Research Square

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Prognostic significance of platelet-lymphocyte ratio in extrapulmonary neuroendocrine carcinoma

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Abstract

Background

Extrapulmonary neuroendocrine carcinoma (EP-NEC) is an aggressive type of cancer with poor prognosis. Although several biological and histological markers are prognostic factors in NEC, the correlation between prognosis and systemic inflammation markers, such as the neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR), is unclear. This study evaluated the association between NLR or PLR and median overall survival (OS) or progression-free survival (PFS) in EP-NEC.

Methods

We retrospectively analyzed the clinical data from patients with unresectable or metastatic EP-NECs who received platinum-based chemotherapy at Chonnam National University Hwasun Hospital from August 2007 to March 2019. The cut-off values for NLR and PLR were 3 and 160, respectively.

Results

In total, 38 patients were analyzed. Both NLR and PLR at diagnosis had no significant associations with the response to initial chemotherapy. However, in the high-PLR group, median overall survival (OS) and progression-free survival (PFS) were poorer than those in the low-PLR group (high vs. low: 10.6 vs. 17.1 months, log-rank $p = 0.007$ and 4.1 vs. 9.3 months, log-rank $p = 0.032$, respectively). However, the high-NLR group had insignificantly poorer median OS and PFS than the low-NLR group. In the multivariate analysis, high PLR and LDH were independent prognostic factors for median OS and PFS.

Conclusions

High PLR was associated with shorter survival of EP-NEC patients receiving platinum-based chemotherapy. Therefore, PLR may be an independent prognostic factor in EP-NEC.

Background

Neuroendocrine carcinoma (NEC) is an aggressive type of cancer that can occur in various organs despite its rare incidence. More than 80% of NEC patients have metastasis at diagnosis and poor survival prognosis[1]. When determined according to the stage at diagnosis in one study, the median survival of localized NEC patients was 20.7 months, but that of patients with distant disease was 5.8 months. Except for NECs of the small intestine (18.8 months) and anal canal (11.1 months), most NECs had a median survival of less than 6 months[2].

Several studies have reported that high NLR and high PLR are related to poor prognosis in various solid tumors, including colorectal cancer, gastric cancer, non-small-cell lung cancer, and pancreatic cancer[3-10]. In small-cell lung cancer, which is histologically similar to extrapulmonary NEC (EP-NEC), the high NLR group showed poor overall survival (OS) and progression-free survival (PFS)[11]. Thus, we can assume that the prognosis of EP-NEC would be associated with NLR and PLR. However, to date, it is unclear whether NLR or PLR is associated with the prognosis of EP-NEC patients who receive systemic chemotherapy. Therefore, we evaluated the prognostic significance of NLR and PLR in patients with EP-NEC.

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 March 2019 at Chonnam National University Hwasun Hospital. We retrospectively reviewed the clinical information and laboratory and radiologic follow-up data from the hospital's electronic medical records. All patients were older than 20 years and received systemic chemotherapies. The peripheral blood samples were tested at diagnosis or before the first chemotherapy. NLR was defined as the ratio of the absolute neutrophil count divided by the absolute lymphocyte count, and PLR was defined as the ratio of the absolute platelet count divided by the absolute lymphocyte count. PFS was defined as the time from initiation of chemotherapy to disease progression or death from any cause before disease progression. The OS was calculated as the time from diagnosis to death from any cause.

2. Statistical analysis

Continuous variables are presented as medians and ranges. The categorical variables are presented as the numbers of patients and percentages. The cut-off value for lactate dehydrogenase (LDH) was 1.5 times the upper limit of normal (ULN), and those for NLR and PLR were 3[12] and 160[11], respectively, as determined by reference to previous studies. The low- and high-NLR groups and the low- and high-PLR groups were compared using the Mann-Whitney U test (age and laboratory data), chi-square test (disease control after chemotherapy and second-line chemotherapy data), Fisher's exact test (sex, primary origin, and final stage before chemotherapy data), or linear by linear association (ECOG performance status, and best response to initial chemotherapy data). Survival analyses and comparisons were performed using the Kaplan-Meier method and log-rank test, respectively. Multivariate analysis of survival was performed according to LDH and PLR data using the Cox proportional hazards model, and hazard ratios and 95% confidence intervals (CI) were calculated. SPSS 21.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. A P value of < 0.05 was considered statistically significant.

3. Ethics statement

The protocol was approved by the Institutional Review Board at Chonnam National University Hwasun Hospital (CNUHH-2020-019). The trial was conducted in accordance with the Declaration of Helsinki 1964.

Results

1. Patient characteristics

In total, 38 patients with unresectable metastatic EP-NEC were analyzed in this study. The median age of the patients was 61.5 years (range 41–74), and there were 29 men (76.3%) and 9 women (23.7%). The primary origins of EP-NEC were the gastrointestinal tract (n = 15, 39.5%), hepatobiliary system (n = 10, 26.3%), and pancreas (n = 4, 10.5%), among others (n = 9, 23.7%). Surgical resection of the primary site at any stage was performed in 14 patients (36.8%), and of these, 8 patients underwent curative resection for stage II or III disease but experienced subsequent recurrence. The other 6 patients underwent palliative surgery, or undiscovered metastasis was detected in these patients after operation.

2. Treatment patterns

All patients received an etoposide plus cisplatin regimen as first-line chemotherapy, and the median number of chemotherapy cycles was 6 (range 2–13). Second-line chemotherapies were administered to 22 patients. After first-line chemotherapy, the numbers of patients who showed complete remission (CR), partial remission (PR), stable disease (SD), or progressive disease (PD) as the best response were 2, 17, 12, and 7, respectively (Table 1).

Table 1
Characteristics of all patients (n = 38)

	Number of patients (%)		
Age, years	Median	61.5	(range 41–74)
Sex	Male	29	(76.3)
	Female	9	(23.7)
Primary origin of NEC	Gastrointestinal	15	(39.5)
	Hepatobiliary	10	(26.3)
	Pancreas	4	(10.5)
	Others	9	(23.7)
Stage at initial diagnosis	I	0	(0.0)
	II	3	(7.9)
	III	5	(13.2)
	IV	30	(78.9)
Primary site resection	Yes	14	(36.8)
	No	24	(63.2)
Final stage before chemotherapy	Metastatic	30	(78.9)
	Recurrent	8	(21.1)
ECOG performance status	0	8	(21.1)
	1	27	(71.1)
	2	3	(7.9)
	3–4	0	(0.0)
Chemotherapy regimen	Etoposide/cisplatin	38	(100.0)
Cycles of chemotherapy	Median	6	(range 2–13)
Best response to chemotherapy	CR	2	(5.3)
	PR	17	(44.7)
	SD	12	(31.6)
	PD	7	(18.4)
Second-line chemotherapy	Yes	22	(57.9)

	Number of patients (%)	
No	16	(42.1)

Abbreviations: NEC, neuroendocrine carcinoma; ECOG, Eastern Cooperative Oncology Group; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

3. Response to systemic chemotherapy according to NLR or PLR

Patients were divided into two groups according to the cut-off values for NLR or PLR, and we compared each group. There was no significant difference in clinical manifestations and laboratory data between the high-NLR and low-NLR groups or the high-PLR and low-PLR groups. Furthermore, there was no significant difference in the best response to first-line chemotherapy between the NLR groups or the PLR groups. The overall disease control rate of first-line chemotherapy was 81.6%, and there was no significant difference according to NLR or PLR. Moreover, there was no significant difference in patients who received second-line chemotherapy according to NLR or PLR (Table 2).

Table 2
Clinical manifestations and laboratory data according to NLR and PLR at diagnosis (n = 38)

		NLR < 3 Number of patients, n = 22	NLR ≥ 3 Number of patients, n = 16	*P*	PLR < 160 Number of patients, n = 22	PLR ≥ 160 Number of patients, n = 16	*P*
Age, years				0.171			0.258
Median	(range)	62.5 (41.0–74.0)	60.5 (46.0–65.0)		62.5 (46.0–74.0)	59.5 (41.0–73.0)	
Sex				0.254			0.450
Male	n = 29	15	14		18	11	
Female	n = 9	7	2		4	5	
Primary origin				0.296			0.964
Gastrointestinal	n = 15	8	7		8	7	
Hepatobiliary	n = 10	8	2		6	4	
Pancreas	n = 4	1	3		2	2	
Others	n = 9	5	4		6	3	
Final stage before chemotherapy				0.426			0.106
Metastatic	n = 30	16	14		15	15	
Recurrent	n = 8	6	2		7	1	
ECOG performance status				0.650			0.548
0	n = 8	7	1		6	2	
1	n = 17	14	13		14	13	
2	n = 3	1	2		2	1	
Laboratory data							
LDH	Mean ± s.d.	554.55 ± 226.71	826.81 ± 696.74	0.460	677.78 ± 578.76	657.38 ± 366.02	0.574
AST	Mean ± s.d.	28.46 ± 14.41	40.31 ± 39.27	0.248	35.05 ± 34.42	31.25 ± 15.87	0.441
CRP	Mean ± s.d.	0.89 ± 0.84	2.14 ± 3.16	0.243	0.95 ± 0.94	2.05 ± 3.15	0.308

		NLR < 3 Number of patients, n = 22	NLR ≥ 3 Number of patients, n = 16	*P*	PLR < 160 Number of patients, n = 22	PLR ≥ 160 Number of patients, n = 16	*P*
Best response to initial chemotherapy				0.706			0.337
CR	n = 2	2	0		2	0	
PR	n = 17	8	9		10	7	
SD	n = 12	7	5		7	5	
PD	n = 7	5	2		3	4	
Disease control after chemotherapy				0.675			0.425
Controlled	n = 31	17	14		19	12	
Uncontrolled	n = 7	5	2		3	4	
Disease control rate (%)		89.5	87.5		86.4	75.0	
Second-line chemotherapy				0.861			0.624
Yes	n = 22	13	9		12	10	
No	n = 16	9	7		10	6	

Abbreviations: NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; AST, aspartate transaminase; CRP, C-reactive protein; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; s.d., standard deviation

4. Survival analysis by NLR and PLR

The overall median OS was 14.5 months, and the overall median PFS of first-line chemotherapy was 6.4 months. The effect of NLR and PLR at diagnosis on survival is shown in Fig. 1. The high-NLR group showed lower median PFS (5.7 months, 95% confidence interval [CI] 3.1–8.3) and median OS (11.1 months, 95% CI 7.8–14.5) than the low-NLR group (median 9.3 months, 95% CI 5.6–13.0 and median 17.1 months, 95% CI 12.5–21.6, respectively), but this difference was not significant (log-rank $P = 0.069$ and log-rank $P = 0.057$, respectively) (Fig. 1A and 1D). However, PLR at diagnosis showed a significant effect on the prognosis of first-line chemotherapy. The high-PLR group showed a significantly lower median PFS (4.1 months, 95% CI 2.7–5.4) and median OS (10.6 months, 95% CI 4.0-17.3) than the low-PLR group (median 9.3 months, 95% CI 7.0-11.6 and median 17.1 months, 95% CI 15.1–19.1, respectively; log-rank $P = 0.032$ and log-rank $P = 0.007$, respectively) (Fig. 1B and 1E).

Univariate analyses for PFS and OS were performed. Ki-67 and AST are well-known prognostic factors in NEC, but these factors were not associated with prognosis in this study. NLR had a higher hazard ratio (HR) than several other factors, but the difference was not significant. However, the high-PLR group showed a significant association with decreased PFS (HR 2.1, 95% CI 1.0–4.0, $P = 0.036$) and OS (HR 2.6, 95% CI 1.3–5.3, $P = 0.009$). Moreover, patients with high LDH levels (more than 1.5 times the ULN) showed significantly poorer PFS (HR 2.6, 95% CI 1.2–5.7, $P = 0.015$) and OS (HR 2.8, 95% CI 1.2–6.3, $P = 0.015$) than those with low LDH levels. In multivariate analysis, high PLR and LDH were independently associated with poor prognosis (Table 3).

Table 3. Univariate and multivariate analysis for progressive-free survival and overall survival

A. Progression-free survival

	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
Age ≥65	0.684	0.348-1.346	0.271			
Sex (male)	1.304	0.591-2.880	0.511			
Ki-67 ≥55%	1.080	0.548-2.126	0.824			
LDH ≥ULN	1.708	0.875-3.331	0.117			
LDH ≥1.5×ULN	2.628	1.204-5.732	0.015	3.424	1.497-7.830	0.004
AST ≥ULN	1.001	0.433-2.317	0.997			
AST ≥2×ULN	0.545	0.074-4.031	0.552			
CRP ≥ULN	1.596	0.786-3.238	0.196			
NLR ≥3.0	1.902	0.940-3.847	0.074			
PLR ≥160	2.060	1.049-4.047	0.036	2.605	1.275-5.322	0.009

B. Overall survival

	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
Age ≥65	0.845	0.410-1.743	0.649			
Sex (male)	1.181	0.508-2.745	0.699			
Ki-67 ≥55%	1.262	0.634-2.513	0.507			
LDH ≥ULN	1.705	0.844-3.442	0.137			
LDH ≥1.5×ULN	2.779	1.224-6.309	0.015	5.029	1.951-12.964	0.001
AST ≥ULN	1.029	0.443-2.391	0.947			
AST ≥2×ULN	0.415	0.055-3.151	0.395			
CRP ≥ULN	1.769	0.811-3.858	0.152			
NLR ≥3.0	1.960	0.967-3.971	0.062			
PLR ≥160	2.584	1.265-5.279	0.009	4.102	1.812-9.285	0.001

Abbreviations: HR, hazard ratio; CI, confidence interval; LDH, lactate dehydrogenase; ULN, upper limit of normal; AST, aspartate transaminase; CRP, C-reactive protein; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio

Discussion

The 2017 WHO classification histologically categorizes neuroendocrine neoplasms (NENs) as well-differentiated (including neuroendocrine tumor [NET] grade 1, 2, and 3) and poorly differentiated (or NEC), which feature small-cell types and large cell-type cells, respectively[13].

Previously, several studies have validated the prognostic factors in NENs. Although the survival times of NEN patients vary according to the stage, grade, and origin[2], only a few studies have distinguished between NETs and NECs. Therefore, this study evaluated patients with unresectable or metastatic EP-NEC who received platinum-based chemotherapy.

Some authors have reported that LDH and AST are independent factors representing poor prognosis in NEC[14–16]. Similarly, LDH was one of the impactful prognostic factors identified in this study. The characteristics of NECs, such as high glucose consumption, high lactate production, a hypoxic tumor environment because of poor vascularization, and high proliferation, could increase LDH levels[15, 17, 18].

However, AST was not a significant prognostic factor in this study. A previous study suggested a cut-off value of AST as 2 times the ULN[15], but there was only one patient with more than 2 times the ULN in this study. Therefore, to determine the prognostic significance of AST, a large number of patients with high AST levels should be included.

The Ki-67 protein is a cellular marker for cell proliferation[19], and the NORDIC NEC study by Sorbye *et al.* showed that NEC patients with Ki-67 < 55% had significantly longer survival than their counterparts with Ki-67 ≥ 55%[14]. However, Ki-67 was not a significant prognostic factor in this study. The NORDIC NEC study included patients with grade 3 NET, which was regarded as NEC according to the previous WHO classification, but we excluded these patients according to the recent classification. This discrepancy in classification could be responsible for the difference in results.

The relationship between the systemic inflammatory response and the outcome of cancer has been a focus of research in recent years. In particular, NLR and PLR have been established as prognostic factors in various solid tumors for predicting treatment outcomes. Recently, Salman *et al.* reported that these markers were associated with PFS in NETs as well[1]. Tumor-associated neutrophils (TANs) have been investigated for their protumorigenic, anti-apoptotic, and angiogenic roles and for promoting tumor progression, tumor invasion, and metastasis[20–22]. NLR is assumed to reflect an increase in TANs, and thus, NLR is considered an easily verifiable surrogate marker for TANs[11]. Although this study could not prove the significance of NLR in survival analysis, there was a remarkable difference in survival between patients with high NLR and those with low NLR (Fig. 1A and 1D). However, it is necessary to investigate the effect of NLR in a large cohort study.

In contrast, the high-PLR group had significantly shorter PFS and OS than the low-PLR group (Fig. 1B and 1E). This can be explained by the role of platelets in the inflammatory response. Platelet activation is

stimulated by chemokines and proinflammatory lipids and is connected with neutrophil recruitment. Therefore, PLR is a well-known inflammatory marker[23, 24]. Moreover, platelets play a remarkable role in tumor proliferation and distant metastasis by shielding tumor cells from immune responses and facilitating cancer growth and dissemination[25–27]. Therefore, PLR is an effective and independent prognostic factor in EP-NEC.

In addition to increased neutrophil and platelet counts, high NLR and PLR represent decreased lymphocyte counts. Lymphocytes play a major role in the cytotoxic cell death of tumor cells and the inhibition of tumor cell proliferation and migration[28, 29]. Thus, decreased lymphocyte counts might be associated with tumor progression and poor prognosis. This is an additional reason that explains the association of NLR and PLR with cancer prognosis.

PLR at diagnosis is easily measurable via peripheral blood samples, and it may be one of most significant and earliest prognostic markers for NEC. It may be helpful to estimate patient prognosis and to determine therapeutic strategies for clinicians.

There were several limitations to this study. First, because the sample size was relatively small, a large prospective cohort study is necessary to generalize these results. Second, although all patients had the same pathologic diagnosis of NEC, the origins of the NECs were quite heterogeneous. Nevertheless, to our knowledge, this is the first study to show that PLR is a significant prognostic factor for PFS and OS in EP-NEC. Further prospective studies optimizing the cut-off values are needed to confirm our results.

Conclusion

In addition to high LDH, high PLR was also significantly associated with decreased survival of EP-NEC patients who received platinum-based chemotherapy. Therefore, PLR may be an independent and easily measurable prognostic factor in EP-NEC at the beginning of diagnosis.

Abbreviations

EP-NEC
Extrapulmonary neuroendocrine carcinoma
NLR
Neutrophil-lymphocyte ratio
PLR
Platelet-lymphocyte ratio
OS
Overall survival
PFS
Progression-free survival
LDH

Lactate dehydrogenase
AST
Aspartate aminotransferase
CRP
C-reactive protein
ECOG
Eastern Cooperative Oncology Group
CI
Confidence interval
ULN
Upper limit of normal
TAN
Tumor-associated neutrophil
NET
Neuroendocrine tumor

Declarations

Ethical approval

The protocol was approved by the Institutional Review Board at Chonnam National University Hwasun Hospital (CNUHH-2020-019). The trial was conducted in accordance with the Declaration of Helsinki 1964.

Consent for publication

No identifying patient information was included in this study.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare no conflicts of interest.

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Authors' contributions

Study conception and design: W.K.B.

Acquisition of data: H.J.K., K.H.L., H.B.

Analysis and interpretation of data: H.J.K., K.H.L., H.J.S., W.K.B., J.E.H.

Manuscript preparation: H.J.K., K.H.L., H.B.

Critical revision of the manuscript: S.H.C., I.J.C., W.K.B., J.E.H.

Statistical analysis: H.J.K., W.K.B., E.C.H., J.E.H.

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Figures

Figure 1. Kaplan-Meier curves of progression-free survival (PFS) and overall survival (OS) in patients with neuroendocrine carcinoma (NEC)

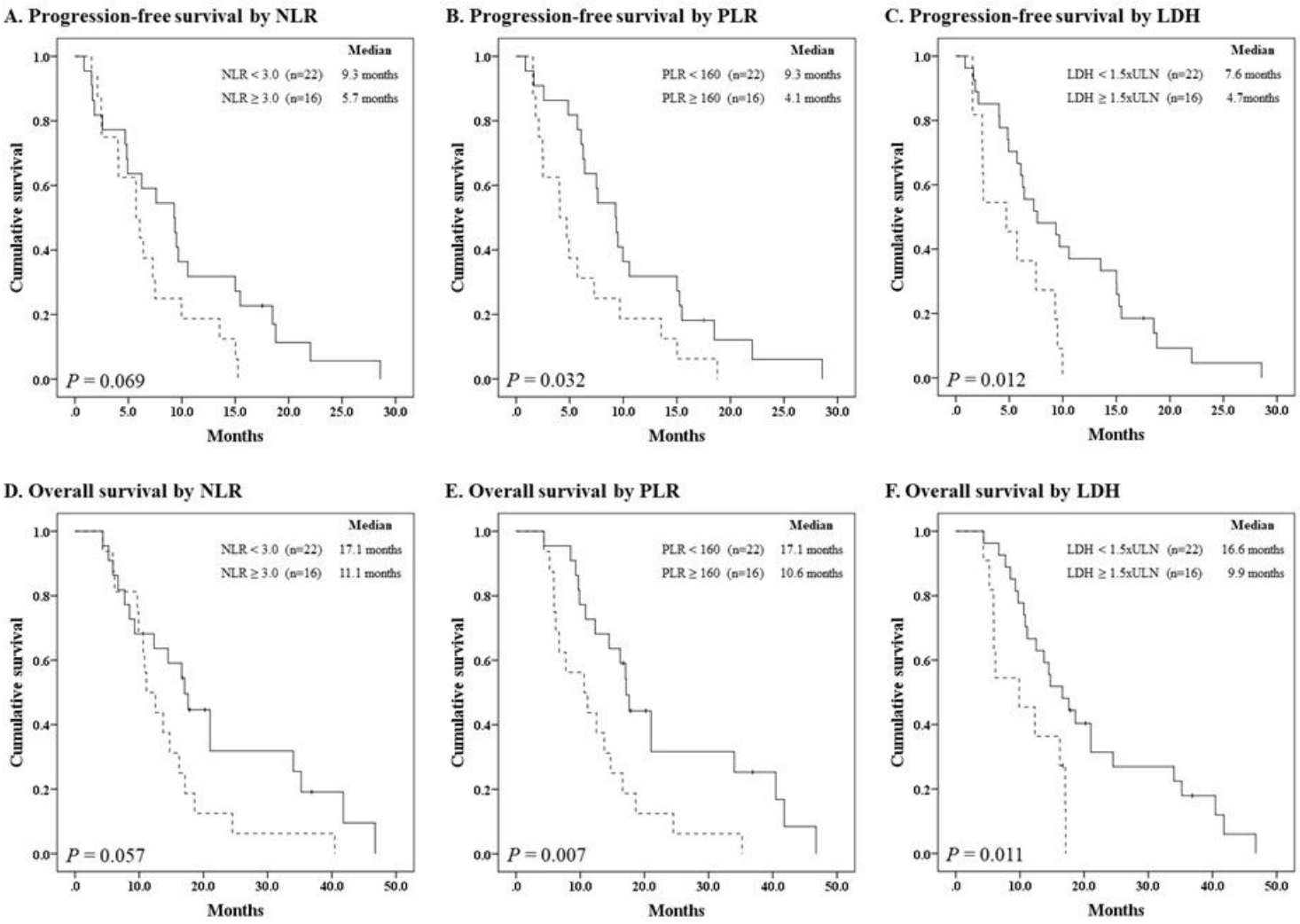


Figure 1

Kaplan-Meier curves of progression-free survival (PFS) and overall survival (OS) in patients with neuroendocrine carcinoma (NEC)