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ORIGINAL RESEARCH

Prognostic Value of the Lung Immune Prognostic Index for Metastatic Non-Small Cell Lung Cancer Patients: A Chinese Cohort Study

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Background: Most cancer-related deaths around the globe are caused by lung cancer. The present treatments for metastatic non-small cell lung cancer (mNSCLC) are cytotoxic chemotherapy (CCT), targeted therapy (TT) and immunotherapy, but the benefit of the same regime varies greatly. Hence, it is important to identify biomarkers to predict the efficacy of modalities. Previous literature suggested certain parameters might be predictive factors. Nevertheless, the utility of these parameters is limited due to the types of solid tumors.

Purpose: The study aimed to examine whether the lung immune prognostic index (LIPI) was related to outcomes of CCT, immune checkpoint inhibitors (ICIs) and TT for mNSCLC patients.

Materials and Methods: A retrospective cohort study between September 2012 and May 2020 was conducted on 350 Chinese mNSCLC patients, including 147 patients receiving ICIs, 103 TT, and 100 CCT. The data were examined to analyze the prognostic value of LIPI among various treatments.

Main Outcomes and Measures: The associations between PFS and good, intermediate, or poor prognostic LIPI scores in ICIs, TT, and CCT were determined, respectively.

Results: In univariable analyses, there was a relevance between a good LIPI score and better PFS among patients receiving ICIs (HR, 0.81; 95% CI, 0.44–1.51), TT (HR, 0.35; 95% CI, 0.16–1.74), and CCT (HR, 0.39; 95% CI, 0.19–0.80). In multivariable analyses, the intermediate LIPI score was linked to better PFS only in patients receiving TT (HR, 0.31; 95% CI, 0.17–0.92) rather than ICIs (HR, 1.12; 95% CI, 0.66–2.45) or CCT (HR, 1.24; 95% CI, 0.49–4.55).

Conclusion: Baseline LIPI value is an important prognostic biomarker for mNSCLC patients treated with TT. Shorter PFS with TT was associated with poor baseline LIPI. Poor LIPI score may be considered as a promising indicator showing which patients are unlikely to respond well to TT. The prognostic value of LIPI can be more clearly determined through prospective clinical study.

Keywords: lung immune prognostic index, metastatic non-small cell lung cancer, prognostic value

Introduction

Most cancer-related deaths around the globe are caused by lung cancer,[1] but the advanced stage of lung cancer has poor prognosis.[2] The present systemic treatments for mNSCLC are CCT, TT, and immunotherapy, but the benefit of the same treatment varies greatly.[3] Considering the side effects caused by chemotherapy agents and targeted drugs, expensive treatment costs of ICIs and unpredictable serious or lethal immune-related adverse events (irAEs), it is crucial to identify biomarkers to predict the efficacy of various therapeutic treatments and to help clinicians select potential beneficiaries before initial treatments. Therefore, many clinicians across the world have undertaken research around the clinical characteristics and the parameters of routine blood tests of NSCLC patients before or during treatments.

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It is known that cancer development is influenced by chronic inflammation.[4] It has been suggested that inflammatory process, which fosters the growth and spread of cancer and activates oncogenic signaling pathways, functions as a mechanism of immune resistance in cancer patients.[5–7] Immunotherapy targets the human immune system and kills tumor cells by activating the autoimmune system. ICIs, as one of the most widely used tumor immunotherapy drugs, can release the inhibition of PD-L1 on T cell effect by specifically binding PD-1 on T cell surface. However, resistance to ICIs prevents patients from gaining satisfactory responses, and at the same time severe irAEs complicate treatments.[8] Poorer outcomes in cancer patients have been linked to peripheral pro-inflammatory state.[9,10] The inflammatory state of peripheral blood commonly signals cancer patients suffer from infection, cachexia and fatigue,[11] which increases the risks and difficulties of cancer treatment. The delayed start time of chemotherapy or targeted drugs and the decrease of drug dose have seriously affected the therapeutic effect and prognosis. In clinical work, peripheral blood mononuclear cells, lymphocytes, neutrophils, cytotoxic lymphocytes and pro-inflammatory cytokines partially represent the body's inflammatory response and intensity.[12,13] The level of LDH, a measurement of tumor burden,[14,15] and dNLR, an assessment of the immune system,[16] have recently been shown crucial for mNSCLC treatment across therapeutic classes and molecular subgroups.[17] Composed of baseline dNLR and LDH, LIPI can partly indicate host tumor burden and immune status.[18] Therefore, LIPI is a promising indicator to predict the patient's prognosis and therapeutic response.

However, whether LIPI is a decisive prognostic factor in mNSCLC patients remains a controversial issue. Firstly, the predictive efficacy of LIPI is inconsistent in mNSCLC patients receiving different treatments. Although some authors reported that it had a predictive value in mNSCLC patients receiving ICIs, TT and CCT, LIPI was independently related to PFS and overall survival (OS) in this study.[17] Others reported that the predictive value was observed only when patients were treated with ICIs but not CCT.[18] Secondly, the cut-off values of each element constituting LIPI differ in clinical studies. NLR >5 was considered an important parameter of systemic inflammation and hence constituted LIPI.[19] As a result, it is necessary to explore the application of LIPI in mNSCLC among races and populations. Compared with other traditional predictive indicators, LIPI has the advantages of being non-traumatic, economical and readily available. More importantly, each basic hematological test index that constitutes LIPI has a clearly defined normal range.

Therefore, our study aimed to investigate whether LIPI was also applicable to Chinese population with mNSCLC, and whether LIPI had prognostic value for ICIs, TT and CCT in Chinese population. To improve survival status, it may be useful to predict the risk of progression and to conduct treatment selection and follow-up strategies accordingly. A retrospective cohort in China was used in this study to examine the influence of LIPI on mNSCLC outcomes.

Methods

Ethics Approval and Consent to Participate

The study (No. KY2020139) was approved by the local ethics committee of Yunnan Cancer Hospital, People's Republic of China, and abode by the Declaration of Helsinki and good clinical practice guidelines. The committee decided not to require informed consent, considering the retrospective nature of the study. All the patients' information was made anonymous in this study.

Patients

A cohort of 360 mNSCLC patients receiving ICIs, TT and CCT between September 2012 and May 2020 at Yunnan Cancer Hospital in China was studied retrospectively. However, 10 patients were excluded because their data were missing or they failed to receive radiography examination on time. The final analysis included 350 patients, who were grouped according to the treatment they received: ICIs, TT or CCT. Medications that ICI-treated mNSCLC patients received included nivolumab, pembrolizumab, atezolizumab, durvalumab, treprizumab, carrelizumab, sintilimab and tislelizumab. In the TT group, patients with EGFR or ALK mutations received appropriate tyrosine kinase inhibitors including gefitinib, erlotinib, afatinib, ositinib and crizotinib based on genetic biopsy testing or peripheral blood Next-Generation Sequencing (NGS) accordingly. In the CCT group, patients received platinum-based dual drug therapy.

The inclusion criteria were as follows: age over 18; cytological and/or pathological confirmed NSCLC; stage IIIB or IV of the eighth edition of the American Joint Committee on Cancer (AJCC) tumor, node, metastasis (TNM) staging

system; treatment with ICIs or TT or CCT; and at least four doses of therapy for ICIs and CCT, at least 3 months of therapy for TT.

The exclusion criteria were as follows: clinical data were missing; ICIs combined with chemotherapy/antiangiogenic agents; CCT combined with antiangiogenic agents; and TT combined with antiangiogenic agents.

LIPI Determination

From electronic medical records, we retrieved the baseline information of total blood cell counts, LDH levels, and albumin levels within 30 days prior to the first treatment. The normal range of white blood cell count was defined as 3.5–9.5×10^9/L, lymphocyte count 1.10–3.20×10^9/L, and neutrophil count 1.8–6.3×10^9/L.

The dNLR (absolute neutrophil count/[white blood cell count-absolute neutrophil count]) and the LDH level per Mezquita et al were used to calculate LIPI composite score,[18] which was developed when dNLR was higher than 3 and LDH was larger than the upper limit of normal (ULN). Three levels of LIPI were identified (good, 0 factor; intermediate, 1 factor; poor, 2 factors). The cutoff for dNLR was determined as >3 according to previous studies,[20] with ULN for LDH being 245U/L. The detection value >245U/L was considered abnormal.

Surveillance Protocol and Outcome

The follow-up of the study was completed on December 23, 2020. Radiological assessments were performed every two cycles of chemotherapy or immunotherapy during treatment per RECIST (Response Evaluation Criteria in Solid Tumors) v1.1 in the CCT and ICIs groups but every 2 months per RECIST in the TT group. Radiological responses and dates of progression were gathered from the medical records.

The tumor registry or medical data were used to determine the date of death. A 20% or greater increase in the main tumor's volume or the development of additional lesions were both considered signs of progression disease (PD). PFS was estimated starting with the date of ICIs, TT or CCT and ending with the date of progression, death or last follow-up. Data for dead or unreachable patients were considered as censored.

Covariates

Covariates covered age, gender, Eastern Cooperative Oncology Group Performance Status (<2 or ≥2), smoking history (yes or no), histologic subtype (non-squamous or squamous), gene status (negative or positive), White Blood Cell Count (normal or abnormal), Lymphocyte Count (normal or abnormal), Neutrophil Count (normal or abnormal), Albumin (≥35 g/L or <35 g/L), LDH (≤ULN or >ULN), dNLR (≥3 or <3), LIPI (good, 0 factor; intermediate, 1 factor; poor, 2 factors).

Statistical Analysis

R language (version 3.6.2) was used to perform statistical analysis. All tests were 2-sided, with P values <0.05 signaling statistical significance. The results of continuous variables with a normal distribution were described with mean, standard deviation (SD), minimum value and maximum value; the independent two-sample *t*-test was used to further compare the results. The results for categorical parameters were described using the group-specific number and percentage of patients in each category, and the chi-square (χ^2) test was adopted to further compare these results. Fisher's exact test was used when the theoretical frequency was <1 for cells >25%.

The relationships between LIPI and PFS were assessed using a univariate and multivariate Cox regression model, and hazard ratios (HR) and 95% confidence intervals (CI) were obtained. All the factors that made meaningful contributions to the simplified model were incorporated into the redeveloped multivariable Cox regression one (enter method). The link between the factors and PFS was examined with the Kaplan–Meier method, and survival curve comparisons were made with the Log rank test (univariate analysis).

Additional sensitivity studies were conducted to verify the reliability of risk estimations. To determine independent risk factors for PFS, multivariate Cox proportional hazards regression analysis with stepwise variable selection was adopted. We used three models: model 1 served as the baseline model; demographic data were added to model 2 on the basis of model 1; and clinicopathological variables were added to model 3 on the basis of model 2.

Results

Patients Demographics and Disease Characteristics

Among the mNSCLC patients, 147 were treated with ICIs, 103 with TT, and 100 with CCT. Baseline characteristics of the three groups, and the pooled dataset are summarized in Table 1.

Table 1 Characteristics of Baseline in 350 Patients with mNSCLC

Variable, N (%)	ICIs Set (N=147)	TT Set (N=103)	CCT Set (N=100)	*P* value
Age, y,				0.115
<65	104 (70.75%)	68 (66.02%)	79 (79.00%)	
≥65	43 (29.25%)	35 (33.98%)	21 (21.00%)	
Sex				<0.001
Female	24 (16.33%)	58 (56.31%)	37 (37.00%)	
Male	123 (83.67%)	45 (43.69%)	63 (63.00%)	
Performance status				<0.001
<2	92 (62.59%)	94 (91.26%)	96 (96.00%)	
≥2	55 (37.41%)	9 (8.74%)	4 (4.00%)	
Smoking history				<0.001
Nonsmoker	60 (40.82%)	77 (74.76%)	59 (59.00%)	
Smoker	87 (59.18%)	26 (25.24%)	41 (41.00%)	
Stage				<0.001
Stage of I–III	38 (25.85%)	0 (0.00%)	0 (0.00%)	
Stage of IV	109 (74.15%)	103 (100.00%)	100 (100.00%)	
Histologic subtype				<0.001
Non squamous	85 (57.82%)	99 (96.12%)	85 (85.00%)	
Squamous	62 (42.18%)	4 (3.88%)	15 (15.00%)	
Gene Status				<0.001
Negative	129 (87.76%)	26 (25.24%)	100 (100.00%)	
Positive	18 (12.24%)	77 (74.76%)	0 (0.00%)	
White Blood Cell Count				0.376
Normal (3.5–9.5)	111 (75.51%)	85 (82.52%)	76 (76.00%)	
Abnormal	36 (24.49%)	18 (17.48%)	24 (24.00%)	
Lymphocyte Count				<0.001
Normal (1.1–3.2)	92 (62.59%)	83 (80.58%)	87 (87.00%)	
Abnormal	55 (37.41%)	20 (19.42%)	13 (13.00%)	

(*Continued*)

Table 1 (Continued).

Variable, N (%)	ICIs Set (N=147)	TT Set (N=103)	CCT Set (N=100)	*P* value
Neutrophil Count				0.169
Normal (1.8–6.3)	91 (61.90%)	75 (72.82%)	63 (63.00%)	
Abnormal	56 (38.10%)	28 (27.18%)	37 (37.00%)	
Albumin				0.684
≥35 g/L	132 (89.80%)	94 (91.26%)	93 (93.00%)	
<35 g/L	15 (10.20%)	9 (8.74%)	7 (7.00%)	
LDH				0.044
≤ULN (245 U/L)	96 (65.31%)	65 (63.11%)	78 (78.00%)	
>ULN	51 (34.69%)	38 (36.89%)	22 (22.00%)	
dNLR				0.896
≥3	108 (73.47%)	76 (73.79%)	76 (76.00%)	
<3	39 (26.53%)	27 (26.21%)	24 (24.00%)	
LIPI groups				0.151
Good	71 (48.30%)	50 (48.54%)	63 (63.00%)	
Intermediate	62 (42.18%)	41 (39.81%)	28 (28.00%)	
Poor	14 (9.52%)	12 (11.65%)	9 (9.00%)	

Abbreviations: ICIs, immune checkpoint inhibitors; TT, targeted therapy; CCT, cytotoxic chemotherapy; LDH, Lactate Dehydrogenase; ULN, upper limit of normal; dNLR, absolute neutrophil count/[white blood cell count-absolute neutrophil count]; LIPI, lung immune prognostic index.

ICIs Group

There was a 12.2 months median follow-up (IQR: 9.6–16.5 months). With median PFS of 6.2 vs 5.1 months (HR, 0.81; 95% CI, 0.44–1.51; $p = 0.510$) (Figure 1A and Table 2), a good LIPI score showed no correlation with prolonged PFS compared with a poor LIPI one. In the multivariable analysis, a good LIPI score exhibited no relevance to prolonged PFS compared with a poor LIPI one (HR, 0.81; 95% CI, 0.43–1.51; $p = 0.509$) (Table 3 and Table 4) when model 2's variables of age and gender were taken into account. The same prognostic connection was found (HR, 0.52; 95% CI, 0.15–1.57; $p = 0.253$) (Table 3 and Table 4) when age, gender, performance status, smoking history, histologic subtype, white blood count, albumin, LDH and dNLR were adjusted in model 3.

TT Group

There was a 21.4 months median follow-up (IQR: 16.7–34.6 months). With median PFS of 8.7 vs 3.6 months (HR, 0.35; 95% CI, 0.16–0.74; $p = 0.006$) (Figure 1B and Table 2), a good LIPI score showed a correlation with prolonged PFS compared with a poor LIPI one. In the multivariable analysis, a good LIPI score exhibited relevance to prolonged PFS compared with a poor LIPI one (HR, 0.34; 95% CI, 0.16–0.74; $p = 0.006$) (Table 3 and Table 4) when model 2's variables of age and gender were taken into account. The same prognostic connection was found (HR, 0.20; 95% CI, 0.10–0.92; p = 0.047) (Table 3 and Table 4) when age, gender, performance status, smoking history, histologic subtype, white blood count, albumin, LDH and dNLR were adjusted in model 3.

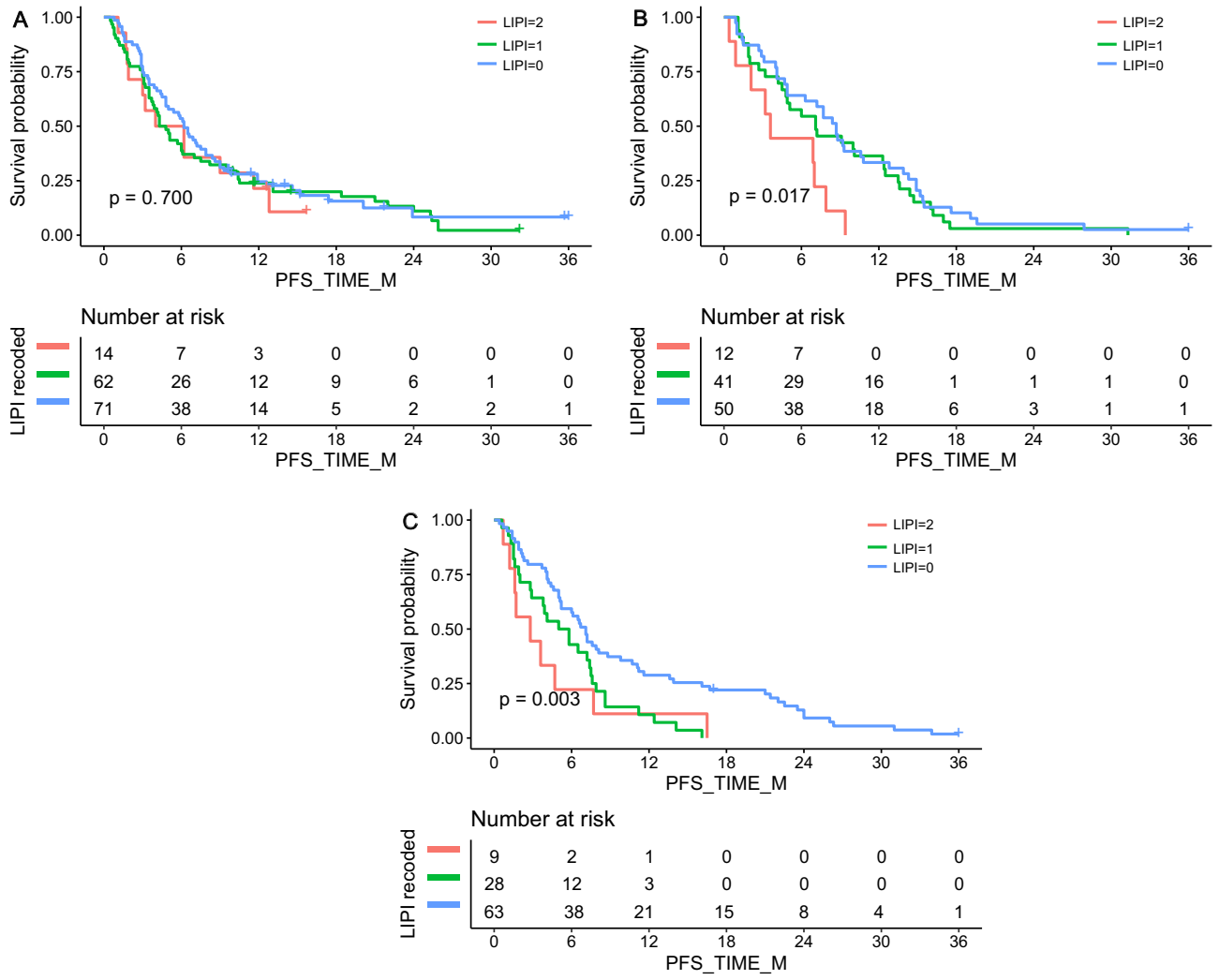

Figure 1 Progression-free survival based on LIPI score and treatment. (**A**) PFS according to LIPI groups in the ICIs set; (**B**) PFS according to LIPI groups in the TT set; (**C**) PFS according to LIPI groups in the CCT set; LIPI, lung immune prognostic index.

CCT Group

There was a 20.5 months median follow-up (IQR: 11.2–30.5 months). With median PFS of 7.1 vs 2.8 months (HR, 0.39; 95% CI, 0.19–0.80; $p = 0.01$) (Figure 1C and Table 2), a good LIPI score showed a correlation with prolonged PFS compared with a poor LIPI one. In the multivariable analysis, a good LIPI score exhibited relevance to prolonged PFS compared with a poor LIPI one (HR, 0.43; 95% CI, 0.21–0.89; $p = 0.023$) (Table 3 and Table 4) when model 2's variables of age and gender were taken into account. But the same prognostic connection was not found (HR, 0.82; 95% CI, 0.11–4.97; $p = 0.921$) (Table 3 and Table 4) when age, gender, performance status, smoking history, histologic subtype, white blood count, albumin, LDH and dNLR were adjusted in model 3.

For each LIPI risk group, we concluded by conducting exploratory post hoc Kaplan Meier analysis of PFS (Figure 1). It was showed by the exploratory supplementary analysis that the good LIPI score was related to better PFS in pooled patients as well as TT set.

Discussion

The retrospective cohort focused on the pretreatment LIPI scores. The mNSCLC patients were divided into 3 groups by LIPI scores developed on the basis of dNLR and LDH: good, intermediate and poor. A notable connection was observed between LIPI scores and the mNSCLC outcomes. Shorter PFS with TT were associated with poor baseline LIPI, which

Table 2 Univariable Analyses of Progression-Free Survival (PFS)

Variable	Hazard Ratio (95% CI)		
	ICIs Set (n=147)	TT Set (n=103)	CCT Set (n=100)
Age, y			
<65	1[Reference]	1[Reference]	1[Reference]
≥65	1.36 (0.93, 1.97)	0.90 (0.56, 1.46)	0.68 (0.40, 1.15)
P value	0.112	0.678	0.152
Sex			
Female	1[Reference]	1[Reference]	1[Reference]
Male	1.25 (0.78, 2.01)	0.96 (0.62, 1.50)	1.20 (0.79, 1.82)
P value	0.358	0.872	0.392
Performance status			
<2	1[Reference]	1[Reference]	1[Reference]
≥2	1.60 (1.13, 2.29)	1.15 (0.52, 2.56)	1.24 (0.45, 3.40)
P value	0.009	0.732	0.675
Smoking history			
Nonsmoker	1[Reference]	1[Reference]	1[Reference]
Smoker	1.23 (0.86, 1.76)	0.88 (0.53, 1.45)	0.94 (0.62, 1.43)
P value	0.257	0.607	0.786
Histologic subtype			
Non squamous	1[Reference]	1[Reference]	1[Reference]
Squamous	1.18 (0.83, 1.67)	2.24 (0.54, 9.28)	0.96 (0.54, 1.71)
P value	0.367	0.265	0.890
Gene Status			
Negative	1[Reference]	1[Reference]	1[Reference]
Positive	1.18 (0.71, 1.98)	0.73 (0.44, 1.22)	NA
P value	0.525	0.226	
White Blood Count			
Normal (3.5–9.5)	1[Reference]	1[Reference]	1[Reference]
Abnormal	0.83 (0.55, 1.24)	0.76 (0.42, 1.36)	1.73 (1.08, 2.78)
P value	0.363	0.355	0.023
Lymphocyte Count			
Normal (1.1–3.2×10^9/L)	1[Reference]	1[Reference]	1[Reference]
Abnormal	0.69 (0.48, 1.00)	1.17 (0.68, 2.01)	1.47 (0.81, 2.66)
P value	0.051	0.582	0.207

(*Continued*)

Table 2 (Continued).

Variable	Hazard Ratio (95% CI)		
	ICIs Set (n=147)	**TT Set (n=103)**	**CCT Set (n=100)**
Neutrophil Count			
Normal (1.8–6.3)	1[Reference]	1[Reference]	1[Reference]
Abnormal	0.63 (0.44, 0.92)	0.71 (0.42, 1.21)	1.87 (1.22, 2.87)
P value	0.015	0.206	0.004
Albumin			
≥35 g/L	1[Reference]	1[Reference]	1[Reference]
<35 g/L	1.39 (0.78, 2.48)	0.47 (0.17, 1.32)	1.83 (0.83, 3.99)
P value	0.260	0.151	0.132
LDH			
≤ULN (245 U/L)	1[Reference]	1[Reference]	1[Reference]
>ULN	1.31 (0.91, 1.88)	1.58 (0.99, 2.53)	1.97 (1.20, 3.22)
P value	0.144	0.055	0.007
dNLR			
≥3	1[Reference]	1[Reference]	1[Reference]
<3	0.94 (0.64, 1.39)	1.28 (0.77, 2.13)	1.79 (1.10, 2.90)
P value	0.765	0.344	0.018
LIPI group			
Poor	1[Reference]	1[Reference]	1[Reference]
Intermediate	0.92 (0.49, 1.73)	0.41 (0.19, 0.88)	0.73 (0.35, 1.56)
P value	0.802	0.023	0.422
Good	0.81 (0.44, 1.51)	0.35 (0.16, 0.74)	0.39 (0.19, 0.80)
P value	0.510	0.006	0.010

Table 3 Multivariable Analyses of Progression-Free Survival

Variable	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
	ICIs (n=147)	**TT (n=103)**	**CCT (n=100)**
Age, y			
<65	1[Reference]	1[Reference]	1[Reference]
≥65	0.95 (0.58–1.56)	0.82 (0.49–1.36)	0.75 (0.42–1.32)
P value	0.842	0.434	0.317

(*Continued*)

Table 3 (Continued).

Variable	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
	ICIs (n=147)	TT (n=103)	CCT (n=100)
Sex			
Female	1[Reference]	1[Reference]	1[Reference]
Male	1.21 (0.66–2.21)	0.85 (0.44–1.64)	1.48 (0.81–2.70)
P value	0.543	0.625	0.198
Performance status			
<2	1[Reference]	1[Reference]	1[Reference]
≥2	1.56 (1.01–2.43)	1.78 (0.51–6.16)	1.86 (0.66–5.30)
P value	0.047	0.363	0.243
Smoking history			
Nonsmoker	1[Reference]	1[Reference]	1[Reference]
Smoker	1.06 (0.67–1.68)	0.97 (0.46–2.06)	0.74 (0.41–1.31)
P value	0.800	0.944	0.300
Histologic subtype			
Non squamous	1[Reference]	1[Reference]	1[Reference]
Squamous	1.06 (0.72–1.55)	0.687 (0.09–5.03)	1.06 (0.55–2.04)
P value	0.78	0.712	0.866
White Blood Count			
Normal (3.5–9.5)	1[Reference]	1[Reference]	1[Reference]
Abnormal	0.90 (0.58–1.40)	0.87 (0.42–1.80)	1.58 (0.92–2.70)
P value	0.643	0.701	0.096
Albumin			
≥35 g/L	1[Reference]	1[Reference]	1[Reference]
<35 g/L	1.15 (0.58–2.28)	0.21 (0.05–0.95)	2.09 (0.93–4.67)
P value	0.699	0.042	0.073
LDH			
≤ULN (245 U/L)	1[Reference]	1[Reference]	1[Reference]
>ULN	1.29 (0.89–1.87)	1.58 (0.96–2.60)	1.97 (1.18–3.28)
P value	0.177	0.072	0.009
dNLR			
≥3	1[Reference]	1[Reference]	1[Reference]
<3	1.02 (0.65–1.58)	1.81 (0.96–3.43)	1.33 (0.78–2.26)
P value	0.943	0.067	0.301

Table 4 Adjusted Hazard Ratios of Progression-Free Survival by LIPI

Variable	ICIs	*P* value	TT	*P* value	CCT	*P* value
	Hazard Ratio (95% CI)		Hazard Ratio (95% CI)		Hazard Ratio (95% CI)	
Model 1						
LIPI						
LIPI=2	1[Reference]		1[Reference]		1[Reference]	
LIPI=1	0.92 (0.49, 1.73)	0.802	0.41 (0.19, 0.88)	0.023	0.73 (0.35, 1.56)	0.422
LIPI=0	0.81 (0.44, 1.51)	0.510	0.35 (0.16, 0.74)	0.006	0.39 (0.19, 0.80)	0.010
Model 2						
LIPI						
LIPI=2	1[Reference]		1[Reference]		1[Reference]	
LIPI=1	1.02 (0.54, 1.92)	0.959	0.40 (0.18, 0.89)	0.025	0.81 (0.38, 1.75)	0.594
LIPI=0	0.81 (0.43, 1.51)	0.509	0.34 (0.16, 0.74)	0.006	0.43 (0.21, 0.89)	0.023
Model 3						
LIPI						
LIPI=2	1[Reference]		1[Reference]		1[Reference]	
LIPI=1	1.12 (0.66, 2.45)	0.959	0.31 (0.17, 0.92)	0.034	1.24 (0.49, 4.55)	0.867
LIPI=0	0.52 (0.15, 1.57)	0.253	0.20 (0.10, 0.92)	0.047	0.82 (0.11, 4.97)	0.921

Notes: Model 1 was unadjusted. Model 2 was adjusted for age (<65 vs ≥65), and sex (male vs female). Model 3 was adjusted for age (<65 vs ≥65), sex (male vs female), performance status (<2 vs ≥2), Smoking history (nonsmoker vs smoker), histologic subtype (nonsquamous vs squamous), white Blood Count (normal vs abnormal), Albumin (≥35 g/L vs <35 g/L), LDH (≥ULN (245 U/L vs <ULN)), dNLR (≥3 vs <3).

combined dNLR higher than 3 and LDH larger than ULN. But no correlation was found between poor baseline LIPI and ICIs or CCT. It can be hypothesized that LIPI may serve as a critical indicator showing which patients are unlikely to respond well to TT. This may partly explain why not all mNSCLC patients with epidermal growth factor receptor (EGFR)/anaplastic lymphoma kinase (ALK) mutation can achieve long-term survival after receiving targeted agents based on status of gene mutation. Conclusions of a research conducted by Minami et al were consistent with the conclusions of our research. Namely, poor LIPI was a significant prognostic factor of PFS in NSCLC patients harboring EGFR mutations.[21]

However, inconsistent research results and conclusions have also been reported by other similar clinical studies. First appearing in the study by Mezquita, L., LIPI, the composite index, was formed to examine the relation between baseline dNLR, LDH and immunotherapy resistance in mNSCLC patients. Mezquita et al indicated that pretreatment LIPI was associated with worse outcomes for ICIs, but not for CC.[18] Meanwhile, Kazandjian et al suggested that the good baseline LIPI score was related to longer OS regardless of receiving ICIs, CCT and TT. Therefore, better LIPI scores have better clinical benefits irrespective of treatment modalities for patients with mNSCLC.[17] It can be seen that in non-Asian population the relationship between LIPI and different treatments of mNSCLC patients is also different. According to the PIONEER study (NCT01185314), a prospective molecular epidemiology study in Asian patients with newly diagnosed advanced lung adenocarcinoma, the overall EGFR mutation frequency of the mainland China subset was 50.2%.[22] However, EGFR mutations were observed in approximately 20% of NSCLC patients in non-Asian populations.[23] The difference of EGFR mutation frequency in the population may potentially affect the relationship between baseline LIPI score and treatment response and prognosis.

Huang et al also reported in their study that the LIPI was a clinically significant prognostic factor for NSCLC patients receiving systemic therapy including ICIs, CCT and TT. Higher LIPI score was a prognostic factor for OS and PFS in

NSCLC patients receiving ICIs and for OS in patients receiving CCT or TT. But no association was observed between LIPI score and PFS in NSCLC patients receiving CCT or TT.[24] Though Huang et al's research also centered around Chinese NSCLC population, their conclusion was inconsistent with our conclusion. The reason may be the inclusion criteria of Huang et al's study did not limit the recruiters to NSCLC patients with clinical stage III or IV. Compared with early NSCLC stages, advanced clinical stages mean relatively worse outcomes regardless of treatment regime.

dNLR, a basic element of LIPI, and NLR derive from hematological test indicators, and are consequently considered representing the immune status and systemic inflammatory response of the body. Furthermore, dNLR and NLR are the systemic inflammatory markers in many infectious diseases and solid tumors including lung cancer.[25–27] Rudolf Virchow discovered leukocytes within tumors and postulated that inflammation accelerated cellular proliferation, associating inflammation with cancer for the first time.[28] Inflammation is regarded as one of the six basic mechanisms underlying tumor development and as one of the distinguishing features of cancer because inflammatory cells can stimulate angiogenesis, cancer cell proliferation and invasion.[29,30] Hence, NLR has predictive value of treatment response for cancer patients. Elevated dNLR is a negative prognostic biomarker for NSCLC patients receiving CCT and ICIs, including the patients with programmed cell death-ligand 1 (PD-L1) tumor proportion score (TPS) ≥50%.[31] In recent years, dNLR has become an alternative parameter to NLR.[32] NLR may have value as a predictive biomarker in mNSCLC patients with EGFR mutations treated with TT. Yun et al observed that patients with baseline NLR ≥ 5 had a worse median PFS and median OS than patients with baseline NLR < 5.[33] Nevertheless, Xu et al revealed elevated NLR (≥2.57) was significantly associated with lower disease control rate (DCR) and shorter PFS.[34] Similarly, the cut-off value of NLR was not always consistent in the correlation between pretreatment NLR and the treatment response and prognosis of ICIs. According to one study, there was an independent association between the pretreatment NLR ≥5 and worse OS and PFS in NSCLC patients receiving nivolumab.[35] In another research, the NLR ≥ 3 was considered a useful marker for the prediction of the unsatisfactory treatment response or of disease progression in mNSCLC patients receiving nivolumab.[36] Although many studies reported that NLR and dNLR were associated with treatment responses and clinical outcomes, the cut-off values of NLR and dNLR were different. The cut-off value of NLR was determined according to published literature or operating characteristic (ROC) curves.[37] More importantly, NLR, dNLR and other hematological parameters commonly used to represent the immune status are dynamic indicators. Fluctuations may occur before and at any stage during treatment.[38] Therefore, which NLR and dNLR ratio at the treatment stage is the optimal predictor of treatment reaction and prognosis remains uncertain. High-quality prospective clinical trials are needed to further validate the results.

LDH is a NAD-dependent kinase with three subunits of LDHA, LDHB and LDHC and can form six tetramer isoenzymes. Human serum contains five isozymes found in different organs and tissues. Increased energy needs associated with greater rates of cellular proliferation are a key feature of cancer cells. Increased glucose absorption and aberrant LDH activity, which controls the conversion of glucose to lactic acid, are strongly linked to metabolic alterations in rapidly proliferating cancer cells.[39] High serum LDH levels are common in aggressive cancer patients and are typically associated with a poor prognosis in many cancer types. People with high serum LDH levels can merely marginally benefit from the most potent treatments that can dramatically improve the outcomes of melanoma patients. Most importantly, LDH isoforms participate in cancer metabolism, especially the oncogenic and/or immune suppressive processes. Therefore, instead of a simple indicator of tumor burden, serum LDH is a complicated biomarker linked to the activation of several oncogenic signaling pathways and to the metabolic process, invasiveness and immunogenicity of malignant tumors.[40] Besides functioning as a crucial enzyme in cancer metabolism, elevated LDH also alters the tumor microenvironment (TME) to enable neoplastic cells to inhibit and escape the immune system. LDH-A alters the TME by increasing lactate production and promotes resistance to CCT/TT/radiotherapy by strengthening immune-suppression in the TME.[15] On the contrary, the deletion of LDH-A in myeloid cells triggers antitumor immunity in a K-Ras murine model of lung carcinoma.[41] A meta-analysis of 76 studies comprising22882patients showed that median cut-off of serum LDH was 245 U/L. Overall, higher LDH levels were associated with shorter OS and PFS, and higher LDH level was associated with worse survival outcomes in melanoma, lung carcinomas and other solid tumors.[42]

Based on the analysis above, LIPI and its elements, dNLR and LDH, have various correlations with treatment response and clinical prognosis accordingly to different treatment modalities. However, it is obvious that the cut-off values of LIPI and dNLR are inconsistent in different studies. A discrepancy between our findings and previous ones may

result from sample sizes, differences in the populations covered, calculation methods of cut-off values and the heterogeneity of therapeutic regimen.

It is necessary to acknowledge the limitations of our exploratory analysis. The analysis was performed on a relatively small dataset. Potential biases may exist due to the nature of a post hoc evaluation with missing laboratory values and molecular information. As the primary prognostic indicator in immunotherapy for NSCLC patients, PD-L1 expression data were absent in the study, causing another limitation of the analysis. Since dNLR and LDH levels can change after treatment, LIPI is a dynamic index. Hence, LIPI may differ at different time points. Though the optimal timing for LIPI is unknown, the LIPI value can be viewed as a useful prognostic marker for potential stratification in prospective trials after further validation.

Conclusion

Baseline LIPI value is an important prognostic biomarker for mNSCLC patients treated with TT. Shorter PFS with TT were associated with poor baseline LIPI, which combined dNLR higher than 3 and LDH larger than ULN. But no correlation was found between poor baseline LIPI and ICIs or CCT. Poor LIPI score may be considered a promising indicator showing which patients are unlikely to respond well to TT. The prognostic value of the LIPI score can be more clearly determined through thorough prospective clinical study.

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Disclosure

The authors report no conflicts of interest in this work.

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