Neutrophil or platelet-to-lymphocyte ratios in blood are associated with poor prognosis of pulmonary large cell neuroendocrine carcinoma

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Background: Pulmonary large cell neuroendocrine carcinoma (LCNEC) is a rare clinical subtype of lung cancer which has a poor prognosis for patients. This study aimed to explore the relationship between blood-based inflammatory markers, namely neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), and the prognosis for pulmonary LCNEC.
Methods: Peripheral leukocyte and platelet counts of 106 LCNEC patients were measured within the week leading up to their surgery. Serum neuron specific enolase (NSE) was detected by ELISA. Overall survival (OS) was analyzed by Kaplan-Meier method and compared by log-rank test.
Results: The NLR and PLR cut-off values based on survival receiver operating characteristic curve (ROC) were 2.52 and 133.6, respectively. A correlation was found between dichotomized NLR and tumor size (P=0.006), and PLR and NLR were significantly correlated with each other (P<0.001). Patients with high NLR or PLR had shorter survival than those with low NLR (HR =2.46, 95% CI: 1.508–4.011, P<0.001) or PLR (HR =2.086, 95% CI: 1.279–3.402, P=0.003). Serum NSE also had a significant effect on patient survival (HR =2.651, 95% CI: 1.358–5.178, P=0.004). The effects of peripheral blood lymphocytes (P=0.001), neutrophils (P=0.023) and platelets (P=0.051) on patient survival were compared by log-rank test. In multivariate survival analysis, NLR (P<0.001) and T category were vital for the prognoses of LCNEC patients.
Conclusions: The inflammatory or immunological markers, NLR and PLR in blood, were independent factors of survival prediction for patients with LCNEC, which implied that cellular immunity was involved in the progression of LCNEC. Peripheral blood lymphocytes and neutrophils have a fundamental effect on survival. Whether or not NLR and PLR can be useful biomarkers in efficacy prediction of immunotherapy in LCNEC calls for further investigation.

Keywords: Pulmonary large cell neuroendocrine carcinoma (pulmonary LCNEC); inflammatory biomarkers; neutrophil-to-lymphocyte ratio (NLR); platelet-to-lymphocyte ratio (PLR); immunotherapy

Introduction

Pulmonary large cell neuroendocrine carcinoma (LCNEC), an extraordinarily rare malignant solid tumor, accounts for approximately 3% of all lung cancer cases (1). The prognosis for patients of LCNEC has been unpromising up to now. A systematic analysis derived from the SEER database showed that the 3-year OS and 5-year OS rates of LCNEC were 22.8% and 16.8%, respectively (2). LCNEC is a neuroendocrine carcinoma with similar manifestations to small cell lung cancer (SCLC) (3). However, the classical chemotherapy regimen for SCLC is less effective for LCNEC (4). Immune checkpoint inhibitors have recently shed some light on treatment of LCNEC, regardless of the positive expression of PD-1/PD-L1 (5,6), and inflammation and immunity have been uncovered as being of potential importance in the development of LCNEC.

Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are inflammation-associated indexes. It has been reported that NLR and PLR have performed well as predictors of survival and prognosis for a variety of malignant solid tumors (7-13), including non-small cell lung cancer (NSCLC) (10,14). Moreover, two recent studies have shown that NLR and PLR had predictive value in the treatment of NSCLC with checkpoint inhibitors, with higher NLR and PLR suggesting worse prognosis in immunotherapy (15-19).

In LCNEC, and even neuroendocrine tumors, however, the role of inflammatory markers has seldom been studied. In this study, we investigated the association between inflammatory markers and LCNEC patient survival and tried to estimate the prognostic value of NLR and PLR in LCNEC, which the aim of providing some clues regarding the prediction efficacy of NLR and PLR in LCNEC immunotherapy.

Methods

Patients and samples

A total of 106 patients who were diagnosed with LCNEC and underwent surgery at Shanghai Pulmonary Hospital between January 2011 and August 2016 were enrolled and followed up until March 2019. The inclusion criteria were in accordance with the World Health Organization (WHO) diagnostic criteria for LCNEC (3), while patients with autoimmune diseases and other primary tumors were excluded.

The patients' demographics and clinical characteristics were collected. Peripheral platelet and white blood cell count and serum neuron specific enolase (NSE) ELISA tests were performed within the week leading up to the surgery. The expression of neuroendocrine markers in the resected tumor samples (SYN, synaptophysin; CGA, chromogranin A, and CD56) was confirmed by immunohistochemistry.

Overall survival (OS) was defined as the time from the date of surgery to death or the date of the last follow-up. The survival time of patients who were still alive at the last date of follow-up was given as censored data.

Statistical analysis

A chi-square test, Fisher's exact test, and a correlation test were used to analyze the distribution of clinical characteristics data. The relative risk factor calculated by x-tile (version 3.6.1) was used to determine the optimal cut-off values for the continuous variables. The patients' OS was analyzed by the Kaplan-Meier diagram and compared by log-rank method. A multivariate Cox regression model was used to test the independent factors related to OS, and the hazard rates (HR) were calculated. All tests were bilateral, and a difference was considered significant when $P<0.05$. Data analysis was performed using SPSS software (version 24.0, IBM). The area under the curve (AUC) was calculated by a survival-dependent receiver operating characteristic curve (ROC) package in R language (version 3.6.1).

Results

### Clinicopathological characteristics and inflammatory markers of LCNEC patients

The demographic and clinicopathological characteristics of 106 patients with LCNEC are shown in *Table 1*. All of the patients were histologically diagnosed as LCNEC after surgery. Among them, 48 (45.3%) patients were at TNM stage I, 22 (20.8%) were at stage II, 29 (27.4%) were at stage III, and 7 (6.6%) were at stage IV. The patients ranged in age between 41 and 82 years, with a mean age of 65.6 years.

Both NLR and PLR levels showed no difference between the groups according to gender, age (<65 *vs.* ≥65), smoking history, TNM stage, lymph node metastasis, or neuroendocrine markers in the tumor. Since T staging is a rank variable, a correlation test was performed at NLR =2.52 (P=0.057). We therefore believe that there is a certain correlation between inflammatory index and tumor size. On

Table 1 Demographic and clinicopathological characteristics of 106 patients with LCNEC

Characteristic	Number of patients =106 (100%)	NLR		P	PLR		P
		<2.52	≥2.52		<133.6	≥133.6	
Gender							
Male	101 (95.3%)	63	38	0.427	68	33	0.735
Female	5 (4.7%)	4	1		3	2	
Age (year)							
<65	55 (51.9%)	37	18	0.37	36	19	0.73
≥65	51 (48.1%)	30	21		35	16	
Smoking history							
No	55 (51.9%)	31	24	0.436	33	22	0.364
Yes	51 (48.1%)	36	15		38	13	
TNM stage							
I	48 (45.3%)	32	16	0.866	32	16	0.489
II	22 (20.8%)	12	10		13	9	
III	29 (27.4%)	18	11		20	9	
IV	7 (6.6%)	5	2		6	1	
T category							
T1	42 (39.6%)	30	12	0.057	28	14	0.947
T2	48 (45.3%)	30	18		32	16	
T3	9 (8.5%)	4	5		7	2	
T4	7 (6.6%)	3	4		4	3	
Tumor size (cm)							
<4.5	72 (67.9%)	52	20	0.006*	52	20	0.065
≥4.5	30 (28.3%)	13	17		16	14	
T category (1, 2, 3 *vs.* 4)							
T1+T2+T3	99 (93.4%)	64	35	0.25	67	32	0.569
T4	7 (6.6%)	3	4		4	3	
N category							
N0	60 (56.6%)	40	20	0.508	41	19	0.596
N1	12 (11.3%)	6	6		9	3	
N2	28 (26.4%)	18	10		17	11	
N3	6 (5.7%)	3	3		4	2	
N category (0, 1, 2 *vs.* 3)							
N0+N1+N2	100 (94.3%)	64	36	0.593	67	33	0.946
N3	6 (5.7%)	3	3		4	2	
Neuroendocrine markers (CD56, SYN, CGA)							
1 positive NE marker	26 (24.5%)	17	9	0.747	16	10	0.578
≥2 positive NE markers	68 (64.2%)	42	26		46	22	
Neuron specific enolase (ng/mL)							
<28.44	83 (78.3%)	57	26	0.035*	59	24	0.075
≥28.44	13 (12.3%)	5	8		6	7	

*, the results were significantly different, which means the P value is less than 0.05. LCNEC, large cell neuroendocrine carcinoma; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.
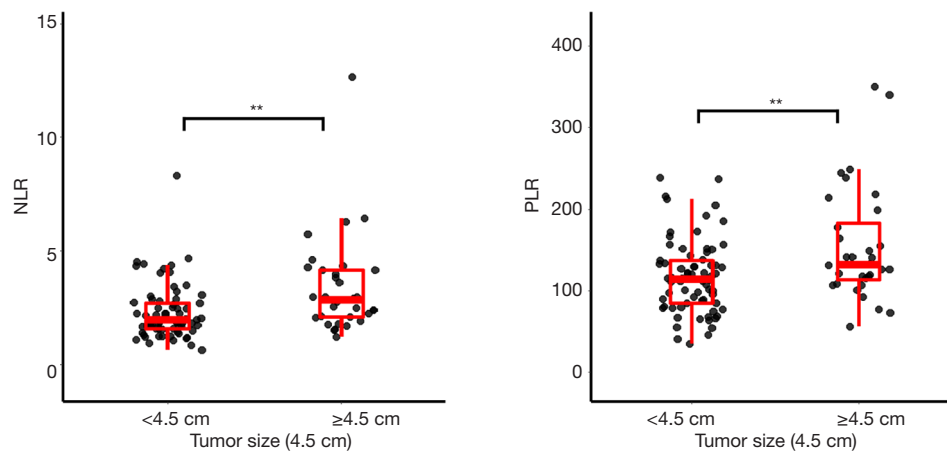
Figure 1 The distribution and dispersion trend of inflammatory index between tumor sizes less than 4.5 cm and larger than 4.5 cm. **, the results were significantly different, which means the P value is less than 0.05.
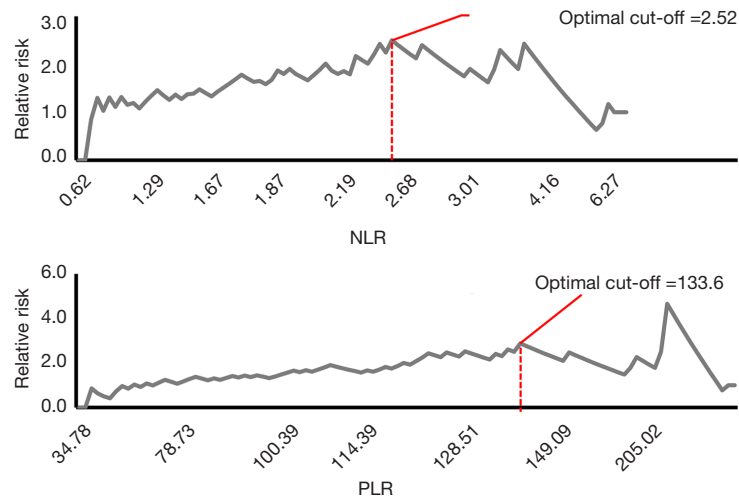
Figure 2 The risk coefficient series of PLR and NLR cut-off for the best discrimination of survival. PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio.

account of this, correlation analysis was conducted when tumor size =4.5 cm (P=0.006 NLR, P=0.065 PLR). This showed that tumor size was significantly correlated with NLR and PLR (P=0.001); when the tumors were larger, the inflammatory markers were higher (*Figure 1*).

Additionally, NSE, which is often used in the diagnosis of neuroendocrine carcinoma, was associated with dichotomized NLR distribution (P=0.035).

Dichotomized inflammatory markers

NLR and PLR were dichotomized by a series of cut-offs

to determine the best cut-off values of NLR and PLR in survival prediction of LCNEC. The best cutoffs of NLR (2.52) and PLR (133.6) were defined as those with the most appropriate relative risk coefficient in the x-tile (*Figure 2*), and the same method was used to determine the cut-offs of the absolute counts of lymphocytes (1.52×10^9), neutrophils (3.8×10^9), and platelets (254×10^9).

The AUC of the dichotomized NLR and PLR (0.629 and 0.612, respectively) were calculated in the time-dependent ROC (*Table 2*). Among the many indicators, NLR has the largest AUC, indicating its high predictive value.

Table 2 The optimal cut-off values based on OS

Peripheral blood index	Mean value	Minimum value	Maximum value	Cut-off value	AUC
NLR	1.61	0.62	12.66	2.52	0.629
PLR	128.12	34.78	350	133.6	0.612
Lymphocyte ($\times 10^9$)	0.80	4.54	1.9503	1.52	0.604
Neutrophil ($\times 10^9$)	1.56	12.43	4.5474	3.8	0.565
Platelet ($\times 10^9$)	104	466	224.50	254	0.552

OS, overall survival; AUC, area under the curve; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.
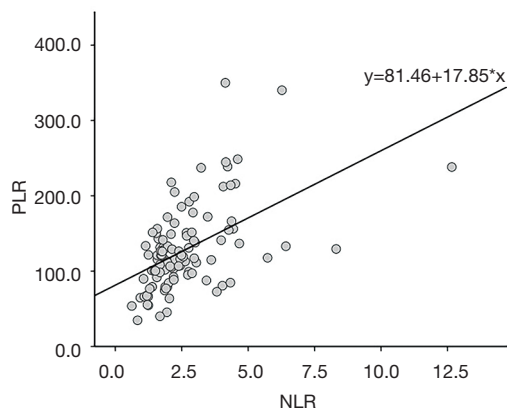
Figure 3 Scatter plots of NLR and PLR. PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio.

Table 3 Kappa test between dichotomized inflammatory markers

Inflammatory marks	NLR		P	Kappa
	<2.52	≥2.52		
PLR			<0.001	0.427
<133.6	54	16		
≥133.6	12	24		

NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Correlation between NLR and PLR in LCNEC patients

As shown in *Figure 3*, NLR and PLR in patients with LCNEC were linearly correlated to each other with a Pearson's correlation coefficient of 0.525 (P<0.001). As *Table 3* shows, a positive correlation between the dichotomized NLR and PLR was consistently found, with a kappa coefficient of 0.427 (P<0.001). This indicates that the NLR is closely related to the PLR.

Low NLR or PLR was predictive factor of unfavorable prognosis in LCNEC patients

Univariate OS analysis was performed on the 106 patients. The median survival was 2.01 years, and the 3- and 5-year survival rates were 34% and 36%, respectively.

Kaplan-Meier survival analysis with a log-rank test suggested that NLR (P<0.001) had a distinct significance in the OS of LCNEC patients (*Figure 4A*), with those in the low-NLR group surviving for longer. The survival outcomes for patients with a low PLR were also more positive (P=0.003) (*Figure 4B*). Patients with low NSE were also found to survive significantly longer than patients with high NSE (P=0.003), although the number of patients with high NSE was small (*Figure 4C*).

NLR is an independent predictive factor for the OS LCNEC patients in multivariate Cox regression

First, univariate Cox regression analysis of survival demonstrated that low NLR (HR =2.46, 95% CI: 1.508–4.011, P<0.001), PLR (HR =2.086, 95% CI: 1.279–3.402, P=0.003) and NSE (HR =2.651, 95% CI: 1.358–5.178, P=0.004) were protective factors for LCNEC patients. T category (T1, 2, 3 *vs.* T4) and N category (N0, 1, 2 *vs.* N3) also had important effects on LCNEC patient survival (*Table 4*).

To find out whether NLR and PLR were independent factors affecting survival, multivariate Cox regression analysis was performed using forward LR method. NLR (P<0.001) finally entered the model, while PLR failed to enter the model (*Table 4*). This may have been caused by the two indicators being too closely correlated (*Table 3*) and suggested that PLR was an independent prognostic factor for the LCNEC patients. T staging (P<0.001) had a decisive influence on the prognosis of the patients, which was higher than the effect of lymph node metastasis on
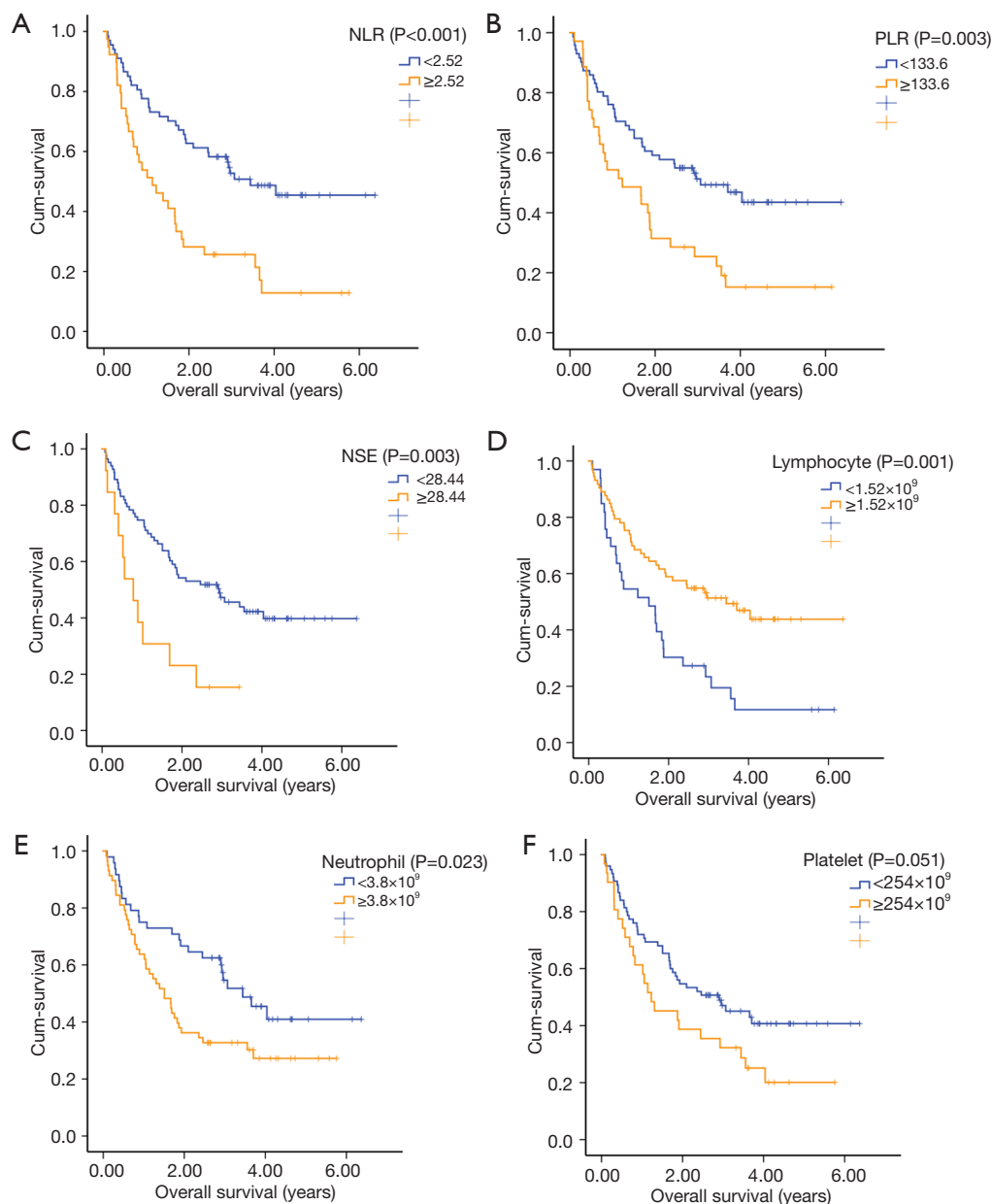
Figure 4 Survival curve of each index. (A) Survival curves of LCNEC patients grouped by dichotomized NLR; (B) survival curves of LCNEC patients grouped by dichotomized PLR; (C) survival curves of LCNEC patients grouped by NSE =28.44 ng/mL; (D) survival curves of LCNEC patients grouped by dichotomized lymphocyte; (E) survival curves of LCNEC patients grouped by dichotomized neutrophil; (F) survival curves of LCNEC patients grouped by dichotomized platelet. NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LCNEC, large cell neuroendocrine carcinoma; NSE, neuron specific enolase.

Table 4 Cox regression model of correlation factors, univariate and multivariate analysis

Associated factors of survival	Univariable analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
NLR						
≥2.52 *vs.* <2.52	2.46	1.508–4.011	<0.001*	2.747	1.594–4.733	<0.001*
PLR						
≥133.6 *vs.* <133.6	2.086	1.279–3.402	0.003*			
NSE (ng/mL)						
<28.44 *vs.* ≥28.44	2.651	1.358–5.178	0.004*			
Age (year)						
≥65 *vs.* <65	0.915	0.564–1.483	0.717			
Gender						
Male *vs.* female	2.029	0.812–5.071	0.154	2.798	0.985–7.948	0.053
Smoking history						
Yes *vs.* no	0.702	0.428–1.152	0.162			
T category						
T4 *vs.* T1+T2+T3	7.307	3.111–17.161	<0.001*	5.456	2.181–13.65	<0.001*
N category						
N3 *vs.* N0+N1+N2	2.925	1.166–7.338	0.022*			

*, the results were significantly different, which means the P value is less than 0.05. NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; NSE, neuron specific enolase.

their survival (*Table 4*).

The impact of lymphocytes, neutrophils and platelets on survival

As previously mentioned, the close correlation between NLR and PLR implied that it was most likely the number of lymphocytes that contributed to the survival predictive effects in patients with LCNEC. Based on this inference, we performed log-rank tests on absolute counts of peripheral lymphocytes. The result showed that the absolute lymphocyte count had a significant effect on the prognosis, and the prognosis of the group with a high lymphocyte count was better than that of the group with a low lymphocyte count (*Figure 4D*).

We conducted subsequent analysis on two other factors, neutrophils and platelets, to examine their effect on survival. The absolute count of neutrophils also had a statistically significant effect on the survival of LCNEC patients (*Figure 4E*). As with the effect of the absolute platelet count on survival (*Figure 4F*), patients with a low neutrophil count had a better prognosis than those in the high-count group. Therefore, the effect NLR and PLR have on survival can essentially be attributed to these three factors, particularly lymphocytes.

Discussion

LCNEC was first proposed in 1991 as a high-level neuroendocrine carcinoma distinct from SCLC, and was then included by the WHO in its new lung cancer classification (20). Despite LCNEC and SCLC each demonstrating neuroendocrine markers, the two differ remarkably in relation to both pathological morphology and genetic mutation profiling (21). Due to their neuroendocrine characteristics, chemotherapy (platinum/etoposide) and radiotherapy are the typical non-surgical treatment options (22). However, these traditional treatments are less effective for patients with LCNEC. No efficient novel treatment regimens have been widely

recognized in the last two decades, and the prognosis for LCNEC remains poor. Recently, several case reports have suggested that anti-PD-1/PD-L1 immunotherapy may provide a promising treatment option for LCNEC.

There is a lack of understanding surrounding the immunological characteristics of LCNEC. In 1985, the significance of NLR was first found in relation to respiratory inflammation, and patients with low NLR had better clinical outcomes (23). Up until now, the clinical significance of NLR has been revealed in a variety of infectious diseases, as well as in several kinds of cancer (24-27). For NSCLC, both NLR and PLR were reportedly reduced during concurrent chemoradiotherapy (P<0.001) (14), and were regarded as independent prognostic factors after pulmonary lobectomy (10). However, little is known about the significance of NLR and PLR for patients with LCNEC.

To our knowledge, this is the first report to reveal a close relationship between NLR or PLR and the prognosis of LCNEC patients. In this study, low NLR suggested favorable outcomes, while high NLR suggested poor survival, which is consistent with studies conducted on other kinds of cancer (11-13,18). Inflammatory markers in the peripheral blood, namely NLR and PLR, were found to be useful predictive prognostic factors for LCNEC.

Previous studies have uncovered that higher NSE (>44 ng/mL) was significantly associated with brain metastases in SCLC patients (28). In our study, higher NSE level (>28.44 ng/mL) was shown to be strongly related to shorter survival in LCNEC patients. Meanwhile, in a meta-analysis of castration-resistant prostate cancer, higher NSE and CGA hinted at an undesirable prognosis (29). In general, we can speculate that higher serum NSE may indicate poor prognosis for neuroendocrine neoplasms, including LCNEC.

In this study, we made a key observation that lymphocytes (P=0.001) and neutrophils (P=0.023) had a significant effect on LCNEC survival. Meanwhile, we found platelets (P=0.051) had a considerable effect on the survival of LCNEC patients. These findings suggest that these 3 factors (lymphocytes, neutrophils and platelets) are behind the impact NLR and PLR have on survival. This is a point that has generally been overlooked or not fully explored in existing research. Higher lymphocyte counts predicted longer survival, which is consistent with previous clinical studies of absolute lymphocyte counts in immunotherapy for NSCLC (30-32). Furthermore, generally, low neutrophil count results in longer survival, the mechanism behind which may be related to the cancer-promoting effect of neutrophils (33-35).

Additionally, we made the interesting observation that the levels of serum NSE in the high and low NLR groups seemed to be marginally different (P=0.035). Although serum NSE is a relevant indicator of neuroendocrine tumors, the combination of NLR or PLR with NSE may also hold some value for the clinical study of LCNEC.

Our data suggested that NLR and PLR levels were associated with tumor size. We proposed that tumor size probably affects the number of lymphocytes and other immunocytes in peripheral blood. This intriguing pattern implies that as the tumor grows, the lymphocyte-associated immune response may be downregulated.

Recently, NLR and PLR in NSCLC patients were demonstrated to be strongly correlated with the outcome of immuno-checkpoint inhibitors (15,33). Besides PD-L1 expression and TMB (tumor mutation burden), NLR and PLR may be additional biomarkers for the prediction of checkpoint inhibitors PD-1/PD-L1 antibodies (6). Checkpoint inhibitors were suggested in 2 case reports to be effective in LCNEC in spite of PD-L1 expression (36). Whether NLR and PLR hold promise as biomarkers in LCNEC for the prediction of checkpoint inhibitors efficacy is worthy of further study.

Conclusions

Due to the rarity of LCNEC, it is difficult to perform a study with a large cohort. In this study, we collected data from 108 cases of postoperative LCNEC, spanning a period of five years, and revealed that immunological markers, particularly NLR and PLR, can be used as predictive factors for the survival of LCNEC. Although dynamic monitoring of NLR and PLR before and after treatment may be more effective in predicting LCNEC survival, we found that one-off NLR and PLR detection before treatment can also hold a predictive value for the OS of LCNEC, particularly for early-stage patients. The value of NLR and PLR as predictive biomarkers for the efficacy of immune checkpoint inhibitors is worthy of further exploration in future clinical studies.

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