Original Article

Association between the modified lung immune predictive index and clinical outcomes of advanced non-small cell lung cancer treated with first-line immune checkpoint inhibitors combined with chemotherapy

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Background: As revealed by previous studies, the modified lung immune predictive index (mLIPI) can predict outcomes in patients with lung cancer receiving single-agent immunotherapy. However, the application value of the mLIPI for patients treated with combination immunotherapy requires further investigation. In this study, we aimed to explore the relationship between the mLIPI and the efficacy of treatment together with the prognosis of patients with advanced non-small cell lung cancer (NSCLC) receiving first-line immune checkpoint inhibitors (ICIs) combined with platinum-based chemotherapy.

Methods: In this retrospective study, we enrolled patients with advanced NSCLC treated with ICIs plus chemotherapy from March 2019 to June 2022. The patients were classified into good, intermediate, and poor/very poor groups according to their mLIPI before treatment. We further calculated the disease control rate (DCR), objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) of the three groups. The predictive ability of the mLIPI was evaluated by plotting a time-dependent receiver operating characteristic (ROC) curve and calculating the area under the curve (AUC).

Results: A total of 209 patients were included in this study. There were 75 patients in the good group, 114 patients in the intermediate group, and 20 patients in the poor/very poor group. The median PFS was 11.2 months [95% confidence interval (CI): 8.763–13.704] in the good group; 8.1 months (95% CI: 7.354–8.846) in the intermediate group; and 5.4 months (95% CI: 2.142–8.658) in the poor/very poor group. The median OS was not reached in the good group, 29.5 months (95% CI: 23.555–35.512) in the intermediate group, and 14.5 months (95% CI: 8.567–20.366) in the poor/very poor group ($P<0.05$). Multivariate analysis showed that the mLIPI was independently associated with PFS and OS ($P<0.05$); the AUC values of the mLIPI for predicting PFS at 3, 6, and 9 months were 0.673, 0.637, and 0.614, respectively, and for predicting OS at 6, 12, and 24 months were 0.715, 0.655, and 0.625, respectively.

Conclusions: The pretreatment mLIPI could be used to predict outcomes in patients with NSCLC receiving first-line ICIs plus chemotherapy.

Keywords: Immune checkpoint inhibitors (ICIs); non-small cell lung cancer (NSCLC); chemotherapy; modified lung immune predictive index (mLIPI)

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Introduction

Lung cancer, one of the most common malignant neoplasms, is the leading cause of death in patients with cancer worldwide (1). Non-small cell lung cancer (NSCLC) accounts for 80–95% of cancers, including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Recently, the emergence of immune checkpoint inhibitors (ICIs) has greatly changed the therapeutic prospect of lung cancer; it has greatly improved the clinical result and prognosis of patients with lung cancer and has become a vital part of the treatment. Many clinical studies have shown that ICI treatment is more effective than standard chemotherapy in prolonging survival time and improving long-term prognosis (2,3). The survival benefits of ICIs are well known; however, up to 60% of patients with advanced NSCLC do not benefit from ICI immunotherapy (4). Therefore, identification of reliable biomarkers and screening for therapeutic targets are critical aspects of lung cancer treatment and management.

Presently, programmed death ligand 1 (PD-L1) expression is a well-recognized biomarker that enables doctors to select patients who are more likely to benefit from ICI treatment. High PD-L1 expression correlates with the improved efficacy of treatment and the prognosis of patients with lung cancer receiving immunotherapy (5,6). However, PD-L1 is still insufficient as a predictive marker. Several clinical trials have shown that high PD-L1 expression is associated with improved outcomes only in patients receiving pembrolizumab, and similar correlations have not been observed in patients with lung cancer treated with other ICIs (7,8). Therefore, other lung cancer biomarkers should be explored.

Recently, the relationship between peripheral blood parameters, including neutrophil-to-lymphocyte ratio (NLR) and lactate dehydrogenase (LDH), and the prognosis of patients with tumors has gradually attracted the attention of researchers. The mentioned parameters have been shown to possess certain predictive value for tumor responses by clinical studies (9-11). Compared with biomarkers such as tumor PD-L1 expression, microsatellite instability, tumor mutational burden, and tumor-infiltrating lymphocytes (TILs), peripheral blood markers are more accessible and economical. Moor *et al.* (12) established the modified lung immune predictive index (mLIPI) composed of NLR, LDH, and Eastern Cooperative Oncology Group-performance Status (ECOG-PS), which was markedly correlated with clinical outcomes in patients with advanced NSCLC receiving nivolumab monotherapy, and could be used as a potential new marker to predict the efficacy of treatment and the prognosis of patients with lung cancer receiving immunotherapy. However, in clinical practice, ICIs are widely used in combination with chemotherapy as a first-line therapy for patients with advanced NSCLC having a negative driver gene. It is currently unclear whether the mLIPI has the same application value for patients treated with combination immunotherapy.

Here, we aimed to explore the association between the baseline mLIPI and clinical survival outcomes in patients with advanced NSCLC receiving first-line immunotherapy plus chemotherapy. We present this article in accordance with the STARD reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1525/rc).

Highlight box

Key findings

- The pretreatment modified lung immune predictive index (mLIPI) can predict tumor responses in patients with non-small cell lung cancer (NSCLC) receiving first-line immune checkpoint inhibitors (ICIs) + chemotherapy.

What is known and what is new?

- The mLIPI could recognize various prognostic subgroups of patients treated with ICIs and exhibited the best statistical accuracy in predicting progression-free survival and objective response rate in Chinese patients with advanced NSCLC.
- The following are added to this study: exploring the relationship between the mLIPI and the efficacy of treatment and the prognosis of patients receiving immunotherapy + chemotherapy.

What is the implication, and what should change now?

- The mLIPI may be a novel biomarker for predicting the prognosis of patients with advanced NSCLC treated with ICIs combined with chemotherapy.

Methods

Study population

This retrospective study was performed at the First Affiliated Hospital of Wenzhou Medical University. The patients were enrolled according to the following inclusion criteria from March 2019 to June 2022: (I) pathological confirmation of NSCLC; (II) stage IIIB–IV according to the Eighth Edition of the TNM Stage Classification of Malignant Tumor (13); (III) ICIs combined with platinum-based chemotherapy as the first-line regimen; and (IV) patients undergone at least two cycles of ICIs plus chemotherapy. The exclusion criterion was as follows: missing relevant data.

The blood count and biochemical data of the enrolled patients within a week before the initial immunochemotherapy as well as clinical data including gender, age, smoking history, histology, stage, metastasis, and PD-L1 expression were collected from electronic medical records. All patients were scored on the basis of the mLIPI, specifically, NLR ≥3, LDH >1.5× the upper limit of the normal value, and ECOG-PS ≥2 were assigned 1 point each. The patients were divided into good (0 points), intermediate (1 point), and poor/very poor (≥2 points) groups according to the total score.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the institutional review board of the First Affiliated Hospital of Wenzhou Medical University (No. 2023R128). Individual consent for this retrospective analysis was waived.

Treatment and therapeutic effect assessment

The patients enrolled in this study received programmed cell death protein 1 (PD-1) ICIs (pembrolizumab, sintilimab, tislelizumab, or camrelizumab) combined with chemotherapy as the first-line regimen. All chemotherapy regimens were platinum-based chemotherapy, and other chemotherapeutic agents included nab-paclitaxel/paclitaxel, pemetrexed, and gemcitabine, which were selected according to pathological subtypes. The patients were treated every 3 weeks.

Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) was used to estimate response to treatment, which consisted of complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD). Disease control rate (DCR) referred to the proportion of patients who achieved CR, PR, or SD after treatment, whereas objective response rate (ORR) referred to the proportion of patients who achieved CR or PR after treatment. Progression-free survival (PFS) was defined as the period from the start of ICI treatment to disease progression or death, and overall survival (OS) was determined as the period from the date of initial treatment to death or last follow-up evaluation.

Statistical analysis

All statistical analyses were performed using SPSS 26.0 (IBM Corp., Armonk, NY, USA). Statistical significance was indicated by two-sided P values <0.05. Frequency and percentages were used to represent baseline characteristics. The data of categorical variables were analyzed by the Chi-squared test. Survival curves were plotted by the Kaplan-Meier (KM) method, and the log-rank test was performed to compare differences among the three groups. A Cox proportional hazard regression model was used for univariate and multivariate analyses. A time-dependent receiver operating characteristic (ROC) curve was plotted and the area under the curve (AUC) was calculated to evaluate the predictive ability of the model. The predictive accuracy was evaluated by calculating the concordance index (C-index).

Results

Patient characteristics

A total of 209 patients were included in this study. The majority of patients were male (n=189, 90.4%), and about half of the cases were aged ≥65 years (n=108, 51.7%). Among them, 165 (78.9%) were smokers, and 193 (92.3%) had good physical conditions (ECOG-PS 0–1) at baseline. Squamous cell carcinoma was the main pathological subtype (n=105, 50.2%), followed by adenocarcinoma (n=97, 46.4%). Before treatment, over half of the patients were diagnosed as stage IV (n=146, 69.9%), and 10.5%, 14.4%, and 34.0% of the cases showed liver, brain, and bone metastases, respectively (*Table 1*). The cases received two to 32 cycles of treatment, with a median of six cycles. According to the mLIPI, there were 75 patients in the good group, 114 patients in the intermediate group, and 20 patients in the poor/very poor group. Except for ECOG-PS and gender, no significant difference in other clinical baseline characteristics was found among different

Table 1 Patients characteristics

Features	Total (n=209)	mLIPI =0 (n=75)	mLIPI =1 (n=114)	mLIPI ≥2 (n=20)	P value
Gender					0.028
Female	20 (9.6)	8 (10.7)	7 (6.1)	5 (25.0)	
Male	189 (90.4)	67 (89.3)	107 (93.9)	15 (75.0)	
Age (years)					0.446
<65	101 (48.3)	38 (50.7)	56 (49.1)	7 (35.0)	
≥65	108 (51.7)	37 (49.3)	58 (50.9)	13 (65.0)	
Smoking status					0.333
Never	44 (21.1)	18 (24.0)	20 (17.5)	6 (30.0)	
Former/current	165 (78.9)	57 (76.0)	94 (82.5)	14 (70.0)	
Histology					0.278
Adenocarcinoma	97 (46.4)	42 (56.0)	46 (40.4)	9 (45.0)	
Squamous carcinoma	105 (50.2)	31 (41.3)	63 (55.3)	11 (55.0)	
Other[†]	7 (3.3)	2 (2.7)	5 (4.4)	0 (0.0)	
Clinical stage					0.827
IIIB–C	63 (30.1)	24 (32.0)	34 (29.8)	5 (25.0)	
IV	146 (69.9)	51 (68.0)	80 (70.2)	15 (75.0)	
ECOG-PS					<0.001
0–1	193 (92.3)	75 (100.0)	107 (93.9)	10 (50.0)	
2–3	16 (7.7)	0 (0.0)	7 (6.1)	10 (50.0)	
Liver metastases					0.331
No	187 (89.5)	64 (85.3)	105 (92.1)	18 (90.0)	
Yes	22 (10.5)	11 (14.7)	9 (7.9)	2 (10.0)	
Brain metastases					0.288
No	179 (85.6)	68 (90.7)	94 (82.5)	17 (85.0)	
Yes	30 (14.4)	7 (9.3)	20 (17.5)	3 (15.0)	
Bone metastases					0.539
No	138 (66.0)	51 (68.0)	76 (66.7)	11 (55.0)	
Yes	71 (34.0)	24 (32.0)	38 (33.3)	9 (45.0)	
LDH					<0.001
>1.5× the upper limit of the normal value	17 (8.1)	0 (0.0)	4 (3.5)	13 (65.0)	
≤1.5× the upper limit of the normal value	192 (91.9)	75 (100.0)	110 (96.5)	7 (35.0)	
NLR					<0.001
≥3	124 (59.3)	1 (1.3)	104 (91.2)	19 (95.0)	
<3	85 (40.7)	74 (98.7)	10 (8.8)	1 (5.0)	

Table 1 (*continued*)

Table 1 (*continued*)

Features	Total (n=209)	mLIPI =0 (n=75)	mLIPI =1 (n=114)	mLIPI ≥2 (n=20)	P value
PD-L1 status					0.087
<1%	27 (12.9)	14 (18.7)	12 (10.5)	1 (5.0)	
≥1%	65 (31.1)	17 (22.7)	43 (37.7)	5 (25.0)	
Unknown	117 (56.0)	44 (58.7)	59 (51.8)	14 (70.0)	
Type of ICIs					0.733
Pembrolizumab	73 (34.9)	30 (40.0)	36 (31.6)	7 (35.0)	
Sintilimab	56 (26.8)	21 (28.0)	30 (26.3)	5 (25.0)	
Tislelizumab	56 (26.8)	16 (21.3)	33 (28.9)	7 (35.0)	
Camrelizumab	24 (11.5)	8 (10.7)	15 (13.2)	1 (5.0)	
Chemotherapy					0.172
Nab-paclitaxel/paclitaxel	100 (47.8)	30 (40.0)	61 (53.3)	9 (45.0)	
Pemetrexed	89 (42.6)	40 (53.3)	40 (35.1)	9 (45.0)	
Gemcitabine	20 (9.6)	5 (6.7)	13 (11.4)	2 (10.0)	

Data are presented as n (%) or n. †, other: adenosquamouscarcinoma (n=2), large-cell neuroendocrine carcinoma (n=1), NSCLC-NOS (n=4). mLIPI, modified lung immune predictive index; ECOG-PS, Eastern Cooperative Oncology Group-performance status; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PD-L1, programmed death ligand 1; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; NOS, not otherwise specified.

mLIPI groups (*Table 1*). By the time of statistical analysis, 116 patients (55.5%) showed disease progression, whereas 51 patients (24.4%) had died. The median follow-up time was 14.1 months.

Clinical outcomes with different mLIPIs

In the survival analysis, the mLIPI was statistically associated with PFS; the median PFS values of the good, intermediate, and poor/very poor groups were 11.2 [95% confidence interval (CI): 8.763–13.704], 8.1 (95% CI: 7.354–8.846), and 5.4 months (95% CI: 2.142–8.658), respectively (P=0.043, *Figure 1*). A similar correlation was observed between the mLIPI and OS, with the median OS being longer in the intermediate group than that in the poor/very poor group: 29.5 (95% CI: 23.555–35.512) and 14.5 months (95% CI: 8.567–20.366), respectively (P=0.001). The median OS of the good group did not reach a specific value (*Figure 1*). Additionally, the DCR was 96.0%, 91.2%, and 85.0% (P=0.208), whereas the ORR was 40.0%, 40.4%, and 30.0% (P=0.673) in the good, intermediate, and poor/very poor groups, respectively, with no significant differences (*Table 2*).

Univariate and multivariate analyses using a Cox proportional hazard model

In the univariate analysis, the mLIPI (P=0.048) and clinical stage [P=0.001; hazards ratio (HR): 2.172; 95% CI: 1.390–3.393] were significantly correlated with PFS. The multivariate analysis showed that the mLIPI (P=0.037) and clinical stage (P=0.001; HR: 2.474; 95% CI: 1.457–4.199) were independent factors affecting the PFS of patients with advanced NSCLC receiving immunotherapy plus chemotherapy (*Table 3*). The univariate analysis for OS indicated that the mLIPI (P=0.002), brain metastasis (P=0.002; HR: 2.713; 95% CI: 1.439–5.115), and gender (P<0.001; HR: 0.256; 95% CI: 0.133–0.492) were statistically associated with the prognosis of the patients. According to the multivariate analysis, only the mLIPI (P=0.026) and gender (P=0.003; HR: 7.387; 95% CI: 1.976–27.617) were independent risk factors affecting the OS of the patients (*Table 4*).

Predictive ability of the mLIPI for PFS and OS

We plotted a time-dependent ROC to assess the predictive ability of the mLIPI (*Figure 2*). The AUC values of the

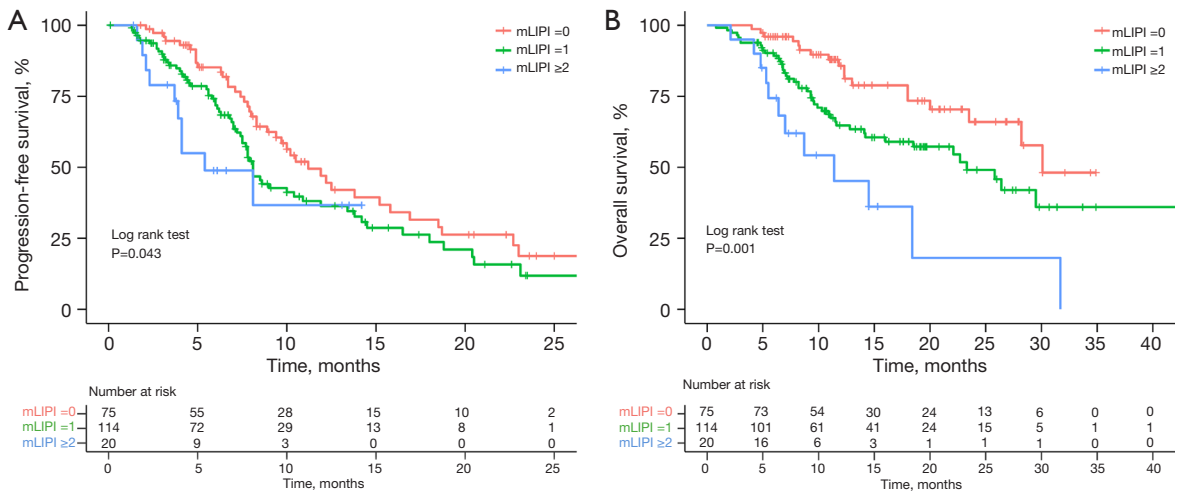

Figure 1 K-M analysis of PFS (A) and OS (B) according to the mLIPI groups. mLIPI, modified lung immune predictive index; K-M, Kaplan-Meier; PFS, progression-free survival; OS, overall survival.

Table 2 Efficacy of the different mLIPI groups

Efficacy	mLIPI =0 (n=75)	mLIPI =1 (n=114)	mLIPI ≥2 (n=20)	P value
ORR	30 (40.0)	46 (40.4)	6 (30.0)	0.673
DCR	72 (96.0)	104 (91.2)	17 (85.0)	0.208

Data are presented as n (%). mLIPI, modified lung immune predictive index; ORR, objective response rate; DCR, disease control rate.

Table 3 Univariable and multivariable analyses of PFS in the 209 patients

Variables	Univariable model			Multivariable model		
	HR	95% CI	P value	HR	95% CI	P value
Gender	0.642	0.360–1.147	0.135	2.124	0.918–4.910	0.078
Age	0.744	0.516–1.073	0.114	0.788	0.536–1.158	0.225
Smoking status	1.081	0.688–1.697	0.736	1.495	0.785–2.846	0.221
Histology	0.831	0.576–1.197	0.320	0.666	0.440–1.008	0.055
Clinical stage	2.172	1.390–3.393	0.001	2.474	1.457–4.199	0.001
Liver metastases	1.658	0.942–2.920	0.080	1.120	0.608–2.061	0.716
Brain metastases	1.082	0.636–1.841	0.770	0.776	0.431–1.394	0.396
Bone metastases	1.399	0.954–2.050	0.085	1.142	0.742–1.760	0.546
PD-L1 status			0.279			0.216
Positive (*vs.* negative)	0.619	0.341–1.123	0.114	0.571	0.304–1.069	0.080
Unknown (*vs.* negative)	0.770	0.452–1.312	0.336	0.707	0.400–1.249	0.232
mLIPI score			0.048			0.037
Intermediate (*vs.* good)	1.466	0.988–2.174	0.057	1.508	0.993–2.290	0.054
Poor/very poor (*vs.* good)	2.156	1.068–4.355	0.032	2.340	1.111–4.928	0.025

PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; PD-L1, programmed death ligand 1; mLIPI, modified lung immune predictive index.

Table 4 Univariable and multivariable analyses of OS in 209 patients

Variables	Univariable model			Multivariable model		
	HR	95% CI	P value	HR	95% CI	P value
Gender	0.256	0.133–0.492	<0.001	7.387	1.976–27.617	0.003
Age	1.425	0.816–2.490	0.213	1.231	0.685–2.210	0.487
Smoking status	0.667	0.365–1.219	0.188	2.169	0.654–7.192	0.206
Histology	0.657	0.372–1.161	0.148	0.599	0.312–1.147	0.122
Clinical stage	1.917	0.982–3.743	0.057	1.669	0.723–3.851	0.230
Liver metastases	1.733	0.813–3.694	0.155	1.339	0.578–3.102	0.496
Brain metastases	2.713	1.439–5.115	0.002	1.661	0.811–3.399	0.165
Bone metastases	1.314	0.748–2.308	0.343	0.958	0.491–1.867	0.899
PD-L1 status			0.282			0.380
Positive (*vs.* negative)	0.727	0.243–2.171	0.568	0.496	0.156–1.581	0.236
Unknown (*vs.* negative)	1.301	0.510–3.321	0.582	0.813	0.296–2.229	0.687
mLIPI score			0.002			0.026
Intermediate (*vs.* good)	2.341	1.179–4.647	0.015	2.436	1.160–5.114	0.019
Poor/very poor (*vs.* good)	5.139	2.051–12.875	<0.001	3.438	1.252–9.439	0.017

OS, overall survival; HR, hazard ratio; CI, confidence interval; PD-L1, programmed death ligand 1; mLIPI, modified lung immune predictive index.

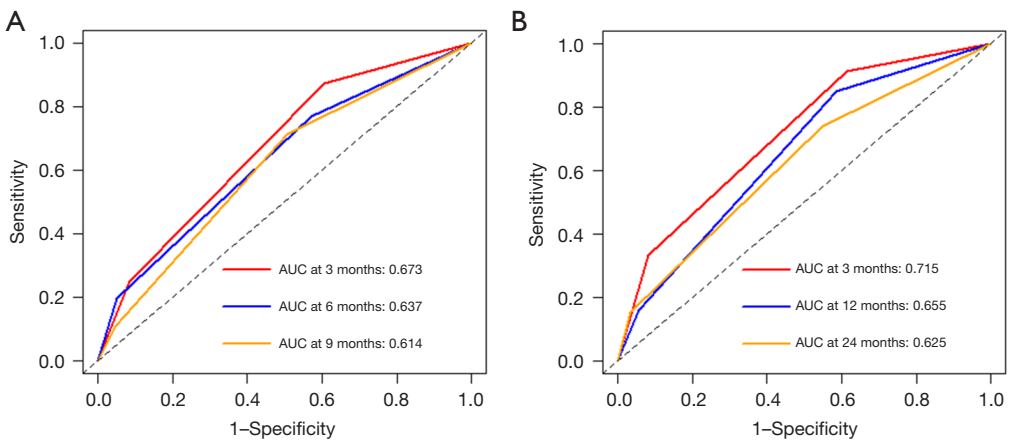

Figure 2 Time-dependent ROC curves of predicting PFS (A) and OS (B) by mLIPI score. AUC, area under the curve; ROC, receiver operating characteristic; PFS, progression-free survival; OS, overall survival; mLIPI, modified lung immune predictive index.

mLIPI for predicting PFS at 3, 6, and 9 months were 0.673 (95% CI: 0.558–0.788), 0.637 (95% CI: 0.551–0.723), and 0.614 (95% CI: 0.533–0.695), respectively. The AUC values of the mLIPI for predicting OS at 6, 12, and 24 months were 0.715 (95% CI: 0.588–0.843), 0.655 (95% CI: 0.567–0.743), and 0.625 (95% CI: 0.509–0.742), respectively. Additionally, we calculated the C-index to evaluate the predictive accuracy of the mLIPI for PFS and OS, which was 0.670 (95% CI: 0.615–0.725) and 0.769 (95% CI: 0.708–0.830), respectively.

Discussion

In the present study, the baseline mLIPI was significantly associated with disease progression and prognosis in patients with advanced NSCLC treated with ICIs plus chemotherapy. The K-M survival analysis showed that a higher mLIPI before treatment was associated with shorter PFS and OS. The OS was not reached in the good group which may be due to the short follow-up period. The multivariate analysis showed that the mLIPI was an independent predictor of PFS and OS, and patients with a higher mLIPI were more likely to show disease progression and death. The time-dependent ROC curve and C-index further indicated that the mLIPI showed a degree of predictive values for clinical outcomes. This suggests that the mLIPI may be a novel biomarker for predicting the prognosis of patients with advanced NSCLC treated with ICIs plus chemotherapy. The DCR and ORR were lower in the poor/very poor group than that in the good and intermediate groups; however, no statistically significant difference was observed.

To date, PD-L1 expression on tumor cells detected by immunohistochemistry is the only biomarker approved by the Food and Drug Administration to predict the efficacy of immunotherapy and has been widely used in clinical practice (14). PD-L1 tumor proportion score (TPS) ≥50% is associated with better response to ICIs; however, a small number of patients with lower PD-L1 expression also respond to ICIs (15,16). Schoenfeld *et al.* (17) confirmed that PD-L1 expression varies depending on the sampling site of tissues, where negative PD-L1 expression was found to be more frequent in primary tumor tissues than in metastatic tissues. Additionally, PD-L1 expression varies in different metastatic sites, where high expression of PD-L1 was mainly observed in the lymph nodes, whereas it was mostly low in metastatic bone sites. They also found that PD-L1 expression was related to the sampling method, with lower levels of PD-L1 in the resection sample compared with those in the biopsy sample from the primary tumor. Therefore, PD-L1 is not a completely reliable biomarker.

In recent years, the relationship between tumors and inflammation has gradually garnered extensive attention. Acute inflammation initiates tumor cell destruction effects, whereas chronic inflammation promotes angiogenesis and tissue remodeling, thereby favoring tumor cell survival and metastasis (18). Among inflammatory cells, lymphocytes exert anti-tumor effects. TILs reflect host immunity and can effectively delay tumor progression. Neutrophils can be divided into subpopulations with different functions and exert both pro- and anti-tumor effects; however, with tumor progression, the pro-tumor effect of neutrophils gradually dominates (19). NLR is defined as the ratio of neutrophils to lymphocytes in peripheral blood that reflects the balance between pro-tumor inflammation and anti-tumor immunoreaction. Therefore, a few researchers regard NLR as a new predictive and prognostic marker of the efficacy of immunotherapy for various malignancies including lung cancer (20). A retrospective study that included patients with lung cancer (55.4%), colorectal cancer (7.4%), nasopharyngeal cancer (6.1%), gastric cancer (4.1%), and hepatocellular carcinoma (4.1%) showed that in patients who received at least one dose of ICIs, an increased baseline NLR was correlated to shorter OS and PFS (21). Diem *et al.* analyzed the correlation between baseline peripheral blood indicators and the prognosis of 52 patients with NSCLC receiving nivolumab monotherapy and finally found that higher NLR was related to shorter OS and worse ORR and DCR but not to PFS (22). In another large, multicenter, retrospective study that included 187 patients with NSCLC treated with nivolumab as a second- or later-line regimen, the results suggested that an NLR of less than five before therapy was associated with improved PFS and OS. However, similar association did not apply to the ORR nor DCR (23). Thus, a higher baseline NLR may predict a poor outcome of immunotherapy in those patients.

Besides NLR, other peripheral blood parameters have been understood to be associated with prognosis in cancer therapy. LDH is an enzyme released by rapidly growing neoplasms and reflects the tumor burden on the body. It is a key enzyme in glycolysis, a major energy metabolic pathway of tumor cells, and its metabolite is lactic acid (24). Large amount of lactate produced by glycolysis is transported outside of cancer cells, acidifying the tumor microenvironment, and thereby facilitating vascular endothelial growth factor secretion and tumor angiogenesis (25). Besides, increased lactic acid concentration in a tumor microenvironment also inhibits the release of lactate from T-lymphocytes into the extracellular space, and T-lymphocyte activation is suppressed, thus promoting tumor immune escape (26). In a humanized NSCLC mouse model, the combination of an LDH inhibitor and pembrolizumab was superior to monotherapy (27). Related studies have shown that increased LDH levels in peripheral blood are associated with a poor cancer prognosis (28,29). The ECOG-PS can be used to evaluate

the general health status and tolerance to cancer treatment from the perspective of the ability of cancer patients to perform activities to decide the corresponding regimens. A recent study showed that patients with NSCLC receiving immunotherapy with a PS score of two exhibited poorer DCR and shorter PFS and OS, thus indicating that ECOG-PS was a strong independent prognostic factor in patients with NSCLC (30).

Moor *et al.* (12) proposed the mLIPI, which covers the above three clinical indicators that are closely related to the prognosis of tumor therapy and divides patients into four subgroups: good, intermediate, poor, and very poor. This study showed that the mLIPI model was relevant to median PFS and OS in patients with advanced NSCLC who received nivolumab monotherapy, and a population with a higher mLIPI at baseline was less likely to benefit from ICIs. Subsequently, Zhao *et al.* performed a retrospective cohort study (31) comparing the predictive value of the mLIPI with that of the other two models of LIPI and EPSILoN (ECOG PS, smoking, liver metastases, LDH, NLR) to examine the efficacy of ICI monotherapy in advanced NSCLC; the results suggested that the mLIPI could recognize various prognostic subgroups of patients treated with ICIs and exhibited the best statistical accuracy in predicting PFS and ORR in Chinese patients with advanced NSCLC. Variables involved in the mLIPI model were conducive to clinical significance. Moreover, they were relatively comprehensive and less controversial. The simple calculation makes mLIPI application possible in clinical setting. Therefore, it has the potential to be a novel predictive biomarker for guiding clinical treatment decisions in NSCLC.

To our knowledge, existing studies on the mLIPI have focused on patients receiving monotherapy. Conversely, in clinical practice, many patients with lung cancer receive ICIs plus chemotherapy. Many clinical studies have shown that compared with traditional standard chemotherapy, the PFS of patients receiving ICIs plus chemotherapy can be significantly improved in both lung squamous cell cancer and non-squamous NSCLC. In the randomized controlled studies KEYNOTE189 and KEYNOTE407, the OS of the combination treatment group was also significantly prolonged (32,33), whereas no significant difference was observed in treatment efficacy and patient prognosis among groups receiving different chemotherapy drugs (34). In the third edition of the National Comprehensive Cancer Network (NCCN) guidelines [2022], the first-line therapy for patients with driver-gene-negative advanced or metastatic NSCLC with high PD-L1 expression (TPS ≥50%) is pembrolizumab monotherapy or pembrolizumab plus platinum-based chemotherapy; for patients with low PD-L1 expression (TPS =1–49%) or negativity (TPS <1%), pembrolizumab plus platinum-based chemotherapy is recommended (35). In a global, multicenter, retrospective study involving 45 centers in 18 countries to determine tumor PD-L1 expression in patients with advanced NSCLC in the real world, Dietel *et al.* showed that only 22% of the patients had a PD-L1 TPS ≥50%, 30% had a PD-L1 TPS =1–49%, and 48% had a PD-L1 TPS <1% (36). Subsequently, a multicenter retrospective observational study (37) assessing PD-L1 expression in patients with NSCLC in China showed similar results; the majority of the patients had a PD-L1 TPS <1% (48.2%), followed by TPS =1–49% (30.3%), and TPS ≥50% (21.5%). Therefore, there is an urgent need to explore the relationship between the mLIPI and the efficacy of treatment together with the prognosis of patients receiving immunotherapy plus chemotherapy.

There are some limitations in our study. First, this was a single-center retrospective study with a small sample size. Therefore, a multi-center and larger sample size is required for further verification. Second, genomic data were lacked in most patients, such as data of PD-L1, and therefore in depth analysis could not be performed. Furthermore, a control group without immunotherapy is needed to further verify the predictive value of mLIPI score in NSCLC patients receiving chemotherapy alone.

Conclusions

In conclusion, mLIPI scores based on NLR, LDH, and ECOG-PS were shown to be correlated with the prognosis of patients with advanced NSCLC treated with first-line immunotherapy combined with chemotherapy, but prospective clinical studies are required for validation.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the institutional review board of the First Affiliated Hospital of Wenzhou Medical University (No. 2023R128). Individual consent for this retrospective analysis was waived.

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