Prognostic Significance of the Neutrophil-Lymphocyte Ratio and Platelet-Lymphocyte Ratio in Neuroendocrine Carcinoma

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Extra-pulmonary neuroendocrine carcinoma is a rare and aggressive cancer. Although several biological and histological markers have been suggested as prognostic factors for this cancer, the prognostic importance of systemic inflammatory markers, including the neutrophil-lymphocyte ratio and platelet-lymphocyte ratio, is unclear. This study aimed to evaluate the association between systemic inflammatory markers and the prognosis of extra-pulmonary neuroendocrine carcinoma. We retrospectively analyzed the clinical data of 85 patients with unresectable or metastatic extra-pulmonary neuroendocrine carcinoma who received platinum-based chemotherapy as first-line chemotherapy from August 2007 to November 2019. We used time-dependent receiver operating characteristic curve analysis to determine the cut-off values. The cut-off values for the neutrophil-lymphocyte ratio and platelet-lymphocyte ratio were 3.0 and 158.5, respectively. There was no significant difference in the Eastern Cooperative Oncology Group performance status score, Ki-67 index, or response to chemotherapy between groups. The high neutrophil-lymphocyte ratio group showed significantly worse overall survival (high vs. low, median 11.1 vs. 21.0 months, log-rank p=0.004) and shorter median progression-free survival, but the latter was not statistically significant. The high platelet-lymphocyte ratio group also showed significantly worse progression-free survival and overall survival than the low platelet-lymphocyte ratio group (high vs. low: median 5.6 vs. 9.8 months, log-rank p=0.047 and median 13.8 vs. 21.0 months, log-rank p=0.013, respectively). In multivariable analysis, a high neutrophil-lymphocyte ratio was an independent prognostic factor for overall survival. The neutrophil-lymphocyte ratio is a potent and readily available prognostic factor for extra-pulmonary neuroendocrine carcinoma.

Key Words: *Neuroendocrine Carcinoma; Neutrophils; Lymphocytes; Prognosis*

INTRODUCTION

Extra-pulmonary neuroendocrine carcinoma (EP-NEC) is a rare and aggressive type of cancer that can occur in various organs and has a poor prognosis. An Izmir Oncology Group study showed more than 80% of NEC patients presented with metastasis at diagnosis and had a poor prognosis.[1] A Surveillance, Epidemiology, and End Results (SEER) database analysis of 162,983 cases showed that the median survival duration in patients with localized EP-NEC was 20.7 months, while that in patients with distant disease it was 5.8 months. EP-NEC patients with distant metastases had a median survival duration of less than 6 months,[2] except for those with NECs of the small intestine

(18.8 months) and anal canal (11.1 months).

Previous studies have evaluated the predictive and prognostic factors of extra-pulmonary NECs. The NORDIC NEC study analyzed the prognostic factors for survival in 305 patients with advanced gastrointestinal NEC. They demonstrated that poor performance status and elevated lactate dehydrogenase (LDH) levels were prognostic factors for survival. In addition, the response rate to chemotherapy was lower when Ki-67 index was <55%, but the survival rate was better.[3] Freis et al.[4] also suggested that LDH and aspartate aminotransferase (AST) levels at diagnosis could help physicians predict patient survival.

Several studies have reported that markers of the host inflammatory response, such as the neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR), are easily measurable and cost-effective prognostic factors for various solid tumors.[5,6] In a previous study on small-cell lung cancer, which is histologically similar to EP-NEC, the high NLR group showed significantly shorter survival and poorer response to chemotherapy than the low NLR group.[7] An Izmir Oncology Group study verified the NLR and PLR as simple laboratory parameters that can be used to identify patients with neuroendocrine tumors (NETs) expected to show worse outcomes.[1] These results suggest that the NLR and PLR may also be associated with the prognosis of EP-NEC. However, previous studies did not use the 2017 World Health Organization (WHO) guidelines for the classification of neuroendocrine neoplasms (NENs), and thus, they did not distinguish between NETs and NECs. Therefore, in this study, we aimed to evaluate significant prognostic factors for EP-NEC and the importance of the NLR and PLR in this context.

MATERIALS AND METHODS

1. Study subjects and data collection

This study included patients diagnosed with unresectable or metastatic EP-NEC according to the 2017 WHO classification from August 2007 to November 2019 at Chonnam National University Hwasun Hospital and Seoul St. Mary's Hospital. We retrospectively reviewed clinical information and data on laboratory and radiologic follow-up from the hospitals' electronic medical records. All patients were older than 19 years and had received platinum-based chemotherapy as first-line chemotherapy. Peripheral blood samples were obtained at diagnosis. The NLR was defined as the ratio of the absolute neutrophil count to the absolute lymphocyte count, and the PLR was defined as the ratio of the platelet count to the absolute lymphocyte count. Progression-free survival (PFS) was defined as the time from the initiation of chemotherapy to disease progression or death from any cause. Overall survival (OS) was calculated as the time from diagnosis to death.

2. Statistical analysis

The cut-off values of the NLR and PLR for predicting OS were calculated using receiver operating characteristic (ROC) curve analysis for time-to-event data, and it was performed with the EZR program[8] and the "survival ROC" package.[9] The median OS of all patients (17.1 months) was applied to ROC curve analysis. The cut-off value for NLR was 3.0 (area under the ROC curve [AUC] 0.607), and that for PLR was 158.5 (AUC 0.624) (Fig. 1). The low and high NLR or PLR groups were compared using the Mann-Whitney U-test for continuous variables and the chi-squared test or Fisher's exact test for categorical variables. Survival analyses were performed using the Kaplan–Meier method and log-rank tests. A Cox proportional hazards regression model was used to detect the association between the prognosis of EP-NEC and sex, primary origin, performance status,
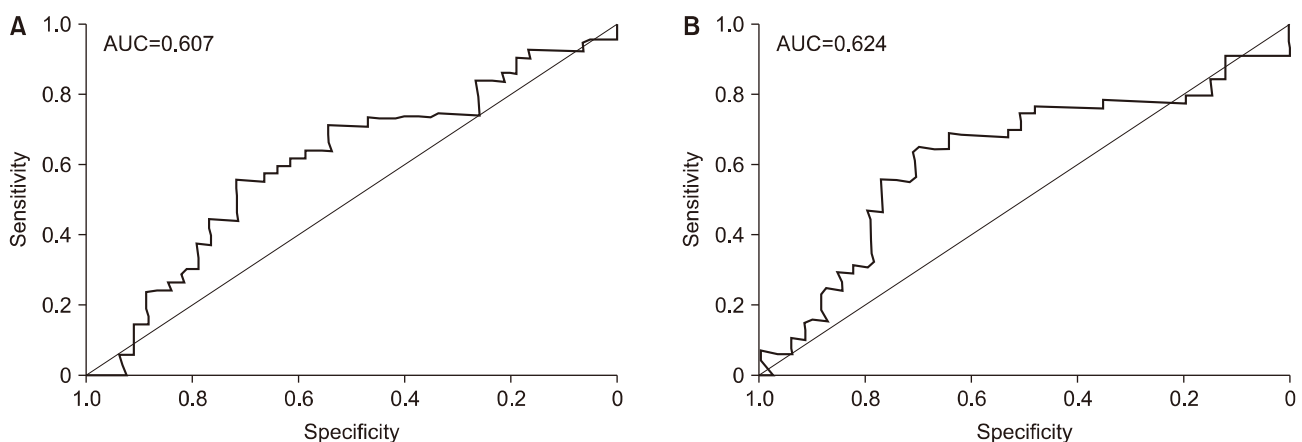
FIG. 1. ROC curve analysis for determining the cut-off values of the NLR and PLR. (A) An NLR of 3.0 accurately predicted a median OS of 17.1 months (AUC 0.607) with 55.4% sensitivity and 71.9% specificity. (B) A PLR of 158.5 accurately predicted a median OS of 17.1 months (AUC 0.624) with 64.9% sensitivity and 69.9% specificity. ROC: receiver operating characteristic, NLR: neutrophil-lymphocyte ratio, OS: overall survival, AUC: area under the ROC curve, PLR: platelet-lymphocyte ratio.

Ki-67, laboratory values (AST, LDH, C-reactive protein), NLR and PLR, with the results expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). SPSS 21.0 (SPSS Inc., Chicago, IL, USA) and EZR[8] were used for statistical analyses. A p value<0.05 was considered statistically significant.

3. Ethics statement

The protocol was approved by the Institutional Review Board of Chonnam National University Hwasun Hospital (CNUHH-2020-019). The trial was conducted in accordance with the Declaration of Helsinki.[10]

RESULTS

1. Patients characteristics

In total, 85 patients with unresectable or metastatic EP-NEC were analyzed in this study. The median follow-up duration was 66.7 months (interquartile range [IQR] 29.2-101.2 months). The median age of the patients was 62.0 years (IQR 52.5-69.5 years). The patients included 52 men (61.2%) and 33 women (38.8%). 41 patients (48.2%) had gastroenteropancreatic (GEP) NEC, and 44 (51.8%) had non-GEP NEC. At diagnosis, 72 patients (84.7%) had an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 or 1; only 13 patients (15.3%) had an ECOG PS score of 2 or 3 (Table 1).

2. Treatment patterns

All patients initially received platinum-based chemotherapy, and the median number of chemotherapy cycles was 5 (IQR 3-6). The best response to chemotherapy was evaluated. Among the 85 patients, 39 (45.9%) achieved an objective response and 63 (74.1%) achieved disease control. Among 73 patients with disease progression, 47 patients (64.4%) received second-line chemotherapy (Table 1).

3. Clinical manifestations and laboratory data according to the NLR and PLR

Patients were divided into two groups according to cut-off values for the NLR and PLR for comparison. The number of patients with a high NLR was 36 (42.4%), and that with a high PLR was 41 (48.2%). There were no significant differences in age, ECOG PS score, origin, stage at diagnosis, pathologic type, Ki-67 index, or best response to chemotherapy between the high and low NLR groups. There were more men in the high NLR group. The median AST, C-reactive protein (CRP), and LDH levels were significantly higher in the high NLR group (high vs. low, median AST [U/L], 25.0 vs. 30.0, p=0.022; median CRP [mg/dL], 0.5 vs. 1.84, p=0.002; median LDH [IU/L], 465.0 vs. 539.0, p=0.044, respectively). In the comparison between the low and high PLR groups, all factors were similar, except pathologic type. Patients with a high PLR were more likely to have small-cell NEC. There were no differences in AST, CRP, or LDH levels between the low and high PLR groups (Table 2).

TABLE 1. Characteristics of all patients (n=85)

	Number of patients (%)
Age, years, median (IQR)	62.0 (52.5-69.5)
Sex	
Male	52 (61.2)
Female	33 (38.8)
ECOG Performance status	
PS 0-1	72 (84.7)
PS 2-3	13 (15.3)
Primary origin	
GEP	41 (48.2)
Non-GEP	44 (51.8)
Stage	
Metastatic/unresectable	53 (62.4)
Recurrent	32 (37.6)
Pathologic type	
Small cell type	40 (47.1)
Large cell type	8 (9.4)
Others	37 (43.5)
Ki-67	
<55%	42 (49.4)
≥55%	43 (50.6)
Chemotherapy regimen	
Etoposide/Cisplatin	83 (97.6)
5-Fluorouracil/Leucovorin/Oxaliplatin	1 (1.2)
Paclitaxel/Cisplatin/Bevacizumab	1 (1.2)
Cycles, median (IQR)	5 (3-6)
Best response for chemotherapy	
Complete response	16 (18.8)
Partial response	23 (27.1)
Stable disease	24 (28.2)
Progressive disease	22 (25.9)
Second-line chemotherapy (n=73)	
No	26 (35.6)
Yes	47 (64.4)

IQR: interquartile range, GEP: gastroenteropancreatic, ECOG: Eastern Cooperative Oncology Group, PS: performance status.

4. Survival analysis by the NLR and PLR

The median OS was 17.1 months, and the median PFS was 7.9 months. The high NLR group had a significantly shorter OS than the low NLR group (high vs. low, median 11.1 [95% CI 8.6-13.7] vs. 21.0 [95% CI 13.9-28.2] months, log-rank p=0.004). Additionally, the high NLR group showed a shorter PFS, but the difference was not significant (high vs. low, median 5.6 [95% CI 2.7-8.5] vs. 10.0 [95% CI 7.4-12.6] months, log-rank p=0.073). In contrast, the high PLR group had a shorter PFS (high vs. low, median 5.6 [95% CI 3.8-7.4] vs. 9.8 [95% CI 6.3-13.4] months, log-rank p=0.047) and OS (high vs. low, median 13.8 [95% CI 9.0-18.5] vs. 21.0 [95% CI 13.7-28.3] months, log-rank p=0.013) than the low PLR group (Fig. 2).

On univariate analysis, a poor performance status (ECOG PS score 2-3), high Ki-67 index (≥55%), high NLR, and high PLR were significantly associated with PFS and OS. Higher AST and CRP levels were associated with poorer PFS and OS. LDH levels were associated with OS but not

TABLE 2. Clinical manifestations and laboratory data according to the NLR and PLR at diagnosis (n=85)

	NLR<3.0 Number of patients (%), n=49	NLR≥3.0 Number of patients (%), n=36	p	PLR<158.5 Number of patients (%), n=44	PLR≥158.5 Number of patients (%), n=41	p
Age, years, median (IQR)	59.0 (51.0-69.0)	65.0 (58.8-68.0)	0.069	62.0 (53.5-70.0)	63.0 (53.0-67.0)	1.000
Sex			0.007			0.971
Male	24 (49.0)	28 (77.8)		27 (61.4)	25 (61.0)	
Female	25 (51.0)	8 (22.2)		17 (38.6)	16 (39.0)	
ECOG PS			0.362			0.870
0-1	43 (87.8)	29 (80.6)		37 (84.1)	35 (85.4)	
2-3	6 (12.2)	7 (19.4)		7 (15.9)	6 (14.6)	
Origin			0.299			0.440
GEP	26 (53.1)	15 (41.7)		23 (52.3)	18 (43.9)	
Non-GEP	23 (46.9)	21 (58.3)		21 (47.7)	23 (56.1)	
Stage			0.482			0.275
Metastatic/Unresectable	29 (59.2)	24 (66.7)		25 (56.8)	28 (68.3)	
Recurrent	20 (40.8)	12 (33.3)		19 (43.2)	13 (31.7)	
Pathologic type			0.380			0.038
Small cell type	20 (40.8)	20 (55.6)		15 (34.1)	25 (61.0)	
Large cell type	5 (10.2)	3 (8.3)		6 (13.6)	2 (4.9)	
Others	24 (49.0)	13 (36.1)		23 (52.3)	14 (34.1)	
Ki-67			0.096			0.748
<55%	28 (57.1)	14 (38.9)		21 (47.7)	21 (51.2)	
≥55%	21 (42.9)	22 (61.1)		23 (52.3)	20 (48.8)	
Laboratory data at diagnosis						
AST (U/L), median (IQR)	25.0 (20.0-29.0)	30.0 (22.0-56.8)	0.022	23.5 (19.5-32.3)	28.0 (22.0-43.0)	0.078
CRP (mg/dL), median (IQR)	0.5 (0.2-1.4)	1.84 (0.4-5.9)	0.002	0.5 (0.2-1.9)	1.1 (0.3-3.9)	0.099
LDH (IU/L), median (IQR)	465.0 (379.0-642.0)	539.0 (403.0-1046.3)	0.044	469.5 (369.0-686.8)	523.0 (399.0-783.0)	0.220
Best response for chemo-therapy			0.183			0.949
Complete response	11 (22.4)	5 (13.9)		9 (20.5)	7 (17.1)	
Partial response	9 (18.4)	14 (38.9)		11 (25.0)	12 (29.3)	
Stable disease	16 (32.7)	8 (22.2)		13 (29.5)	11 (26.8)	
Progressive disease	13 (26.5)	9 (25.0)		11 (25.0)	11 (26.8)	

NLR: neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio, IQR: interquartile ratio, ECOG PS: Eastern Cooperative Oncology Group performance status, GEP: gastroenteropancreatic, AST: aspartate aminotransferase, LDH: lactate dehydrogenase, CRP: C-reactive protein.

PFS. On multivariable analysis, a high NLR was found to be independently associated with poor OS (HR 1.955, 95% CI 1.2-3.3, p=0.012) but not with poor PFS. Both higher Ki-67 indices and elevated CRP levels were associated with poor PFS. The ECOG PS score was also an independent prognostic factor for PFS and OS (Table 3).

DISCUSSION

The WHO disease classification of NENs was updated in 2017. Previously, NEC grade 3 referred to NETs with a Ki-67 index >20% or a mitosis rate >20/10 high-power fields.[11] However, it was possible for well-differentiated NETs with high levels of Ki-67 to be technically classified as NECs, although they may have shown a poor response to platinum-based chemotherapy used for NEC.[12] Therefore, in the updated classification, NEC grade 3 tumors were divided into poorly differentiated and well-differentiated NETs for better risk stratification and treatment

decision-making.[13-15]

Several previous studies have validated the prognostic factors for NENs, but only a few studies have distinguished between NETs and NECs according to the revised classification. NETs and NECs have similarities in morphology and immune phenotype, but they vary in terms of grade, behavior, and molecular signatures, such as genetic mutations and response to therapy.[15,16] To identify prognostic factors for poorly differentiated NEC treated with systemic chemotherapy, the clinical and pathologic review was based on the updated classification.

Although most of the studies conducted so far included both NETs and NECs, several markers were suggested as prognostic factors for NENs. Elevation of LDH and AST levels and high Ki-67 levels (>55%) were reported to be associated with a poor prognosis.[3,4,17]

In this study, LDH was identified as an independent prognostic factor for OS via univariable and multivariable analyses. Therefore, patients with higher LDH levels are
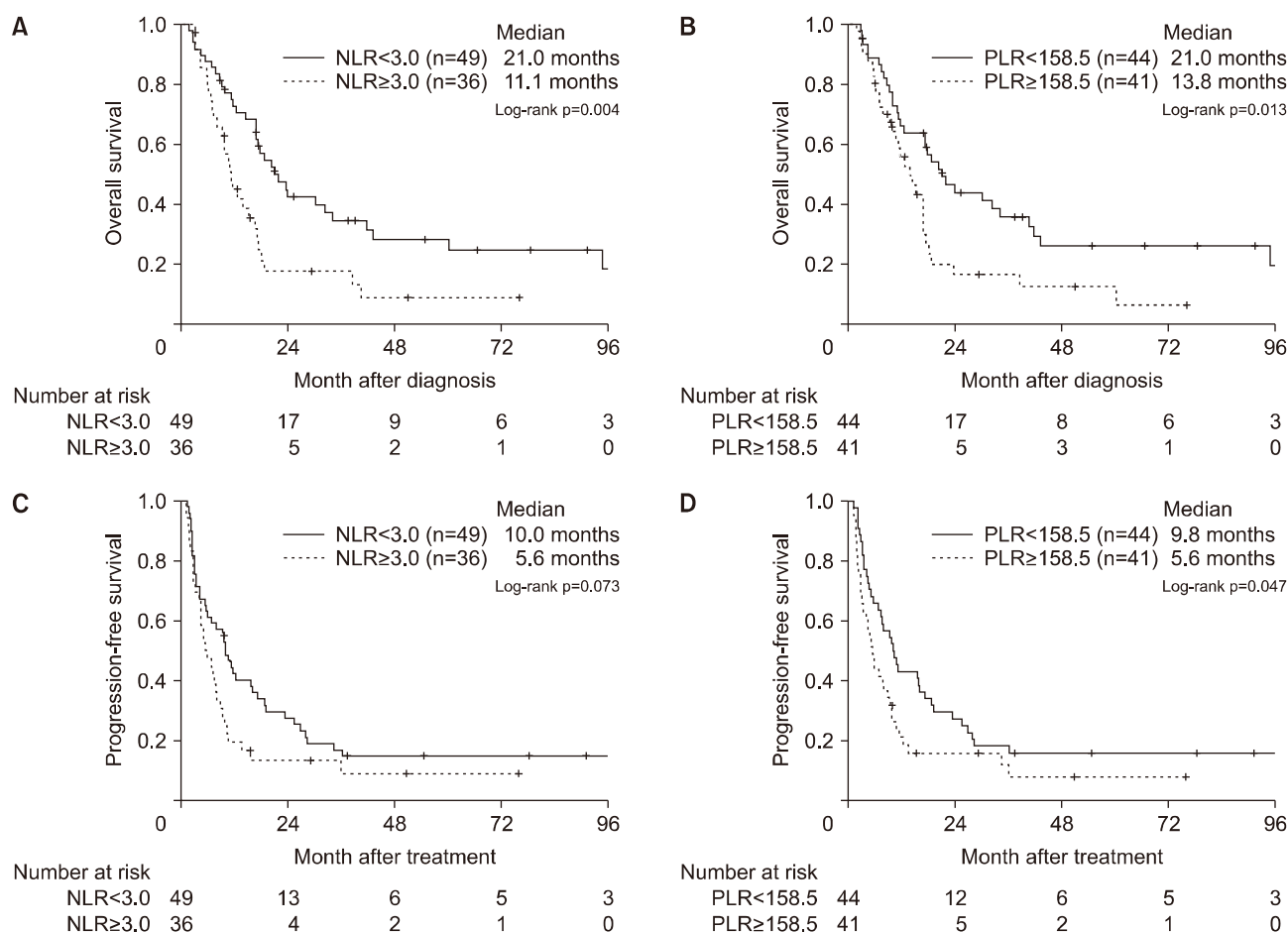
FIG. 2. Kaplan–Meier curves of PFS and OS in patients with extra-pulmonary neuroendocrine carcinoma. (A) OS stratified by the NLR. (B) OS stratified by the PLR. (C) PFS stratified by the NLR. (D) PFS stratified by the PLR. OS: overall survival, NLR: neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio, PFS: progression-free survival.

expected to have a shorter survival duration. NECs are characterized by high glucose consumption, lactate production, and proliferation, as well as a hypoxic tumor environment due to poor vascularization, which can lead to increased LDH levels; this may in turn lead to a poor prognosis.[4,18,19]

A previous study on GEP-NECs suggested that a high AST level (≥2 times the upper limit of normal) may indicate a poor prognosis.[4] Similarly, higher AST levels were associated with a poorer prognosis on univariate analysis. However, almost all patients in this study had normal AST levels; thus, it was difficult to determine the role of AST as a prognostic factor.

The Ki-67 protein is a marker of cell proliferation, and increased expression of Ki-67 has been reported to be correlated with poor prognosis in several solid tumors.[20-22] The NORDIC NEC study by Sorbye et al.[3] showed that NEC patients with Ki-67 levels <55% had significantly longer survival than their counterparts. Consequently, they set the Ki-67 cut-off level at 55%. In multivariable analysis, the patient group with a high Ki-67 index (≥55%) had significantly poorer OS and PFS rates. Therefore, the level of Ki-67 may be a valuable biomarker in NEC. However, it should

be noted that the Ki-67 index can only be determined by performing a biopsy, and there may be differences in Ki-67 levels among various parts of a particular tissue.

The relationship between the systemic inflammatory response and cancer outcomes has been under the spotlight for years. Inflammatory cells act as tumor promoters by producing an attractive environment for tumor growth, DNA damage, and angiogenesis, all of which favor neoplastic spread and metastasis.[23,24] Markers of systemic inflammation, such as CRP, NLR, and PLR, have emerged as prognostic markers for many solid tumors.[5,6,24] Recently, Salman et al.[1] reported that the NLR and PLR were associated with PFS in patients with NETs.

CRP is a widely used acute phase reactant that reflects tissue injury. Several events, such as tissue damage and inflammation due to tumor growth, as well as cytokines and chemokines produced by tumor cells, increase the plasma CRP level.[24] In this study, CRP, as a continuous variable, was associated with poor PFS in multivariable analysis. However, CRP is a non-specific inflammatory marker, and thus, several conditions, such as infection, trauma, and non-neoplastic inflammation, can influence its levels; these factors should be considered while evaluating CRP-related

TABLE 3. Univariate and multivariate analyses for overall survival (A) and progression-free survival (B)

	Univariate			Multivariate		
	HR	95% CI	p	HR	95% CI	p
A. Overall survival						
Male	1.187	0.706-1.993	0.518			
Primary tumor site						
GEP		Reference				
Others	1.151	0.698-1.897	0.581			
ECOG Performance status						
0-1		Reference				
2-3	2.984	1.564-5.693	0.001	2.701	1.406-5.188	0.003
Ki-67 ($\geq$55%)	1.727	1.038-2.874	0.035			
AST (continuous)	1.006	1.001-1.010	0.008			
CRP (continuous)	1.078	1.011-1.149	0.022			
LDH (continuous)	1.000	1.000-1.001	0.041			
NLR ($\geq$3.0)	2.090	1.250-3.496	0.005	1.955	1.159-3.296	0.012
PLR ($\geq$158.5)	1.903	1.138-3.181	0.014			
B. Progression-free survival						
Male	1.308	0.813-2.106	0.268			
Primary tumor site						
GEP		Reference				
Others	1.143	0.720-1.813	0.571			
ECOG Performance status						
0-1		Reference				
2-3	2.084	1.134-3.831	0.018	2.226	1.199-4.132	0.011
Ki-67 ($\geq$55%)	1.691	1.058-2.701	0.028	1.645	1.020-2.654	0.041
AST (continuous)	1.004	1.001-1.008	0.008			
CRP (continuous)	1.075	1.018-1.136	0.010	1.071	1.015-1.130	0.012
LDH (continuous)	1.000	1.000-1.001	0.132			
NLR ($\geq$3.0)	1.530	0.957-2.448	0.076			
PLR ($\geq$158.5)	1.595	1.002-2.539	0.049			

HR: hazard ratio, CI: confidence interval, GEP: gastroentero-pancreatic, ECOG: Eastern Cooperative Oncology Group, AST: aspartate amino-transferase, LDH: lactate dehydrogenase, CRP: C-reactive protein, NLR: neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio.

findings.

A high NLR represents increased neutrophil counts; a high PLR represents increased platelet counts; and both represent decreased lymphocyte counts. The protumorigenic role of tumor-associated neutrophils (TANs), which are distinct from naive neutrophils, in anti-apoptotic activity; angiogenesis; and tumor progression, invasion, and metastasis has been previously investigated.[25-27] The NLR is assumed to reflect an increase in the number of TANs and is considered an easily verifiable surrogate marker for TANs.[7] Platelet activation is stimulated by chemokines and proinflammatory lipids and is linked with neutrophil recruitment. Moreover, platelets play an important role in tumor proliferation and distant metastasis by shielding tumor cells from the immune response against them, thus facilitating cancer growth and dissemination.[28-30] Because lymphocytes play a major role in cytotoxic tumor cell death and the inhibition of tumor cell proliferation and migration, a decreased lymphocyte count is associated with tumor progression and a poor prognosis.[31-33] This study showed that the NLR is an independent prognostic factor for OS in patients with EP-NEC. Although there was no significance on multivariate analysis, a remarkable prognostic distinction was noted between the low and high PLR groups. A large cohort study is necessary to confirm the significance of PLR. The NLR and PLR can be easily measured by peripheral blood sampling, and thus, they hold potential as significant and early prognostic markers for EP-NEC. Overall, the NLR and PLR may be helpful for clinicians to estimate patients' prognoses. In addition, several studies have evaluated the association between the NLR and efficacy of immune checkpoint inhibitors (ICIs) in patients with solid tumors. These studies have shown that a high NLR is related to poorer outcomes and is an easily available prognostic predictor in patients receiving ICI treatment.[34] Unfortunately, EP-NEC has few treatment options, and it is not clear which factors have the potential to predict the effect of ICIs. Thus, it is necessary to evaluate the association between the NLR and effect of ICI treatment against EP-NEC in the future.

We had expected that the NLR and PLR would be related to the response to chemotherapy in EP-NEC, as well as OS,

but this was not evident. In previous studies, the level of Ki-67 was associated with the response to platinum-based chemotherapy.[35] However, both the NLR and PLR groups in this study had varying Ki-67 indices. Furthermore, differences in the origins of primary cancer might explain the variations in response to chemotherapy.

There were several limitations to this study. First, the sample size was relatively small; thus, a large prospective cohort study is necessary to determine the generalizability of these results. Second, though all cases were pathologically diagnosed as EP-NEC, the origins were quite heterogeneous. Nevertheless, to the best of our knowledge, this is the first study to show that the NLR are significant prognostic factors for survival in EP-NEC. Further cohort studies are needed to determine the validity of the cut-off values used in this study and to confirm our results.

Systemic inflammatory markers are associated with the prognosis of EP-NEC. The NLR is an easily measurable and independent prognostic factor that reflects the OS in patients with EP-NEC. ECOG PS score, Ki-67 levels, and CRP levels may also be prognostic factors for EP-NEC.

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CONFLICT OF INTEREST STATEMENT

None declared.

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