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Prognostic Value of the Lung Immune Prognostic Index for Progression-Free Survival and One-Year Survival in Advanced Non-Small Cell Lung Cancer Treated with Platinum-Based Chemotherapy

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ABSTRACT

Background: Evidence regarding the prognostic value of the Lung Immune Prognostic Index (LIPI) in Indonesian patients with advanced non-small cell lung cancer (NSCLC) receiving platinum-based chemotherapy remains limited. This study aimed to evaluate baseline LIPI for progression-free survival (PFS) and one-year survival in patients with stage IV NSCLC receiving platinum-based chemotherapy.

Subjects and Method: This retrospective cohort included 111 patients with pathologically confirmed stage IV NSCLC receiving platinum-based chemotherapy at Dr. Moewardi Hospital, Surakarta, Indonesia. Records from January 2023 to June 2025 were sampled consecutively. Baseline LIPI was the independent variable; PFS and one-year survival were the dependent variables; and clinical factors were covariates. LIPI was calculated from pretreatment leukocyte and neutrophil counts and serum lactate dehydrogenase measured with the Mindray BS-600M before the first chemotherapy cycle. Progression was determined using RECIST 1.1 or the treating physician's assessment, and survival status was obtained from records and telephone follow-up. Kaplan-Meier, log-rank, and Cox regression analyses were used.

Results: Good, intermediate, and poor LIPI were observed in 27 (24.3%), 53 (47.7%), and 31 (27.9%) patients, respectively. Median PFS was 272, 141, and 144 days across these groups, without a significant overall difference (p= 0.062). LIPI was not independently associated with PFS (overall p= 0.162); M1c2 metastasis independently predicted progression (aHR= 1.94; 95% CI=1.09 to 3.43; p= 0.024). One-year survival differed across LIPI groups (p=0.038), but LIPI was not independently associated with mortality after adjustment (overall p=0.274). Squamous cell carcinoma independently predicted one-year mortality relative to adenocarcinoma (aHR= 2.62; 95% CI=1.46 to 4.69; p=0.001).

Conclusion: Baseline LIPI stratified one-year survival but was not an independent predictor of PFS or one-year mortality after multivariable adjustment. Metastatic burden and histopathology provided stronger independent prognostic information in this cohort.

Keywords: lung cancer, platinum chemotherapy, progression-free survival, survival

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BACKGROUND

Lung cancer remains one of the most frequently diagnosed cancers and the leading cause of cancer mortality worldwide. Global Cancer Observatory (GLOBOCAN) in 2022 estimates indicate approximately 2.48 million new cases and 1.82 million deaths, and the global burden is expected to rise as populations grow and age (Bray et al., 2024; Ji et al., 2025; Zhou et al., 2024). In Indonesia, lung cancer is a major cause of cancer death, and national guidance emphasizes earlier diagnosis and evidence-based management (Andarini et al., 2023; Andarini et al., 2024).

The management of advanced NSCLC is increasingly guided by histopathology, molecular alterations, disease extent, performance status, and treatment eligibility. Molecular profiling and immune-based therapy have expanded treatment options, but platinum-based chemotherapy remains clinically relevant for many patients (Jeon et al., 2025; Wang et al., 2025). Reliable, inexpensive biomarkers that can be calculated from routine tests may help clinicians describe prognosis in settings where access to complex molecular assays is limited.

The LIPI combines two baseline variables: a derived neutrophil-to-lymphocyte ratio (dNLR) greater than 3 and serum lactate dehydrogenase (LDH) above the laboratory upper limit of normal. Patients with neither risk factor are classified as good, those with one factor as intermediate, and those with both factors as poor. The index integrates host inflammatory status and tumor metabolic activity. Neutrophil-dominant inflammation may promote tumor growth and immune suppression, while elevated LDH can reflect hypoxia, glycolytic activity, necrosis, and tumor burden (Miholjcic et al., 2023; Mishra and Banerjee, 2019; Park and Chung, 2024; Xue et al., 2025; Yang et al., 2021).

LIPI was initially developed in advanced NSCLC treated with immune checkpoint inhibitors, where poorer categories were associated with shorter PFS and overall survival (Mezquita et al., 2018). Subsequent studies and meta-analyses have supported its prognostic value across systemic treatments, although estimates vary with therapy, disease stage, population characteristics, and the timing of LIPI measurement (Huang et al., 2021; Riudavets et al., 2024; Wang et al., 2024; Xiong et al., 2023; Zhi et al., 2024). Evidence specifically addressing platinum-based chemotherapy in Indonesian patients remains limited. Local differences in stage at presentation, treatment access, laboratory reference ranges, and case mix may affect both the distribution and prognostic performance of LIPI. Evaluating LIPI in an Indonesian platinum-treated cohort is therefore important to determine whether this inexpensive routine-laboratory index provides prognostic information beyond established clinical factors in the local setting.

This study therefore assessed the prognostic value of baseline LIPI for PFS and one-year survival in patients with advanced NSCLC who received platinum-based systemic chemotherapy at Dr. Moewardi Hospital, Surakarta. The primary question was whether LIPI independently predicted progression free survival and one-year mortality after adjustment for relevant demographic and clinical factors.

SUBJECTS AND METHOD

1. Study Design

This retrospective cohort study used medical-record data from Dr. Moewardi Hospital, Surakarta, Indonesia. Eligible patients were diagnosed with NSCLC between 1 January 2023 and 30 June 2025. Data collection was performed in September 2026.

2. Population and Sample

The source population comprised patients with advanced NSCLC treated at Dr. Moewardi Hospital. Consecutive sampling was applied to available records. The minimum sample size was calculated using a survival-analysis formula based on median survival of 12.1 months for intermediate LIPI and 7.5 months for poor LIPI reported by Huang et al. (2021), a 12-month accrual period, 12-month follow-up, a two-sided alpha of 0.05, 90% power, and a median-survival ratio of 0.619. The calculated sample was 64.27, rounded to 65; allowing 10% for incomplete records increased the minimum target to 72. Of 1,685 records screened, 1,574 were excluded because they did not meet one or more eligibility criteria, and 111 were analyzed. The retrospective screening log did not preserve mutually exclusive counts for individual exclusion reasons.

Inclusion criteria were age greater than 18 years; pathologically confirmed NSCLC; availability of age, sex, smoking history, histopathology, serum LDH, and routine blood differential data; receipt of platinum-based systemic chemotherapy; and stage IV disease (IVA or IVB). Patients were excluded if progression or one-year survival data were unavailable; records were incomplete; an autoimmune disease, acute myocardial infarction, pulmonary embolism, acute infection, or sepsis was present when blood was sampled; death was unrelated to malignancy or could not be ascertained; or targeted therapy or immunotherapy was received.

3. Study Variables

The principal independent variable was baseline LIPI. Other covariates were sex, age, smoking history, stage, histopathology, brain metastasis, and TNM metastatic category. The dependent outcomes were PFS and one-year survival.

4. Operational Definition of Variables

Baseline LIPI was calculated from leukocyte, absolute neutrophil, and serum LDH results documented after the NSCLC diagnosis and before the first cycle of platinum-based chemotherapy. dNLR was calculated as the absolute neutrophil count divided by the difference between total leukocyte count and absolute neutrophil count. A dNLR greater than 3 was considered elevated. Serum LDH was measured using the Mindray BS-600M system; the institutional upper limit of normal was 300 U/L. LIPI was classified as good when neither risk factor was present, intermediate when one factor was present, and poor when both factors were present.

PFS was measured in days from the date of NSCLC diagnosis to the first documented progression according to RECIST 1.1 or the treating physician's recorded clinical or radiological assessment. If death occurred before a radiological evaluation, the date of death was treated as a progression event. One-year survival was measured from diagnosis to death within one year; patients without a recorded death by the end of the one-year observation period were censored. Metastatic categories were recorded as M1a, M1b, M1c1, or M1c2 in accordance with the ninth-edition TNM framework (Rami-Porta et al., 2024).

5. Study Instruments and Data Collection

Data were obtained from hospital medical records and included diagnosis date, age, sex, smoking history, histopathology, stage,

metastatic category, brain metastasis, serum LDH, leukocyte and neutrophil counts, treatment, progression date, and survival status. When death was not recorded in the medical record, the family was contacted by telephone to ascertain whether the patient was alive. Statistical analyses were performed using IBM SPSS Statistics version 26.

6. Data Analysis

Continuous and categorical variables were summarized descriptively. Data normality was assessed using the Kolmogorov–Smirnov test. Survival was estimated using Kaplan–Meier analysis and compared across LIPI groups with the log-rank test. Cox proportional-hazards regression estimated crude hazard ratios (cHRs) and adjusted hazard ratios (aHRs) with 95% confidence intervals. The prespecified candidate covariates were sex, age, smoking history, stage, histopathology, brain metastasis, TNM metastatic category, and LIPI. All candidate variables were assessed in bivariable models, and variables with p <0.250 were entered into the multivariable model; no additional variables were forced into the models. The PFS model included 111 events and nine estimated parameters (approximately 12.3 events per parameter). The one-year mortality model included 59 events and eleven estimated parameters (approximately 5.4 events per parameter), indicating a risk of overfitting and requiring cautious interpretation. Formal multicollinearity diagnostics and formal testing of the proportional-hazards assumption were not performed. Two-sided p values below 0.050 were considered statistically significant.

7. Research Ethics

This study was approved by the Health Research Ethics Committee of Dr. Moewardi General Hospital, Surakarta, Indonesia (Ethical Clearance No. 1.450/VIII/HREC/-2026; issued 24 August 2026). The approval letter identifies Yunita as the principal investigator and Dr. Moewardi Hospital, Surakarta, as the study site.

RESULTS

1. Sample Characteristics

Among 111 included patients, 63 (56.8%) were men, 59 (53.2%) were aged 60 years or older, and 70 (63.1%) had stage IVB disease. Adenocarcinoma was the predominant histopathological subtype (70 patients; 63.1%), followed by squamous cell carcinoma (38; 34.2%). Brain metastasis was documented in 33 patients (29.7%). The most frequent metastatic category was M1a (36; 32.4%), followed by M1c1 (34; 30.6%), M1c2 (24; 21.6%), and M1b (17; 15.3%).

LIPI was good in 27 patients (24.3%), intermediate in 53 (47.7%), and poor in 31 (27.9%). Mean serum LDH was 390.97 U/L (SD= 299.68), with 60 patients (54.1%) above 300 U/L. Mean dNLR was 3.62 (SD= 2.17), and 55 patients (49.5%) had dNLR greater than 3. During one-year follow-up, 59 patients (53.2%) died and 52 (46.8%) remained alive. The overall median PFS was 162 days, and median one-year survival was 304 days.

Table 1. Demographic and Clinical Characteristics

Category or summary	N	%
Sex		
Male	63	56.8
Female	48	43.2
Age		
<60 years	52	46.8

Category or summary	N	%
≥60 years	59	53.2
Stage		
IVA	41	36.9
IVB	70	63.1
Histopathology		
Adenocarcinoma	70	63.1
Squamous cell carcinoma	38	34.2
Large cell carcinoma	2	1.8
Adenosquamous carcinoma	1	0.9
Smoking history		
No	59	53.2
Yes	52	46.8
LIPI		
Good	27	24.3
Intermediate	53	47.7
Poor	31	27.9
Brain metastasis		
No	78	70.3
Yes	33	29.7
TNM metastatic category		
M1a	36	32.4
M1b	17	15.3
M1c1	34	30.6
M1c2	24	21.6
One-year outcome		
Alive	52	46.8
Died	59	53.2

Table 2. Laboratory Parameters and Survival Outcomes

Characteristic	Mean	SD	Median	Min.	Max..
LDH, U/L	390.97	299.68	323.00	167	2,975
dNLR	3.62	2.17	3.00	1.17	17.15
PFS, days	-		162.00	24	796
One-year survival, days	-		304.00	29	365

Note: dNLR=derived neutrophil-to-lymphocyte ratio; LDH=lactate dehydrogenase; LIPI=Lung Immune Prognostic Index; PFS=progression-free survival; SD=standard deviation.

2. Survival Analysis by LIPI

All 111 patients were counted as having a PFS event, and none were censored. Events comprised documented clinical or radiological progression and deaths occurring before radiological evaluation; however, the analytic output did not separately tabulate these two event types. Median PFS was 272 days in the good LIPI group, 141 days in the intermediate group, and 144 days in the poor group. The difference across groups did not reach statistical significance (log-rank chi-square=5.57; p=0.062). Although the good group had a visibly longer PFS, the intermediate and poor groups had similar median estimates.

Table 3. Kaplan-Mejer Survival Estimates According to LIPI Category

Outcome and LIPI	N	Events	Mean days (95% CI)	Median days (95% CI)	Log-rank χ^2	p
PFS – Good	27	27	269.26 (218.23 to 320.29)	272.00 (171.92 to 372.08)	5.57	0.062
PFS – Intermediate	53	53	183.60 (146.04 to 221.17)	141.00 (115.52 to 166.48)		
PFS – Poor	31	31	190.74 (145.32 to 236.16)	144.00 (103.10 to 184.90)		
PFS – Overall	111	111	206.43 (180.55 to 232.32)	162.00 (130.23 to 193.77)		
One-year survival – Good	27	9	314.19 (281.16 to 347.21)	Not reached	6.56	0.038
One-year survival – Intermediate	53	29	253.79 (222.12 to 285.47)	303.00 (not estimable)		
One-year survival – Poor	31	21	245.97 (209.09 to 282.84)	249.00 (168.29 to 329.71)		
One-year survival – Overall	111	59	266.30 (245.68 to 286.92)	304.00 (not estimable)		

Note: CI=confidence interval; LIPI=Lung Immune Prognostic Index; PFS=progression-free survival.

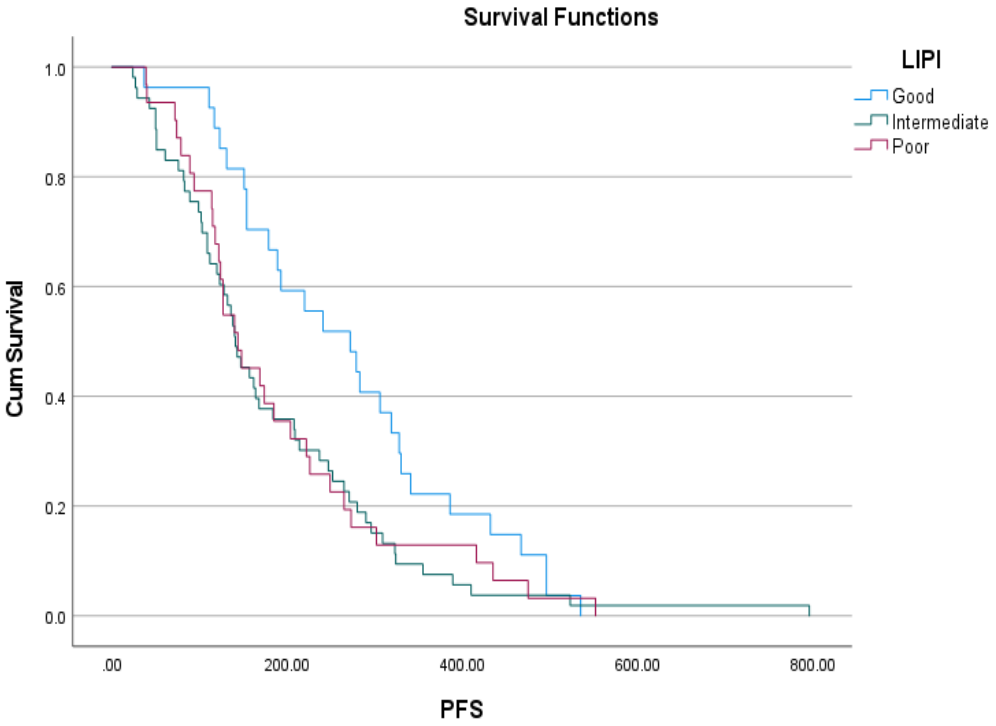


Figure 1. Kaplan–Meier Progression-Free Survival According to LIPI

One-year survival differed significantly across LIPI categories (log-rank χ^2=6.56; p=0.038). The proportion alive at one year was 66.7% in the good group, 45.3% in the

intermediate group, and 32.3% in the poor group. Median one-year survival was not reached in the good group, 303 days in the intermediate group, and 249 days in the poor group.

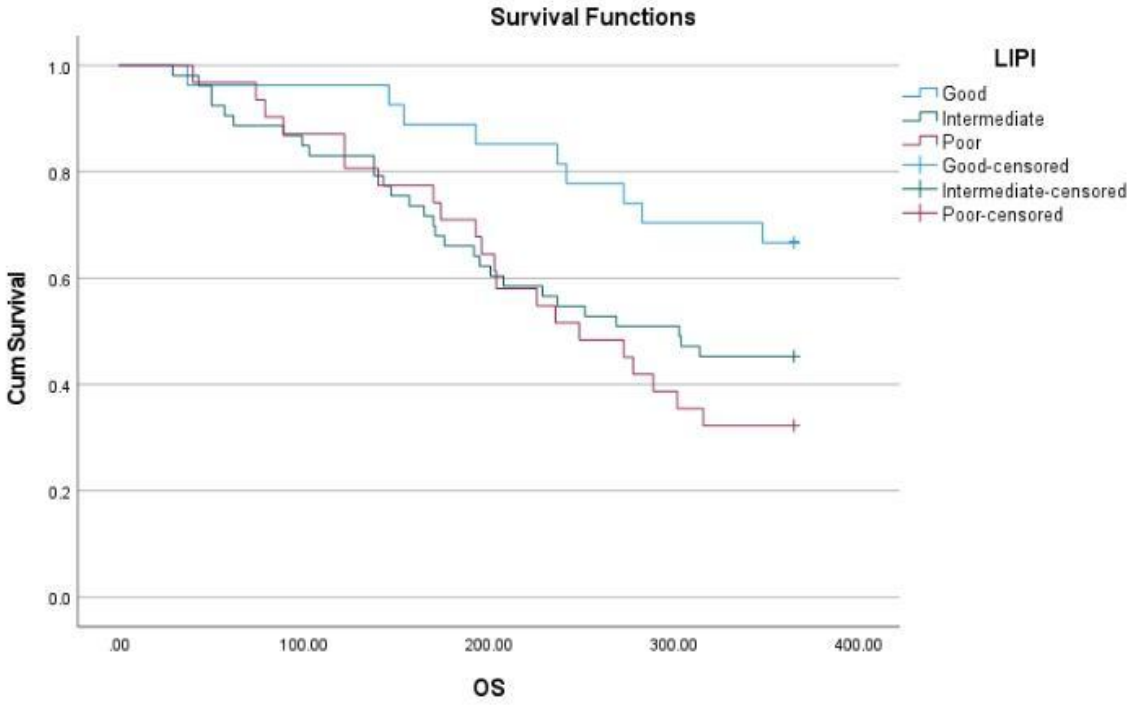


Figure 2. Kaplan–Meier One-Year Survival According to LIPI Category

3. Cox Regression for Progression-Free Survival

In bivariable analysis, intermediate LIPI was associated with a higher progression hazard than good LIPI (cHR=1.72; 95% CI= 1.08 to 2.75; p=0.024), whereas poor LIPI was not statistically significant (cHR= 1.61; 95% CI=0.96 to 2.71; p=0.073); the overall LIPI p value was 0.067. M1c2 disease was also associated with progression relative to M1a (cHR=1.81; 95% CI=1.06 to 3.06; p= 0.028).

After adjustment for sex, histopathology, metastatic category, and LIPI, LIPI was not an independent predictor of PFS (overall p= 0.162). Intermediate LIPI had an aHR of 1.60 (95% CI=0.98 to 2.61; p=0.058), and poor LIPI had an aHR of 1.29 (95% CI=0.74 to 2.24; p=0.368). M1c2 disease remained independently associated with progression relative to M1a (aHR=1.94; 95% CI=1.09 to 3.43; p=0.024).

Table 4. Multivariable Cox regression for progression-free survival

Variables	Adjusted HR	95% CI	p
Female sex vs male	0.81	0.54 to 1.22	0.310
Histopathology overall	—	—	0.244
Squamous vs adenocarcinoma	1.33	0.84 to 2.10	0.219
Large cell vs adenocarcinoma	1.46	0.34 to 6.31	0.615
Adenosquamous vs adenocarcinoma	5.75	0.71 to 46.71	0.102
TNM metastasis overall	—	—	0.122

Variables	Adjusted HR	95% CI	p
M1b vs M1a	1.13	0.62 to 2.06	0.694
M1c1 vs M1a	1.41	0.86 to 2.32	0.176
M1c2 vs M1a	1.94	1.09 to 3.43	0.024
LIPI overall	—	—	0.162
Intermediate vs good	1.60	0.98 to 2.61	0.058
Poor vs good	1.29	0.74 to 2.24	0.368

Note: CI=confidence interval; HR=hazard ratio; LIPI=Lung Immunoe Prognostic Index.

4. Cox Regression for One-Year Survival

In bivariable analysis, LIPI was associated with one-year mortality (overall p=0.046). Poor LIPI was associated with higher mortality than good LIPI (cHR=2.69; 95% CI= 1.23 to 5.87; p=0.013), while intermediate LIPI was at the significance boundary (cHR= 2.11; 95% CI=1.00 to 4.47; p=0.050). Squamous cell carcinoma was associated with higher mortality than adenocarcinoma (cHR=2.65; 95% CI=1.57 to 4.46; p<0.001).

In the multivariable model, LIPI was no longer independently associated with mortality (overall p=0.274). The adjusted estimates were 1.88 for intermediate LIPI (95% CI=0.87 to 4.04; p=0.108) and 1.65 for poor LIPI (95% CI=0.72 to 3.75; p=0.236). Histopathology remained significant overall (p=0.012), and squamous cell carcinoma independently predicted one-year mortality relative to adenocarcinoma (aHR= 2.62; 95% CI=1.46 to 4.69; p=0.001).

Table 5. Multivariable Cox regression for One-Year Mortality

Variable	Adjusted HR	95% CI	p
Female sex vs male	0.81	0.46 to 1.42	0.462
Stage IVB vs IVA	1.92	0.23 to 16.21	0.549
Histopathology overall	—	—	0.012
Squamous vs adenocarcinoma	2.62	1.46 to 4.69	0.001
Large cell vs adenocarcinoma	2.01	0.24 to 16.67	0.518
Adenosquamous vs adenocarcinoma	2.91	0.35 to 24.19	0.323
Brain metastasis: yes vs no	1.18	0.67 to 2.09	0.562
TNM metastasis overall	—	—	0.666
M1b vs M1a	0.63	0.08 to 4.95	0.664
M1c1 vs M1a	0.83	0.09 to 7.81	0.873
M1c2 vs M1a	1.10	0.11 to 10.65	0.936
LIPI overall	—	—	0.274
Intermediate vs good	1.88	0.87 to 4.04	0.108
Poor vs good	1.65	0.72 to 3.75	0.236

Note: CI=confidence interval; HR=hazard ratio; LIPI=Lung Immune Prognostic Index.

DISCUSSION

This study evaluated baseline LIPI in a cohort of patients with stage IV NSCLC receiving platinum-based systemic chemotherapy. LIPI separated one-year survival curves in Kaplan-Meier analysis but was not independently associated with either PFS or one-year mortality after multivariable adjustment. After multivariable adjustment, M1c2 metastatic disease remained significantly associated with progression, while

squamous cell carcinoma remained significantly associated with one-year mortality. These findings suggest that LIPI may serve as supplementary information for initial prognostic assessment rather than as a primary prognostic measure in this cohort.

The intermediate group was the largest LIPI category, and the proportion of poor LIPI was higher than in several prior cohorts. Huang et al. (2021) reported good, intermediate, and poor LIPI in 59.6%, 32.5%, and 7.9% of patients in its chemotherapy cohort. Xiong et al. (2023) reported baseline proportions of 45.2%, 41.1%, and 13.7%, and Zhi et al. (2024) reported 58.4%, 35.4%, and 6.2%. In the present cohort, the corresponding proportions were 24.3%, 47.7%, and 27.9%. The higher proportion of intermediate and poor categories may reflect differences in stage, metastatic burden, systemic inflammation, local LDH thresholds, or treatment population.

The PFS pattern was directionally consistent with a more favorable prognosis in the good LIPI group, but the overall log-rank comparison was not significant. Median PFS was 272 days for good LIPI compared with 141 and 144 days for intermediate and poor LIPI. Huang et al. (2021) likewise found a nonsignificant difference in the chemotherapy cohort, with median PFS of 10.6, 9.4, and 5.3 months across good, intermediate, and poor groups (p=0.123). By contrast, its pooled analysis associated higher LIPI with shorter PFS across systemic therapies and within the chemotherapy subgroup. This difference between an individual cohort and a pooled estimate is compatible with a modest effect that may be difficult to detect in smaller, clinically heterogeneous samples.

The timing of LIPI measurement may also matter. Xiong et al. (2023) found that baseline LIPI did not significantly separate PFS, whereas LIPI recalculated after two treatment cycles produced clearer discrimination and remained independently associated with progression. In the present study, only the pretreatment value was assessed. Baseline inflammatory and metabolic measurements may not capture treatment-related changes in tumor activity or host response that become prognostically informative during therapy.

Studies dominated by immune checkpoint inhibitor treatment have generally reported stronger associations. Zhi et al. (2024) observed progressively shorter PFS across worsening LIPI categories and significant adjusted hazards for intermediate and poor LIPI. A meta-analysis by Wang et al. (2024), including 21 studies and 9,010 patients treated with immune checkpoint inhibitors, also found poorer PFS and overall survival with increasing LIPI. The weaker independent association in this chemotherapy-only cohort may therefore reflect differences in treatment mechanism, stage distribution, sample size, or the biological relationship between systemic inflammation and treatment response.

M1c2 metastatic disease independently predicted progression. This category denotes multiple extrathoracic metastases in more than one organ and therefore represents extensive metastatic burden. LDH, one component of LIPI, can also rise with increased tumor metabolism, hypoxia, necrosis, and burden (Miholjcic et al., 2023; Mishra and Banerjee, 2019). The attenuation of the LIPI estimate after metastatic category was entered into the model may reflect overlapping prognostic information: the anatomic extent of disease may directly capture some of the tumor burden also reflected by LDH.

The one-year survival analysis showed clearer separation across LIPI categories than the PFS analysis. Two thirds of the good LIPI group remained alive at one year, compared with 45.3% of the intermediate

group and 32.3% of the poor group. The bivariable mortality hazard was also higher for poor LIPI. These results agree with the direction of previous evidence. Huang et al. (2021) reported worse overall survival with higher LIPI in chemotherapy-treated patients, while Mezquita et al. (2018) and Zhi et al. (2024) found marked survival separation in advanced NSCLC treated with immune checkpoint inhibitors. Riudavets et al. (2024) likewise evaluated LIPI in a different locally advanced treatment context, supporting its broader relevance as a systemic prognostic index.

Nevertheless, LIPI did not remain independently associated with one-year mortality. Overall survival is influenced by multiple factors beyond baseline inflammation, including histopathology, metastatic burden, molecular profile, subsequent therapy, clinical condition, and treatment response. Squamous cell carcinoma was the only independent predictor of mortality in the final model, with more than twice the hazard observed for adenocarcinoma. This is consistent with population-based evidence that stage IV NSCLC survival varies by histological subtype, including poorer outcomes for squamous cell carcinoma relative to adenocarcinoma (Abernethy et al., 2017).

The biological rationale for LIPI remains credible despite the loss of independence after adjustment. Elevated dNLR reflects neutrophil predominance relative to other leukocytes and may indicate an inflammatory, immunosuppressive environment. Neutrophils can contribute to angiogenesis, tumor invasion, and immune evasion, whereas reduced lymphocyte representation may indicate weakened antitumor immunity (Park and Chung, 2024; Xue et al., 2025; Yang et al., 2021). Elevated LDH reflects altered tumor metabolism and may accompany hypoxia, glycolysis, and greater disease burden (Miholjcic et al., 2023; Mishra and Banerjee, 2019). LIPI is therefore best interpreted as a composite systemic marker whose effect may overlap with direct clinical measures of disease extent.

This study has several limitations. Its retrospective, single-center design limits causal interpretation and generalizability, and each LIPI stratum contained relatively few patients. Results may have been influenced by prognostic factors that were not recorded in the medical records and by selection bias because only records with sufficiently complete data were analyzed. The cohort included only patients receiving platinum-based chemotherapy, preventing direct comparison with immunotherapy or chemoimmunotherapy. LIPI was measured only at baseline, and survival follow-up was limited to one year. The one-year mortality model had relatively few events per estimated parameter, and formal multicollinearity diagnostics and proportional-hazards testing were not performed. In addition, reason-specific screening exclusions and the separate numbers of documented progression and death-before-evaluation PFS events were not available. Information regarding longer-term survival and serial changes in dNLR or LDH was therefore unavailable.

In conclusion, baseline LIPI separated one-year survival curves but was not significantly associated with PFS or one-year mortality after multivariable adjustment. In the adjusted analyses, M1c2 metastatic disease was associated with a higher risk of progression, whereas squamous cell carcinoma was associated with higher one-year mortality. LIPI may provide supportive information for initial prognostic assessment using routine laboratory data; however, it should be interpreted alongside metastatic burden, histopathology, and other relevant clinical factors. Prospective multicenter studies with larger samples, serial LIPI

measurement, and comparison across systemic treatment modalities are warranted based on these findings.

AUTHOR CONTRIBUTIONS

Yunita was the principal investigator. Hartanto Dwi Nugroho, Artrien Adhiputri Ana Rima Setijadi, and Harsini served as thesis supervisors. Specific contribution roles and final approval of this manuscript must be confirmed by all authors before submission.

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CONFLICT OF INTEREST

The authors declare that the study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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