review of 1168 patients who were newly diagnosed with stage T1N(+) and T2–T4 ESCC at our hospital. The NLR of each ESCC patient prior to treatment was calculated, and the associations of the NLR with various clinicopathological parameters and prognoses were then examined. In addition, correlations of the proportion of myeloid-derived suppressor cells (MDSCs) and level of interleukin (IL)-6 with the NLR were assessed in 242 ESCC patients.

Results. An elevated NLR was significantly correlated with advanced-stage disease and reduced overall survival (OS) of ESCC patients. Furthermore, the levels of IL-6 in tumors and MDSCs in the peripheral circulation were significantly correlated with the prognoses of ESCC, and the NLR was positively correlated with MDSC levels in the circulation and IL-6 staining intensity in tumor specimens. Moreover, a high NLR was significantly associated with reduced OS in the 926 patients treated with concomitant chemoradiotherapy, but not in the 242 patients who underwent surgical intervention.

Conclusion. The NLR may represent a clinically useful biomarker to guide ESCC treatment decisions. Patients with a higher NLR may be an optimal subgroup for IL-6- and MDSC-targeted therapy.

Esophageal cancer remains an aggressive disease, characterized by a high recurrence rate and poor overall survival (OS).[1] Surgery has been the main treatment option for esophageal cancer in the past.[2] The postoperative mortality rate[3] and high rate of relapse after esophagectomy have prompted investigation of multidisciplinary management, such as concomitant chemoradiotherapy (CCRT) with or without surgery.[4,5] Factors involved in the treatment decision include baseline clinical stage, location of the primary tumor, and histology. Furthermore, the prognoses of these patients have been shown to depend on patient characteristics, tumor status, extent of surgical resection, and response to CCRT.[6,7] Thus, identification of prognostic factors is critical for estimating the prognosis and for selecting appropriate treatment strategies.

Systemic inflammation is a recognized characteristic of malignancy,[8] and numerous inflammatory markers have been investigated as prognostic indicators for cancer patients.[9] Host inflammatory responses also play an important role in tumor development and progression.[10] The neutrophil-to-lymphocyte ratio (NLR) is an inflammatory- and immunologically-based index.[11,12] A change in the NLR may reflect broader changes in the tumor microenvironment,[13] and an elevated NLR in many solid tumors has been associated with reduced survival.[13–15]

Electronic supplementary material The online version of this article (https://doi.org/10.1245/s10434-018-6944-1) contains supplementary material, which is available to authorized users.

Miao-Fen Chen and Ping-Tsung Chen contributed equally to this work.

First Received: 4 June 2018;
Published Online: 25 October 2018

M.-F. Chen, MD, PhD
e-mail: miaofen@adm.cgmh.org.tw

However, the predictive value of the NLR in the immune and treatment responses of esophageal cancer is still unclear. Esophageal cancer exists as two distinct histological types: esophageal squamous cell carcinoma (ESCC) and adenocarcinoma. More than 90% of patients with esophageal cancer in our hospital have ESCC. Myeloid-derived suppressor cells (MDSCs) and a subset of cytokines have been reported to induce an immunosuppressive tumor microenvironment to promote cancer metastasis.[16,17] We previously reported that interleukin (IL)-6 plays an important role in the induction of MDSCs and is significantly associated with a poor prognosis in patients with ESCC.[18,19] In addition, IL-6 is a cytokine that can elicit neutrophil proliferation, thereby increasing the NLR[20] in some cancers. In the present study, we determined the predictive role of an elevated NLR in the prognosis of patients with ESCC, and its relationship with the levels of IL-6 and circulating MDSCs in this population group.

MATERIALS AND METHODS

Study Population and Study Design

The data were sourced from our Hospital Cancer Registry and the death registration (CGRD) in this study. CGRD is a high-quality cancer registry that provides sufficient information regarding individual demographics, disease stage, tumor histology, and primary treatment details. This study adhered to strict confidentiality guidelines and was approved by the Institutional Review Board of our hospital. From the database, we included patients who were newly diagnosed with esophageal cancer, since 1 January 2007, and all medical records of the esophageal cancer cohort were extracted and analyzed. Patients with other cancer diagnoses prior to the first esophageal cancer diagnosis, those who received only supportive treatment in the CGRD records, and those who had no complete blood count data pretreatment were excluded from this study. A total of 1168 patients with a histologically confirmed diagnosis of ESCC and clinical stage T1N(+) or T2–T4 were enrolled in our study. The curative treatment for T1N(+) or T2–T4 esophageal cancer was in accordance with the guidelines proposed by the oncology team at our hospital. Surgery was considered for all physiologically fit patients with localized, resectable esophageal cancer. If surgery was contraindicated or refused by the patient, CCRT with a radiotherapy dose of 40–66 Gy was administered (see Table 1 for the clinical and treatment characteristics of these patients). Hematological parameters were analyzed using a hematology analyser (Sysmex XE-2100; Sysmex Corporation, Kobe, Japan). The NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. In addition, 242 ESCC patients enrolled in the study had available data regarding IL-6 levels and/or the pe of MDSCs in the peripheral circulation. To assess the predictive value of the NLR, NLR was redefined as a binary variable by finding the value from a receiver operating characteristic (ROC) curve that maximized the percentage correctly classified for predicting the survival of these 242 ESCC patients. The optimal cut-off for NLR was 3 (59.7% sensitivity and 59% specificity; $p = 0.037$). Accordingly, all ESCC patients were divided into two groups according to the pretreatment NLR: the high (≥ 3) and low (< 3) NLR groups.

TABLE 1 Characteristics of T1N(+) T2–T4 ESCC patients with curative-intent treatment

	No. of patients		*p* value
	NLR < 3	NLR ≥ 3	
No. of patients	524	644	
Age, years			
< 50	162	182	0.429
50–64	263	346	
> 64	99	116	
Sex			
Female	23	32	0.642
Male	501	612	
Tumor stage			< 0.001*
$\leq$ T2	74	44	
T3–T4	450	600	
Tx policy			< 0.001*
Definite CCRT	387	539	
Surgery $\pm$ Tx[a]	137	105	
Distant metastasis			< 0.001*
No	382	411	
Yes	142	233	
Status			< 0.001*
Alive	130	95	
Dead	394	549	

ESCC esophageal squamous cell carcinoma, *NLR* neutrophil-to-lymphocyte ratio, *CCRT* concomitant chemoradiotherapy, *Tx* treatment

*Statistical significance ($p < 0.05$)

[a]Neoadjuvant/adjuvant treatment

Immunohistochemical Staining

Formalin-fixed and paraffin-embedded tissues collected at diagnosis from 216 patients with ESCC who completed curative treatment were subjected to immunohistochemical (IHC) analysis (Table 3). The IHC data were assessed using the semiquantitative immunoreactive score, and positive staining was defined as an immunoreactive score ≥ 2.[18] The main endpoints were OS, disease-specific

survival, and pathological complete response (pCR). A pCR was defined as the absence of residual invasive tumor in the surgical specimen in patients undergoing surgical intervention.

Myeloid-Derived Suppressor Cell Isolation, Flow Cytometry, and Enzyme-Linked Immunosorbent Assay of Interleukin (IL)-6 Levels

Ninety-four ESCC patients received complete staging, none of whom had been treated with chemotherapy, radiotherapy, or surgery prior to sampling (electronic supplementary Table 1). The human MDSC subset characterized as CD11b + CD33 + HLA-DR− was sorted from the peripheral blood (details are described in the electronic supplementary Methods).

Statistical Analysis

The Kaplan–Meier method was used to plot survival curves, and the log-rank test was used to determine differences in the survival curves between the two groups. The Cox proportional hazard model was used to compute hazard ratios with 95% confidence intervals after adjustment for esophageal cancer treatment and clinical characteristics. All analyses were conducted using SAS statistical software, version 9.2 (SAS Institute, Cary, NC, USA).

RESULTS

Correlations between the Baseline Neutrophil-to-Lymphocyte Ratio (NLR) and Clinicopathological Characteristics of Esophageal Squamous Cell Carcinoma Patients

A total of 1168 patients met the inclusion criteria and were subsequently selected for this study (Tables 1, 2). Most of the patients were male (n = 1113, 95%), and $>$ 80% of patients were $<$ 65 years of age at diagnosis. There were 72 (6%) cases with stage I–II disease, 721 (62%) cases with stage III disease, and 375 (32%) cases with stage IV disease. Of these patients, 242 (20%) received surgery with or without (neo-)adjuvant treatment, while the remaining patients received radiotherapy and chemotherapy. The pretreatment NLR was calculated as the ratio of the absolute neutrophil to lymphocyte count, and the median pretreatment NLR of the overall cohort was 3.2, ranging from 0.72 to 68.76. At baseline, 644 (55%) patients had a high NLR ($\geq$ 3) and 524 (45%) patients had an NLR $<$ 3. The relationships between clinicopathological variables and the pretreatment NLR are shown in Tables 1 and 2 and Fig. 1a. A high NLR at baseline was significantly associated with an advanced clinical stage ($p < 0.001$) and a higher risk of death during follow-up ($p < 0.001$). Squamous cell carcinoma antigen (SCCA) and carcinoembryonic antigen (CEA) are the most widely used tumor markers in various types of cancer. In the present study, 302 and 247 enrolled patients had available data regarding the levels of SCCA and CEA, respectively. Electronic supplementary Table 2 demonstrates that there was a positive correlation between SCCA and NLR ($p \leq 0.001$), but not for CEA. To further examine whether the pretreatment NLR was associated with the outcomes of ESCC patients after curative treatment, Kaplan–Meier survival analysis was used to compare the low and high NLR subgroups. Patients with a high pretreatment NLR had a shorter median OS ($p < 0.001$) (Fig. 1b). Furthermore, a high NLR was significantly associated with reduced OS in the 926 patients treated with CCRT, but not in the 242 patients who underwent surgical intervention (Fig. 1c, d). The results of multivariate analyses revealed that the pretreatment NLR, tumor stage, and tumor resection were independent prognostic factors for OS (Table 2).

TABLE 2 Adjusted hazard ratio of determined factors associated with the prognosis of patients with ESCC

Variable	HR	95% CI	p value
Age, years			
$<$ 65	Ref		
$\geq$ 65	1.06	0.90–1.25	0.475
Sex			
Female	Ref		
Male	1.15	0.84–1.58	0.390
Clinical T stage			
$\leq$ T2	Ref		
T3–T4	1.73	1.36–2.21	$<$ 0.001*
Clinical N stage			
N0	Ref		
N(+)	1.58	1.12–2.21	0.009*
Distant metastasis			
No	Ref		
Yes	1.61	1.41–1.85	$<$ 0.001*
NLR			
$<$ 3	Ref		
$\geq$ 3	1.49	1.30–1.69	$<$ 0.001*
Treatment			
Definite CCRT	Ref		
Surgery ± neoadjuvant/adjuvant Tx	0.42	0.35–0.50	$<$ 0.001*

ESCC esophageal squamous cell carcinoma, *HR* hazard ratio, *CI* confidence interval, *NLR* neutrophil-to-lymphocyte ratio, *CCRT* concomitant chemoradiotherapy, *Tx* treatment

*Statistical significance ($p < 0.05$)

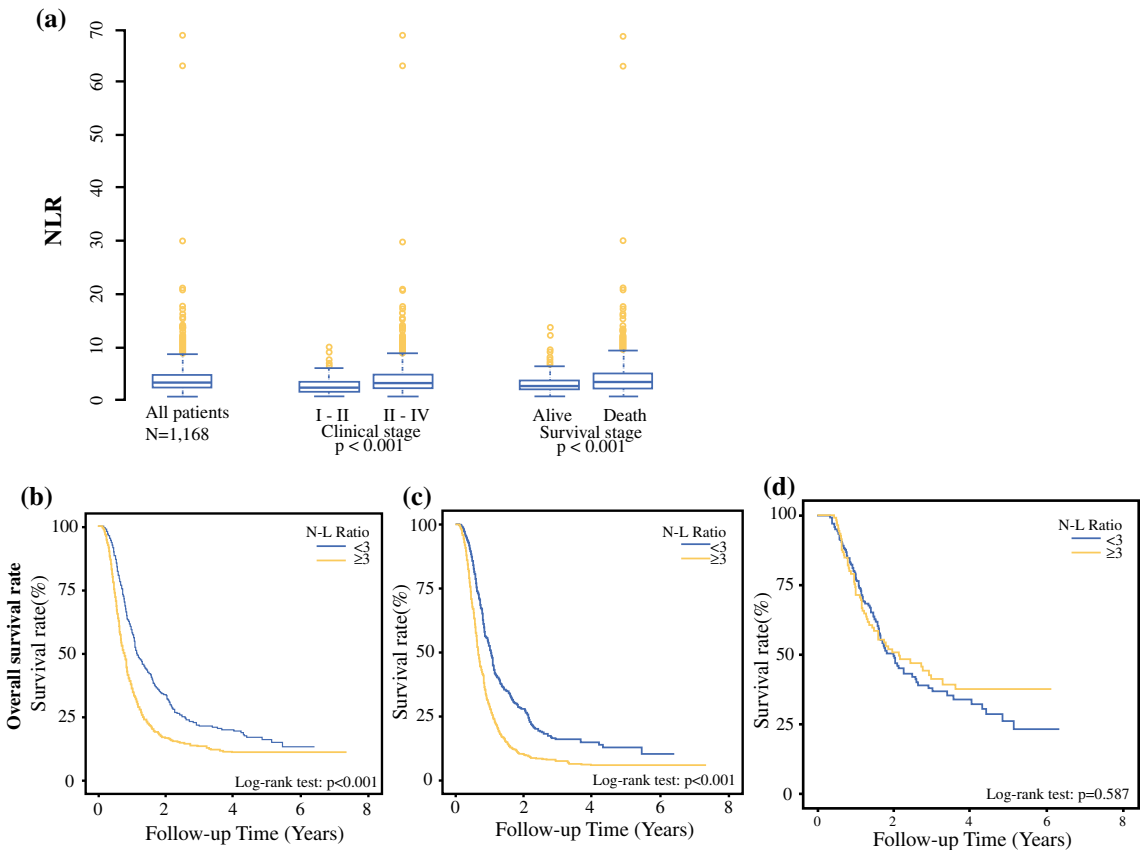

FIG. 1 Correlations between the baseline NLR and prognosis for patients with T1N(+) T2–T4 ESCC. Pretreatment NLR in ESCC patients (**a**). NLR at baseline was elevated in patients with an advanced clinical stage and having a higher risk of death during follow-up. The data show the third (Q3) and first quartile (Q1) range of the data and data outliers. Lines indicate the median values. The survival differences were according to the pretreatment NLR (NLR $\geq$ 3 vs. NLR $<$ 3) in total (**b**); in the subgroup of definite CCRT (**c**); and in the subgroup of surgery (**d**). *NLR* neutrophil-to-lymphocyte ratio, *ESCC* esophageal squamous cell carcinoma, *CCRT* concomitant chemoradiotherapy

Relationships between Pretreatment NLR Status, IL-6 Level, and Clinical Outcome

We previously reported that the IL-6 level was a significant predictor of the prognosis of ESCC patients. We further analyzed the predictive role of the pretreatment NLR in clinical outcome and its correlation with IL-6 levels using data from 242 ESCC patients with known IL-6 levels. Among these patients, 216 had available IHC data for IL-6 staining in tumor specimens (Table 3), and 94 had IL-6 serum-level data. The circulating IL-6 level was significantly correlated with the IL-6 staining level in tumor specimens (Fig. 2a). Figure 2b–d and Table 3 show that the distribution of the pretreatment NLR was significantly associated with IL-6 staining in tumor specimens, clinical stage, and pCR, locoregional failure, and survival rates. Patients with a high pretreatment NLR had a shorter median OS (NLR $\geq$ 3 vs. NLR $<$ 3: 1.14 vs. 3.66 years; $p < 0.001$) (Fig. 2e). According to univariate and multivariate analyses, a high NLR, no tumor resection, disease failure after treatment, and positive IL-6 staining were significantly associated with shorter survival (Tables 4, 5).

Predictive Role of Pretreatment NLR in the Levels of CD11b + CD33 + HLA-DR− Cells and IL-6 in the Peripheral Circulation

Accumulating evidence has reported that MDSCs, a population of cells with suppressive activity, contribute to the negative regulation of immune responses that occur in diseases, including cancer.[16] The percentage of CD11b + CD33 + HLA-DR− cells in the peripheral circulation of 94 patients with ESCC was evaluated by flow cytometry. Detailed patient characteristics at baseline are shown in electronic supplementary Table 1. Peripheral blood mononuclear cells were isolated from esophageal cancer patients and stained to detect MDSCs using fluorochrome-labeled antibodies targeting CD33, CD11b, and HLA-DR. Representative flow cytometry data from two ESCC patients are shown in Fig. 3a. We previously reported that

TABLE 3 Clinicopathological characteristics of ESCC patients with IL-6 IHC

	No. of patients		*p* value
	NLR < 3	NLR ≥ 3	
No. of patients	106	110	
Age, years			
Range	35–86	38–86	0.42
≤ 58 (mean)	55	56	
Tx policy			
CCRT	79	85	0.637
Surgery ± Tx[a]	27	25	
Clinical stage			0.024*
I–II	29	16	
III–IV	77	94	
LN metastasis			0.039*
Negative	32	20	
Positive	74	90	
IL-6 staining			< 0.001*
Negative	69	38	
Positive	37	72	
Response to neoadjuvant Tx			0.779
Response (+)	86	82	
Poor response	17	18	
Unknown	3	10	
pCR s/p neoadjuvant Tx			0.070
Yes	13	6	
No	14	19	
Locoregional recurrence/persistent			0.014*
No	59	43	
Yes	47	67	
Unknown			
Distant metastasis			0.45
Negative	67	64	
Positive	39	46	
Survival time			0.007*
Alive	56	38	
Dead	50	72	

ESCC esophageal squamous cell carcinoma, *IL* interleukin, *IHC* immunohistochemistry, *NLR* neutrophil-to-lymphocyte ratio, *Tx* treatment, *CCRT* concomitant chemoradiotherapy, *LN* lymph node, *pCR* pathological complete response

*Statistical significance ($p < 0.05$)

[a]Neoadjuvant/adjuvant treatment

IL-6-mediated induction of MDSCs was associated with esophageal tumor promotion and poor prognosis. In the present study, the percentage of MDSCs was significantly elevated in cancer patients who developed disease failure after treatment ($p = 0.008$) and who had a higher risk of death during follow-up ($p = 0.019$) (Fig. 3b, c). Figure 3d shows the strong correlation found between IL-6 levels and the percentage of MDSCs in ESCC patients. We further assessed the usefulness of the NLR for predicting the circulating IL-6 level and the MDSC proportion. As shown in electronic supplementary Fig. 1a and b, the values of NLR significantly correlated the levels of circulating MDSC and IL-6. Moreover, the levels of IL-6 and MDSC cells were significantly higher in the NLR ≥ 3 group than in the NLR < 3 group (Fig. 3e, f).

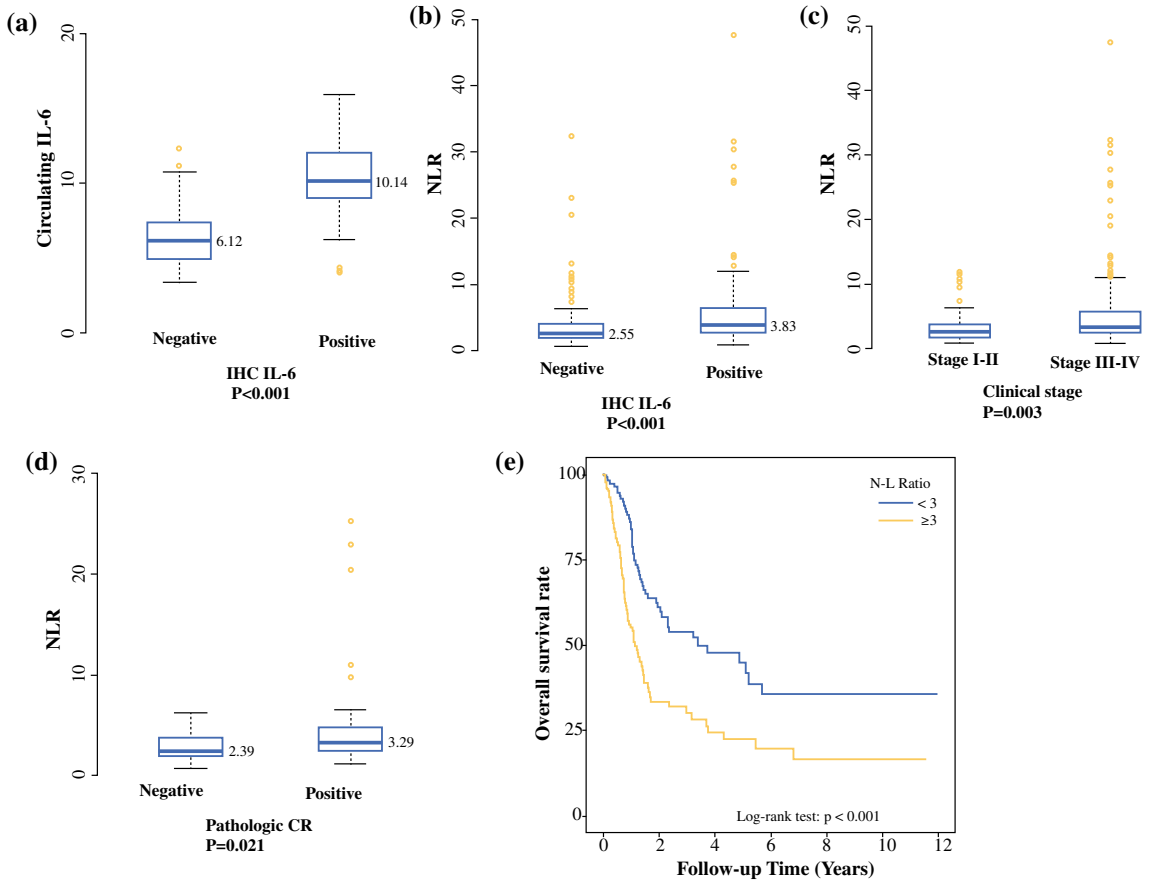

FIG. 2 Relationships between NLR, IL-6 level, and clinical outcome. **a** Circulating IL-6 levels, and **b** NLR levels in the groups of ESCC patients with and without IL-6-positive staining in the tumor specimen; **c** NLR levels in ESCC patients with clinical stage I–II versus clinical stage III–IV; **d** in the surgical group of ESCC patients with and without pCR. The data showed the third (Q3) and first quartile (Q1) range of the data and data outlier. Lines indicate the median values. The OS differences were as per the pretreatment NLR in the group of ESCC patients with the IL-6 staining data (**d**). *NLR* neutrophil-to-lymphocyte ratio, *IL* interleukin, *ESCC* esophageal squamous cell carcinoma, *pCR* pathological complete response, *OS* overall survival, *IHC* immunohistochemical

TABLE 4 Univariate analysis to determine factors associated with prognosis

Variables	*p* value for overall survival	*p* value for disease-specific survival
Clinical T stage (I–II vs. III–IV)	0.023*	0.010*
Clinical N stage (N0 vs. N[+])	0.161	0.077
Positive staining for IL-6	< 0.001*	< 0.001*
NLR (< 3 vs. ≥ 3)	< 0.001*	< 0.001*
Tumor resection	< 0.001*	< 0.001*
Locoregional failure	< 0.001*	< 0.001*
Distant metastasis	0.003*	< 0.001*

IL interleukin, *IHC* immunohistochemistry, *NLR* neutrophil-to-lymphocyte ratio

*Statistical significance ($p < 0.05$)

DISCUSSION

Inflammation plays a crucial role in cancer development by promoting or inhibiting progression and by affecting the response to systemic therapies.[8,17,21] Neutrophils and lymphocytes, which constitute the predominant proportion of total circulating leukocytes, play a key role in host systemic immune responses, but their effects on tumor progression are mostly realized in the tumor microenvironment.[22] Neutrophil, monocyte, and platelet counts in blood have been reported to be promising prognostic factors for some cancers patients.[14,23] The NLR is a cheaper and faster laboratory measurement than any other biomarker, and does not require any additional cost. There

TABLE 5 Multivariate analysis to determine molecular markers associated with the prognosis (OS) of patients

Variable	HR*	95% CI	*p* value
IL-6 staining			
Negative	Ref		
Positive	2.15	1.47–3.14	< 0.001*
Treatment			
Definite CCRT	Ref		
Neoadjuvant CCRT + surgery	0.56	0.35–0.89	0.015*
Clinical stage			
I–II	Ref		
III–IV	0.88	0.53–1.44	0.598
NLR			
< 3	Ref		
≥ 3	1.52	1.05–2.19	0.026*
Disease status			
Control	Ref		
Failure (LR + DM)	7.57	3.96–14.49	< 0.001*

OS overall survival, *HR* hazard ratio, *CI* confidence interval, *IL* interleukin, *CCRT* concomitant chemoradiotherapy, *NLR* neutrophil-to-lymphocyte ratio

*Statistical significance ($p < 0.05$)

have been reports regarding the use of the NLR as a prognostic indicator of survival in esophageal cancer.[14,24,25] In the present study, an advantage of our analyses was that the results were based on a relatively large population of ESCC patients with pure SCCs in our hospital, with available information regarding staging and primary treatment details. Based on the analyses of 1168 ESCC patients who received curative treatment, an elevated pretreatment NLR was significantly associated with an advanced clinical stage and reduced OS. According to univariate and multivariate analyses, a pretreatment NLR ≥ 3 was associated with shorter OS compared with an NLR < 3. Treatments for esophageal cancer include surgery, radiation, chemotherapy, and a combination of these modalities. We further analyzed the predictive value of the NLR according to treatment modality. The data revealed that an increased NLR was an independent prognostic factor for OS in patients treated with CCRT but not those treated with surgery. Based on these results, the NLR is a useful baseline variable for assessing prognosis in ESCC patients considered for curative treatment, especially CCRT.

The pre-existing state of the tumor microenvironment established by a systemic inflammatory response may provide cancer cells with advanced malignant phenotypes and immunosuppressive conditions.[26,27] It was recently suggested that IL-6 modulates both the local tumor microenvironment and systemic inflammatory responses by inducing the differentiation of tumor-infiltrating monocytes into immunosuppressive cells in patients with cancer, thereby allowing cancer cells to acquire an advanced malignant phenotype.[28,29] Furthermore, IL-6 is a chemotactic factor for neutrophils.[30,31] We previously reported that IL-6 is a significant predictor of the prognosis of ESCC, and IL-6-positive esophageal cancer provides a suitable microenvironment for the development of tumor growth and treatment resistance.[18] The results from the present study indicated that increased IL-6 levels in tumors and serum were significantly correlated with the NLR. We further confirmed the predictive power of IL-6 and the NLR on OS in multivariate analyses.

Myeloid cells are the most abundant cells in the tumor microenvironment. The tumor recruits endogenous myeloid cells to tumor-associated macrophages, MDSCs, and neutrophils, modulating these cells to sustain an immunosuppressive environment.[32] Increasing evidence has suggested that neutrophils play an important role in the host's reaction to cancer.[22] An association between the blood NLR and disease progression has been found in numerous malignancies.[22,33] Studies have reported that IL-6 produced by tumors is involved in defective myeloid cell maturation and impaired myelopoiesis, resulting in accumulation and expansion of MDSCs in tumor-bearing hosts.[19,34, 35] MDSCs constitute an immature population of myeloid cells thought to be an important subset of cells that contribute to an immunosuppressive tumor microenvironment, and MDSC numbers are significantly increased in cancer patients.[32,36] We also previously found that IL-6-induced MDSC recruitment provided a microenvironment conducive to tumor growth and the development of treatment resistance in ESCC,[19] and therefore further investigated the correlations between circulating MDSCs and the NLR in ESCC. To date, MDSCs have been defined mainly as CD11b + CD33 + HLA-DR− cell lineages in human cancers.[22,37,38] In the present study, we characterized the proportions of CD11b + CD33 + HLA-DR− myeloid cells in a cohort of ESCC patients. Fluorescence-activated cell sorting (FACS) analyses revealed that the percentage of these MDSCs was correlated with disease status and circulating IL-6 levels. Furthermore, we found a positive correlation between the NLR and circulating MDSC levels in ESCC patients. In the present study, we showed that IL-6 levels in serum and tumors were significantly correlated with the NLR and the level of circulating MDSCs.

The current study is limited by the inherent nature of investigating a hospital-based registry and the non-randomized approach to treatment selection. Furthermore, we could not account for potential unmeasured selection biases regarding performance status, comorbidity, access to healthcare, or other patient-related factors.

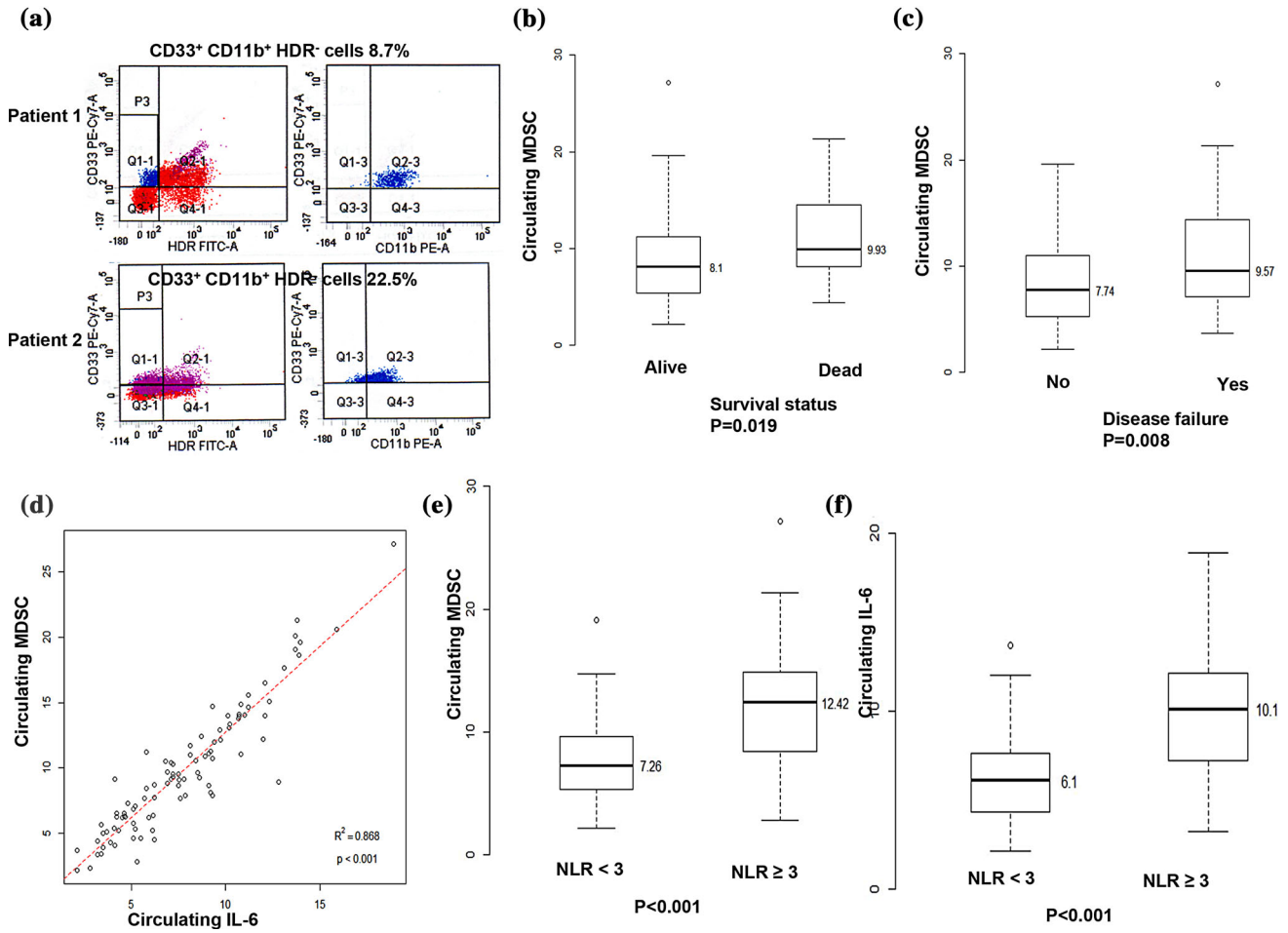

FIG. 3 Correlation pretreatment NLR in the circulating MDSC and IL-6 levels. Flow cytometric analysis of circulating CD11b + CD33 + HLA-DR− cells in isolated PBMCs (**a**). HLA-DR − CD33+ cells were gated, and the CD11b-positive population was then selected. Representative data from two cancer patients are shown (upper row, the patient with pretreatment NLR < 3; lower row, the patient with pretreatment NLR ≥ 3). Box-plot showing elevated circulating MDSC levels was associated with the higher risk of death (**b**) and disease recurrence after treatment (**c**) during follow-up (**d**). There was positive correlation between the levels of MDSC and IL-6 in the peripheral circulation. Box-plot showing circulating MDSC levels (**e**), and circulating IL-6 levels (**f**) in the groups of ESCC patients with pretreatment NLR ≥ 3 versus NLR < 3. Lines indicate the median values. *NLR* neutrophil-to-lymphocyte ratio, *IL* interleukin, *MDSC* myeloid-derived suppressor cells, *PBMCs* peripheral blood mononuclear cells

With the increasing use of immunotherapy, patient selection has become an important issue in assessing efficacy. The suppression of IL-6 levels may enhance the immune response, thereby resulting in improved clinical outcomes in patients with refractory ESCC. In addition, MDSCs have been suggested to be a novel target for multiple cancers, and numerous clinically available agents have been developed.[39] However, less-optimal patient selection might explain why agents targeting MDSCs have not displayed promising efficacies for major types of cancer.[40] Thus, it is imperative to identify clinically feasible parameters highly relevant to the level of MDSCs.

CONCLUSIONS

In the present study, we showed that the blood NLR was relevant to IL-6 and MDSC levels and was a strong prognostic indicator for ESCC patients. We suggest the NLR is an important biomarker for patients that can assist clinicians and patients to make an informed decision regarding treatment options. Discussions based on pretreatment NLR results may help the patient decide whether the side effects of curative treatments are worth the risk, particularly if the patient is considered to have a poor prognosis, as determined by a high pretreatment NLR, or whether a more conservative treatment strategy is preferred.

ACKNOWLEDGMENT The authors would like to thank the Health Information and Epidemiology Laboratory (CLRPG6G0041) for the comments and assistance in data analysis.

FUNDING The work was support by the Ministry of Science and Technology, Taiwan (Grant Number 1052628-B-182A-009-MY3, to M.F. Chen).

COMPLIANCE WITH ETHICAL STANDARDS

CONFLICT OF INTEREST Miao-Fen Chen, Ping-Tsung Chen, Feng-Che Kuan, and Wen-Cheng Chen declare that they have no competing interests. All authors read and approved the final version of the manuscript submitted for publication.

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