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ARTICLE

Neutrophil-to-Lymphocyte Ratio, Platelet-to-Lymphocyte Ratio, and Prognostic Nutritional Index as Prognostic Markers for Lung Carcinoma

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Abstract

Aims/Background Lung cancer (LC) remains one of the most common malignant tumours worldwide, and assessment of its progression is important for ensuring better prognostic outcomes for patients. This study was designed to explore the prognostic role of certain indices, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and prognostic nutritional index (PNI) in patients with LC, to help clinics to better determine the prognosis of patients with LC, and to allow them to intervene in a timely manner.

Methods A retrospective analysis of 116 initially diagnosed patients with LC in China from 2018 to 2020 was conducted. The counts of neutrophils (NEU), lymphocytes (LYM), and monocytes (MON), as well as albumin levels, were obtained from laboratory databases. The PNI was calculated using a specific formula. The progression-free survival (PFS) curves were plotted using the Kaplan–Meier method, and the Log-rank test was used to compare survival among different groups. The potential prognostic role of these indicators was assessed with univariate and multivariate regression analysis.

Results Multivariate Cox regression demonstrated that the PNI (hazard ratio (HR): 0.513, 95% confidence interval (CI): 0.288–0.917, $p = 0.024$), NLR (HR: 2.038, 95% CI: 1.128–3.682, $p = 0.018$), and tumour type (small cell lung cancer vs. non-small cell lung cancer) (HR: 2.145, 95% CI: 1.308–3.520, $p = 0.003$) were significantly associated with PFS. The median PFS for patients with low and high PNI was 10 and 11.5 months, respectively.

Conclusion The NLR, PLR, and PNI are all significantly associated with the prognostic survival of LC patients.

Key words: lung cancer; prognostic nutritional index (PNI); platelet-to-lymphocyte ratio (PLR); neutrophil-to-lymphocyte ratio (NLR); prognosis

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Introduction

Lung cancer (LC) is a fatal disease associated with high incidence and mortality (Bade and Dela Cruz, 2020). Moreover, it ranks first in global cancer-related mortality and stands as the second most prevalent malignancy among both men and women (Li et al, 2022; Siegel et al, 2023). For most patients, the condition has already progressed to an advanced stage upon diagnosis, with a 5-year survival of only 5–10% (Abu Rous et al, 2023). Treatment options include chemotherapy-,

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radiotherapy, targeted agents, and palliative care. Despite major advances in treatment, studies on prognosis are still limited (Mandaliya et al, 2019); as a result, predicting outcomes for individual patients is challenging. Consequently, it is imperative to identify biomarkers that can predict treatment outcomes and survival.

The systemic inflammatory response and nutritional status play a vital role during the neoplastic process and are actively engaged in the genesis and propagation of various types of cancer (Tsunematsu et al, 2023; Papa et al, 2023; Savioli et al, 2022). The inflammatory response triggers chronic oxidative stress and the generation of reactive oxygen species, contributing to cancer development and recurrence. Additionally, the inflammatory response is a key component of the body's immune reaction, and the progression and recurrence of cancer are closely related to immune function (Climent et al, 2019; Zattoni et al, 2023). Furthermore, nutritional status influences the immune system and tumour progression (Hamaker et al, 2021). Peripheral blood parameters including white blood cells (WBCs), neutrophils (NEU), lymphocytes (LYM), and platelets (PLT) are associated with systemic inflammation. Moreover, the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) are prognostic indicators for many malignancies such as biliary tract cancer and gastric cancer (Xu et al, 2021; Smith et al, 2022; Mandaliya et al, 2019; Wang et al, 2020). The prognostic nutritional index (PNI) is a prognostic index that reflects both nutritional and immunological status, which is measured based on the serum albumin (Alb) level and the LYM count in peripheral blood (Ding et al, 2022b). A low PNI predicts poor survival for patients with different malignancies (Xu et al, 2021; Li et al, 2021; Wang et al, 2020). However, data regarding the prognostic significance of systemic inflammation markers and nutritional indices in LC are lacking. Therefore, this study was conducted to determine if the NLR, PLR, and PNI can predict the prognosis of LC.

Clinical and pathological data of LC patients were collected to assess the prognostic value of immunoinflammatory and nutritional indicators in order to identify potential and easily accessible prognostic biomarkers for LC.

Methods

Study Participants

We retrospectively analyzed 116 patients with a confirmed diagnosis of LC, admitted to the Zhanjiang Central People's Hospital from 2018 to 2020. All patients received radical resection, combination chemotherapy, targeted therapy, or immunotherapy.

All patients were confirmed as LC by pathologic biopsy and had complete medical records. Patients with other systemic diseases before treatment, including those involving the blood, heart, brain, and kidney, autoimmune-related diseases, and those who were lost to follow-up were excluded. This study was conducted in strict compliance with the Declaration of Helsinki.

Clinical Data Collection and Processing

Patient information, including age, gender, tumour location, operative time, tumour size, metastatic status, and treatments received, was collected from the electronic medical records. All laboratory tests, including blood collection, processing, and quantification were performed using standard processes. Serum analysis was performed using LABOSPECT automatic analyzer (LABOSPECT 008 AS, Hitachi High-Tech Corporation, Tokyo, Japan) to define Alb levels, whereas peripheral blood cells including NEU, LYM, and PLT were counted by Sysmex analyzer (XN-1000, Sysmex, Tokyo, Japan). The data analyzed were tested using the same testing platform and a unified standard testing method. Progression-free survival (PFS) was analyzed for patients with adequate follow-up, and was defined as the period of time between the start of a patient's treatment and the observation of disease progression or the occurrence of death due to any cause.

NLR was calculated as the absolute neutrophil count divided by the absolute LYM count, and PLR was calculated as the PLT count divided by the absolute LYM count.

The prognostic nutritional index was calculated as follows:

PNI = [10 × Alb (g/L)] + [0.05 × LYM (%)] (Ding et al, 2022a).

Follow-up

Following treatment, patients were required to visit our outpatient clinics for regular follow-up, the frequency of which was set to every three months during the first 2 years, reduced to every 6 months until the fifth year, and once a year thereafter. The follow-up period varied from 4 to 60 months, with a median follow-up of 29 months, and the last follow-up was in November 2023.

Statistical Analyses

For univariate and multivariate analyses of prognostic factors associated with PFS, the cox proportional-hazards model (COX) proportional hazards model was adopted. The log-rank test and Kaplan–Meier analysis were applied for determination of survival curves and rates, with a p-value < 0.05 considered as statistically significant. Statistical analysis was conducted with SPSS software (version 23.0 for Windows, IBM, Chicago, IL, USA).

Results

Patients and Tumour Characteristics

A total of 116 patients with LC were enrolled in this study. Patients and tumour characteristics are summarized in Table 1. There were 82 (70.7%) male and 34 (29.3%) female patients, yielding a male-to-female ratio of 2.4:1.69 (59.5%) patients were aged ≥60 years, and 47 (40.5%) patients were aged <60 years. The primary tumours were located in the right lung in 51 (44%) patients, the left lung in 57 (49.1%) patients, and both lungs in only 8 (6.9%) patients. There were 68 (58.6%) patients in stage I–II, and 48 (41.4%) patients in stage III–IV. Forty-nine (42.2%) patients had cancer metastases. Oncogenic alterations were found in 63

patients, 26 (22.4%) with epidermal growth factor receptor (EGFR) mutations and 37 (31.9%) with an anaplastic lymphoma kinase (ALK) rearrangement (Table 1).

Table 1. Patient and tumour characteristics.

Characteristic	N (116)	Percentage (%)
Age		
Median (range), years	70.5 (35–90)	/
≥60	69	59.5
<60	47	40.5
Gender		
Male	82	70.7
Female	34	29.3
Staging		
I–II	68	58.6
III–IV	48	41.4
Location		
Right side	51	44
Left side	57	49.1
Both sides	8	6.9
Distribution type		
Central	66	56.9
Circumference	50	43.1
Metastatic status		
Yes	49	42.2
No	67	57.8
Style		
SCLC	41	35.3
NSCLC	75	64.7
Mutation status		
EGFR mutation	26	22.4
ALK mutation	37	31.9
No mutation	53	45.7
NLR		
<6.6	64	55.2
≥6.6	52	44.8
PLR		
<249	46	39.7
≥249	70	60.3
PNI		
<43	74	63.8
≥43	42	36.2

Abbreviations: SCLC, small-cell lung cancer; NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index.

Effect of NLR, PLR, and PNI on Prognostic Survival

The mean values for NLR, PLR, and PNI across all patients were (6.6 ± 1.8), (249 ± 34), and (43 ± 8), respectively. We sequentially categorized these patients into the NLR <6.6 (n = 64) group and the NLR ≥6.6 group (n = 52); the PLR <249 group (n = 46) and the PLR ≥249 group (n = 70), and the PNI <43 (n = 74) group and PNI ≥43 group (n = 42). The mean values were used as cutoffs for these groupings. Upon comparison, the differences in clinical data between the groups were not statistically significant ($p > 0.05$) and were comparable (Tables 2,3,4). As indicated by the Kaplan–Meier survival curves, NLR ≥6.6, PLR ≥249, and PNI <43 were associated with poor PFS (Fig. 1). For the comparison of survival outcomes among patients in different groups, the Log-rank test was employed. The median PFS for patients with low and high NLR was 11.5 and 9 months, for patients with low and high PLR the PFS was 12 and 9.5 months, and for patients with low and high PNI the PFS was 10 and 11.5 months, respectively ($p < 0.01$) (Table 5).

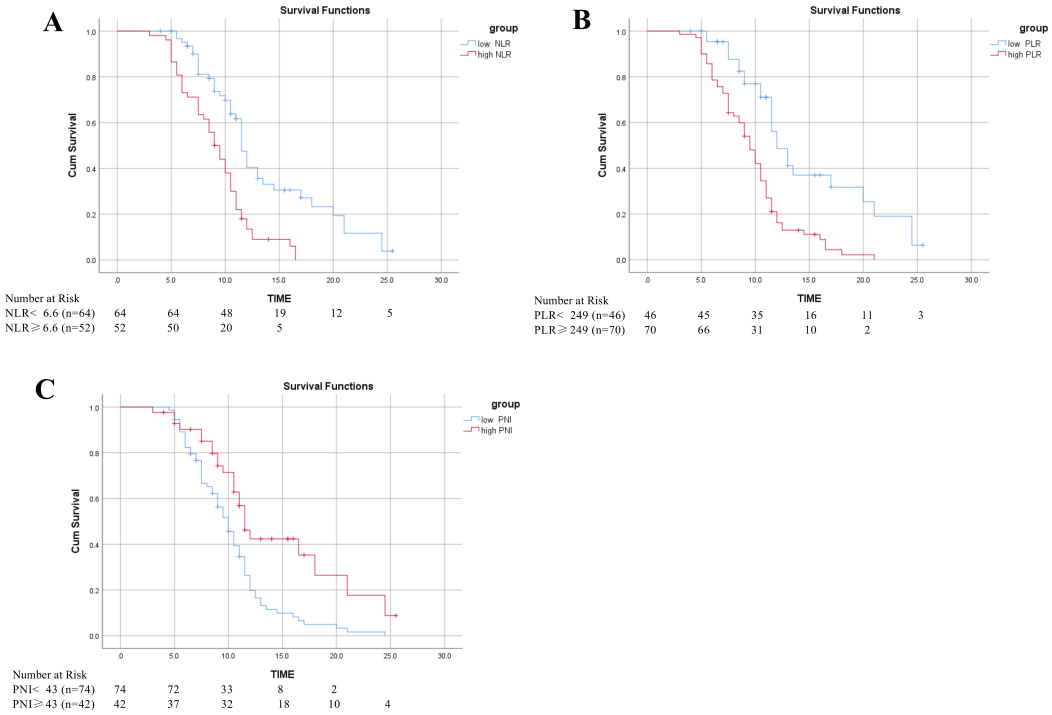

Fig. 1. Kaplan–Meier estimated survival probabilities based on low and high (A) neutrophil-to-lymphocyte ratio (NLR), (B) platelet-to-lymphocyte ratio (PLR), and (C) prognostic nutritional index (PNI).

Risk Factors for Decreased PFS

Each parameter was tested as a predictor of PFS using univariate regression analysis. Age (hazard ratio (HR): 1.018, 95% confidence interval (CI): 1.003–1.034, $p = 0.018$), PLR ≥249 (HR: 2.760, 95% CI: 1.697–4.487, $p < 0.001$), NLR ≥6.6 (HR: 2.539, 95% CI: 1.664–4.042, $p < 0.001$), PNI ≥43 (HR: 0.468, 95% CI: 0.292–0.750, $p = 0.002$), metastatic status (HR: 1.829, 95% CI: 1.204–2.781, p

Table 2. Comparison of baseline information between NLR <6.6 and NLR ≥6.6 groups.

Characteristic	NLR <6.6 (n = 64)	NLR ≥6.6 (n = 52)	χ^2 value	*p*-value
Age			1.242	0.265
≥60 years	41	28		
<60 years	23	24		
Gender			0.845	0.378
Male	43	39		
Female	21	13		
Staging			0.886	0.347
I–II	40	28		
III–IV	24	24		
Location			0.160	0.923
Right side	29	22		
Left side	31	26		
Both sides	4	4		
Distribution type			1.663	0.197
Central	22	24		
Circumference	44	26		
Metastatic status			0.552	0.458
Yes	29	20		
No	35	32		
Style			0.022	0.882
SCLC	23	18		
NSCLC	41	34		
Mutation status			5.533	0.063
EGFR mutation	26	11		
ALK mutation	11	15		
No mutation	27	26		

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; SCLC, small-cell lung cancer; NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.

= 0.005), and small-cell lung cancer (SCLC) (HR: 2.034, 95% CI: 1.337–3.095, p = 0.001) were significant predictors of PFS.

The multivariate analysis included factors such as age, stage, and metastatic status, all of which were identified as significant predictors ($p < 0.05$) in the univariate analysis. According to the results, PNI (HR: 0.513, 95% CI: 0.288–0.917, p = 0.024), NLR (HR: 2.038, 95% CI: 1.128–3.682, p = 0.018), and tumour type (SCLC vs. non-small cell lung cancer (NSCLC)) (HR: 2.145, 95% CI: 1.308–3.520, p = 0.003) were independent prognostic factors for PFS in patients with LC (Table 6).

Discussion

Our study validated the prognostic value of systemic inflammation markers (i.e., NLR, PLR) and PNI in patients with LC. NLR, PLR, and PNI were calculated based on the number of NEU, LYM, PLT, and the level of Alb. NEU and LYM are

Table 3. Comparison of baseline information between PLR <249 and PLR ≥249 groups.

Characteristic	PLR <249 (n = 46)	PLR ≥249 (n = 70)	χ^2 value	*p*-value
Age			1.690	0.194
≥60 years	24	45		
<60 years	22	25		
Gender			1.072	0.301
Male	35	47		
Female	11	23		
Staging			0.138	0.710
I–II	26	42		
III–IV	20	28		
Location			0.031	0.985
Right side	20	31		
Left side	23	34		
Both sides	3	5		
Distribution type			0.491	0.484
Central	28	38		
Circumference	18	32		
Metastatic status			0.693	0.405
Yes	22	28		
No	24	42		
Style			2.859	0.091
SCLC	12	29		
NSCLC	34	41		
Mutation status			2.270	0.321
EGFR mutation	16	21		
ALK mutation	7	19		
No mutation	23	30		

Abbreviations: PLR, platelet-to-lymphocyte ratio; SCLC, small-cell lung cancer; NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.

WBCs that reflect individual systemic and local inflammatory status. NEU produce chemokines, cytokines, and growth factors that may stimulate angiogenesis and facilitate proliferation and migration of tumour cells (Masucci et al, 2019). However, LYM have antitumour effects through T lymphocyte-mediated cellular immunity (Han et al, 2023). High PLT counts are associated with adverse outcomes in various types of cancers, and they enhance tumour growth through the secretion of certain factors (e.g., transforming growth factor-β2 (TGF-β2)). Activated PLT prevent the tumour cells from interacting with cytolytic immune cells by forming layers around the tumour cells (Mandel et al, 2022; Wang et al, 2022). In addition, patients with advanced cancer are often in a state of nutritional depletion, and Alb is one of the indicators that reflect the nutritional status of the body (Luo et al, 2023; Wellhausen et al, 2023). NLR, PLR, and PNI indices have predictive value in patients with can-

Table 4. Comparison of baseline information between PNI <43 and PNI ≥43 groups.

Characteristic	PNI <43 (n = 74)	PNI ≥43 (n = 42)	χ^2 value	*p*-value
Age			2.499	0.114
≥60 years	40	29		
<60 years	34	13		
Gender			0.514	0.473
Male	54	28		
Female	20	14		
Staging			0.871	0.351
I–II	41	27		
III–IV	33	15		
Location			4.669	0.097
Right side	27	24		
Left side	41	16		
Both sides	6	2		
Distribution type			1.466	0.226
Central	39	27		
Circumference	35	15		
Metastatic status			0.464	0.496
Yes	33	16		
No	41	26		
Style			0.759	0.384
SCLC	24	17		
NSCLC	50	25		
Mutation status			3.145	0.208
EGFR mutation	24	13		
ALK mutation	20	6		
No mutation	30	23		

Abbreviations: PNI, prognostic nutritional index; SCLC, small-cell lung cancer; NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.

cer, supporting the findings of our univariate analysis (Chen et al, 2019; Inoue et al, 2022; Mo et al, 2020; Misiewicz and Dymicka-Piekarska, 2023).

Despite the increasing scientific evidence substantiating the predictive value of blood-derived inflammation and nutrition indices, the best predictors among them remain unknown. Through multivariate analysis, a previous study found the NLR to be the only independent predictive factor for complete response among blood-derived inflammation markers (Eren et al, 2020). The LMR was identified as the only independent predictive factor for the effect of neoadjuvant chemotherapy among inflammatory markers in 808 patients with breast cancer (Peng et al, 2020). In addition, the PLR demonstrated superior efficacy in treatment response prediction for gastric cancer compared to NLR (Hu et al, 2020).

In our study, all three markers were significantly associated with PFS in patients with LC in univariate analysis. However, only the PNI and NLR were sig-

Table 5. Progression-free survival of different groups.

Group	MST (months)	95% CI	χ^2 value	*p*-value
NLR			5.164	<0.01
<6.6	11.5	10.838–12.162		
≥6.6	9	7.845–10.155		
PLR			5.751	<0.01
<249	12	10.206–13.794		
≥249	9.5	8.508–10.492		
PNI			4.512	<0.01
<43	10	8.956–11.044		
≥43	11.5	10.325–12.675		

Abbreviations: MST, median survival time; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index.

Table 6. Univariate and multivariate COX regression analysis of PFS.

	Univariate analysis			Multivariate analysis		
Factor	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age (per year)	1.018	1.003–1.034	0.018	1.002	0.984–1.020	0.841
Female (vs. Male)	0.982	0.625–1.544	0.938			
Stage III–IV (vs. I–II)	1.777	1.170–2.699	0.007	0.154	0.016–1.519	0.109
Right side (vs. Left side)	0.980	0.701–1.371	0.907			
Central (vs. Circumference)	0.860	0.563–1.313	0.860			
Metastatic status (Yes vs. no)	1.829	1.204–2.781	0.005	8.176	0.792–84.396	0.078
SCLC (vs. NSCLC)	2.034	1.337–3.095	0.001	2.145	1.308–3.520	0.003
EGFR mutation (Yes vs. no)	1.362	0.847–2.190	0.203			
ALK mutation (Yes vs. no)	0.921	0.591–1.435	0.715			
NLR (≥6.6 vs. <6.6)	2.539	1.664–4.042	0.000	2.038	1.128–3.682	0.018
PLR (≥249 vs. <249)	2.760	1.697–4.487	0.000	1.731	0.884–3.387	0.109
PNI (≥43 vs. <43)	0.468	0.292–0.750	0.002	0.513	0.288–0.917	0.024

Abbreviations: HR, hazard ratio; CI, confidence interval; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index.

nificantly associated with PFS according to the multivariate analysis. The PNI is derived from Alb level and LYM counts, reflecting both the inflammatory and nutritional status. Our results suggest that the combination of inflammation and nutrition status better predicts outcomes in patients with cancer. The NLR reflects the active state of neutrophils and lymphocytes in the immune system. Increased neutrophil numbers are associated with inflammatory responses, whereas decreased lymphocyte numbers are associated with stress responses. Therefore, NLR ratio changes can indirectly reflect the strength of the body's inflammatory response and the stress state of the immune system.

Nevertheless, there are certain limitations in our study. First, it is a retrospective and single-center analysis with a relatively small sample size. Second, although we excluded patients with systemic diseases, the evaluation of blood biomarkers may be affected by various other conditions. Therefore, further studies are needed to validate and corroborate our findings.

Conclusion

In LC patients, NLR, PLR, and PNI are all potentially associated with patient prognostic survival, with PNI and NLR being independent predictors of the prognosis in LC patients.

Key Points

- The NLR and PLR reflect inflammatory and immune status and predict prognosis: High NLR and PLR values are associated with poor prognosis in LC patients, indicating a higher inflammatory response and lower immune surveillance capacity in the body. NLR and PLR can serve as independent predictors to assess survival and risk of recurrence in patients with LC.
- The PNI assesses nutrition and immune function and predicts survival: Low PNI values indicate malnutrition and immunosuppression, and are associated with poorer survival and higher complication rates in LC patients. PNI, as a comprehensive index, can effectively predict the prognosis of LC patients by combining serum Alb level and LYM number.
- The NLR, PLR, and PNI are non-invasive, easily accessible, and cost-effective blood markers. They can provide valuable prognostic information through routine blood tests, and can help clinicians develop personalized treatment plans and follow-up strategies to improve treatment outcomes and survival for LC patients.

Availability of Data and Materials

The datas used and/or analyzed during the current study are available from the corresponding author.

Author Contributions

HM, WW and DZ designed the research study. WW, JX and DZ performed the research. HM provided help and advice on the experiments. HL and CY analyzed the data. HL, JX and CY drafted the manuscript. All authors contributed to the important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the Research Ethics Committee of Zhanjiang Central People's Hospital (China) (ZJCH2024013). The Zhanjiang Central People's Hospital Ethics Committee waived the requirement for written informed consent from patients because the study was retrospective and noninterventional.

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Conflict of Interest

The authors declare no conflict of interest.

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