A Low Advanced Lung Cancer Inflammation Index Predicts a Poor Prognosis in Patients With Metastatic Non–Small Cell Lung Cancer

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Introduction: Inflammation plays a crucial role in cancers, and the advanced lung cancer inflammation index (ALI) is considered to be a potential factor reflecting systemic inflammation.

Objectives: This work aimed to explore the prognostic value of the ALI in metastatic non–small cell lung cancer (NSCLC) and classify patients according to risk and prognosis.

Methods: We screened 318 patients who were diagnosed with stage IV NSCLC in Hubei Cancer Hospital from July 2012 to December 2013. The formula for ALI is body mass index (BMI, kg/m^2) × serum albumin (Alb, g/dl)/neutrophil–lymphocyte ratio (NLR). Categorical variables were analyzed by the chi-square test or Fisher's exact test. The overall survival (OS) rates were analyzed by the Kaplan–Meier method and plotted with the R language. A multivariate Cox proportional hazard model was used to analyze the relationship between ALI and OS.

Results: According to the optimal cut-off value determined by X-tile software, patients were divided into two groups (the ALI <32.6 and ALI ≥32.6 groups), and the median OS times were 19.23 and 39.97 months, respectively ($p < 0.01$). A multivariable Cox regression model confirmed that ALI and chemotherapy were independent prognostic factors for OS in patients with NSCLC. OS in the high ALI group was better than that in the low ALI group (HR: 1.39; 95% CI: 1.03–1.89; $p = 0.03$).

Conclusions: Patients with a low ALI tend to have lower OS among those with metastatic NSCLC, and the ALI can serve as an effective prognostic factor for NSCLC patients.

Keywords: advanced lung cancer inflammation index, inflammation, prognosis, non–small cell lung cancer, overall survival

INTRODUCTION

Due to the lack of symptoms in the early stages of lung cancer, only 21% of patients are diagnosed when they are at stage I and 61% of them at advanced stages of lung cancer (Molina et al., 2008; Miller et al., 2019) Because early disease is typically asymp-tomatic, the majority of lung cancers (61%) are diagnosed at stage III or IV; only 21% of cases are diagnosed at stage I. In terms of prognosis, the 5-year survival rate for stage I lung cancer patients is 57%, while that for stage IV patients is significantly lower at 4%. The 5-year relative survival rate for non–small cell lung cancer (NSCLC) patients is 23%, while the 5-year relative survival rate for small-cell lung cancer (SCLC) patients is even lower at 6% (Miller et al., 2019). NSCLC is one of the main causes of cancer-related deaths, and the prognosis of patients with NSCLC is extremely poor. The 5-year overall survival rate of patients with NSCLC at stage IV was less than 5% over the past 10 years (Arbour and Riely, 2019).

Precision medicine is committed to identifying and classifying individual patients to make the best treatment decisions (Vargas and Harris, 2016). Many demographic characteristics and clinicopathological indicators are recognized as prognostic factors for NSCLC patients, and the pathological stage of the tumor is a vital predictor of overall survival (OS). Various combinations of T (primary tumor), N (regional lymph nodes), and M (distant metastasis classification) stages distinguish cancer patients with different survival characteristics (Eberhardt et al., 2015). It has also been confirmed that some demographic characteristics are of great value in predicting the survival time of NSCLC; these include sex, age (Wang et al., 2019), chronic obstructive pulmonary disease (COPD) status (Loganathan et al., 2006; Ytterstad et al., 2016), and smoking status (de Groot and Munden, 2012). Various inflammatory factors, such as the Glasgow prognostic score (GPS) (Sandfeld-Paulsen et al., 2019; Imai et al., 2021), systemic immune-inflammation index (SII) (Tong et al., 2017; Zheng et al., 2021), NLR (Diem et al., 2017; Bongiovanni et al., 2021), and Aarhus composite biomarker score (ACBS) (Sandfeld-Paulsen et al., 2019), have been validated as prognostic markers in lung cancer.

Chronic inflammation can be triggered by the tumor microenvironment (Balkwill and Mantovani, 2001) and plays a vital role in the occurrence, development, and escape of tumors (Perwez Hussain and Harris, 2007). This may be mediated by the excessive secretion of proinflammatory cytokines and other immunosuppressive factors, resulting in damage to DNA (Ikwegbue et al., 2019) and crosstalk in signal transduction pathways. In addition, the susceptibility and severity of cancer may be related to inflammatory cytokines, and the development of cancer is inhibited when inflammatory cytokine expression is lacking or suppressed (Balkwill and Mantovani, 2001). Moreover, inflammation can contribute to cancer-related clinical symptoms, such as anorexia, cachexia, and pain, which seriously affect the quality of life of patients (Batista et al., 2012). There is growing evidence that inflammatory markers can predict the prognosis of patients with various cancers, such as lung cancer (Sarraf et al., 2009), liver cancer (Aleksandrova et al., 2014), and colorectal cancer (Al-Shaer, 2004). Jafri and his colleagues found that the advanced lung cancer inflammation index (ALI), an inflammatory index, can

TABLE 1 | Baseline characteristics and median OS.

Variable	N (%)	Median OS, Months (95% CI)	P
Age			
<65	221 (69.5)	30.60 (21.16–40.04)	0.23
≥65	97 (30.5)	20.93 (12.78–29.10)	—
Gender			
Male	211 (66.4)	22.27 (13.50–31.04)	0.47
Female	107 (33.6)	32.40 (21.60–43.20)	—
Smoking Status			
Never	154 (48.4)	28.13 (19.90–36.38)	0.95
Current or ever	164 (51.6)	22.27 (12.1–32.35)	—
Drinking Status			
Never	240 (75.5)	26.37 (18.00–34.73)	0.80
Current or ever	78 (24.5)	26.2 (12.93–39.50)	—
Location			
Left	186 (58.5)	28.83 (18.98–38.70)	0.38
Right	132 (41.5)	21.00 (11.74–30.13)	—
Family history of cancer			
Yes	60 (81.1)	29.4 (17.09–41.71)	0.40
No	258 (18.9)	25.23 (17.11–33.36)	—
COPD			
Yes	16 (5)	16.90 (3.64–30.16)	0.35
No	302 (95)	26.37 (18.94–33.79)	—
Tuberculosis			
Yes	18 (5.7)	14.67 (7.46–21.87)	0.44
No	300 (94.3)	26.97 (19.95–33.99)	—
Chemotherapy			
Yes	232 (73)	32.40 (25.61–39.20)	0.003
No	86 (27)	14.83 (9.96–19.71)	—
Radiotherapy			
Yes	40 (12.6)	18.4 (11.90–24.91)	0.23
No	278 (87.4)	28.13 (19.66–36.61)	—
LDH			
<274.4	237 (74.5)	31.53 (24.75–38.32)	0.013
≥274.4	81 (25.5)	16.60 (12.81–20.39)	—
ALI			
<32.6	191 (60.0)	19.23 (13.39–25.09)	0.003
≥32.6	127 (40.0)	39.97 (33.51–46.43)	—

evaluate inflammation and predict survival time in patients with advanced NSCLC and that low ALI is considered to be a risk factor for poor OS (Jafri et al., 2013). ALI is a powerful prognostic biomarker for both NSCLC (Jafri et al., 2013) and SCLC (He et al., 2015) patients. It has been confirmed that low ALI is also associated with a poor prognosis in patients with esophageal cancer (Feng et al., 2014; Tan et al., 2021), diffuse large B-cell lymphoma (Park et al., 2017), HPV-negative head and neck squamous cell carcinoma (Gaudioso et al., 2021), melanoma (Cheng et al., 2021), and colorectal cancer (Pian et al., 2021). Our study aims to evaluate the prognostic value of ALI in patients with metastatic NSCLC. The results are consistent with Jafri and colleagues' finding that the ALI can be used as a valuable prognostic indicator for NSCLC patients.

MATERIALS AND METHODS

Study Design

The study is a cross-sectional survey of cancer patients, a total of 318 of whom were pathologically diagnosed with stage IV NSCLC at Hubei Cancer Hospital (HBCH) between July 2012 and December 2013. We selected patients on the basis of the

following inclusion criteria: 1) age >18 years, 2) pathological diagnosis of NSCLC, and 3) metastatic pathologic stage IV according to the American Joint Committee on Cancer (AJCC) Staging Manual (Seventh Edition). The exclusion criteria were as follows: 1) second primary cancer at NSCLC diagnosis, 2) a history of malignancy or hematologic disease, 3) blood test results and clinical symptoms and signs indicating severe infection status, and 4) missing follow-up data. Of the 351 eligible patients, we excluded 33 based on missing data on variables of interest. Finally, 318 patients were analyzed further.

Demographic and Clinical Variables

Related inflammatory indicators, including serum albumin (Alb), neutrophil count, lymphocyte count, and lactate dehydrogenase (LDH) were collected. Furthermore, demographic baseline and clinicopathological characteristics, including age, gender, smoking and drinking status, cancer location, family history, treatment of cancer, and history of lung-related diseases, were obtained through medical records. Body mass index (BMI) was derived using its established derivation formula: body weight (kg)/height squared (m^2). The neutrophil–lymphocyte ratio (NLR) was calculated as follows: peripheral blood absolute neutrophil count divided by absolute lymphocyte count. The formula for the ALI was BMI ×Alb/NLR, where the unit of BMI is kg/m (Molina et al., 2008), and the unit of Alb is g/dl.

Follow-Up

In this study, we defined OS as the period spanning from the date of pathological diagnosis of NSCLC to the date of the final follow-up (i.e., December 31, 2013) or the date of censoring the patient as alive or dead. The follow-up started from the diagnosis in Hubei Cancer Hospital in December 2013 and continued until the end of the follow-up period or the loss of follow-up. During this period, patients underwent routine reexaminations, such as blood laboratory tests and imaging tests.

Statistical Analysis

The optimal cut-off values of ALI and LDH were determined through X-tile and used to convert these factors into categorical variables. The chi-square test and Fisher's exact test were used to analyze the relationships among the categorical variables. The OS rate was analyzed by the Kaplan–Meier method, and the survival differences were assessed for statistical significance using the log-rank test. The median survival time and 95% confidence interval (CI) were reported for each group. Furthermore, survival curves including 95% CIs were generated using R language. The influence of variables on OS was analyzed by multivariate Cox proportional hazard regression, and variables that reached statistical significance ($p < 0.05$) and were associated with ALI were included in the multivariable analysis. Moreover, the hazard ratio (HR) was estimated. All tests were bilateral, and $p < 0.05$ was considered the threshold for statistical significance. Statistical analyses were performed by SPSS 25.0 software.

TABLE 2 | Basic characteristics according to the level of ALI.

Variable	ALI <32.6	ALI ≥32.6	P
Age			
≥65	134 (70.2)	87 (68.5)	0.75
≥65	57 (29.8)	40 (31.5)	—
Gender			
Male	135 (70.7)	76 (59.8)	0.045
Female	56 (29.3)	51 (40.2)	—
Smoking Status			
Never	90 (47.1)	64 (50.4)	0.57
Current or ever	101 (52.9)	63 (49.6)	—
Drinking Status			
Never	147 (77.0)	93 (73.2)	0.45
Current or ever	44 (23.0)	34 (26.8)	—
Location			
Left	118 (61.8)	68 (53.5)	0.14
Right	73 (38.2)	59 (46.5)	—
Family history of cancer			
Yes	37 (19.4)	23 (18.1)	0.78
No	154 (80.6)	104 (81.9)	—
COPD			
Yes	8 (4.2)	8 (6.3)	0.40
No	183 (95.8)	119 (93.7)	—
Tuberculosis			
Yes	14 (7.3)	4 (3.1)	0.11
No	177 (92.7)	123 (96.9)	—
Chemotherapy			
Yes	132 (69.1)	100 (78.7)	0.06
No	59 (30.9)	27 (21.3)	—
Radiotherapy			
Yes	25 (13.1)	15 (11.8)	0.74
No	166 (86.9)	112 (88.2)	—
LDH			
<274.4	127 (66.5)	110 (86.6)	<0.001
≥274.4	64 (33.5)	17 (13.4)	—

RESULTS

Baseline Characteristics

The demographic and clinical variables of the patients who were pathologically diagnosed with NSCLC are shown in **Table 1**. The majority of patients (n = 221) were younger than 65 years old, and 66.4% of patients were male. A history of cigarette smoking and alcohol consumption was reported by 164 (51.6%) and 78 (24.5%) patients, respectively. In total, 16 (5%) patients had a history of COPD, and 18 (5.7%) had a history of tuberculosis. Regarding treatment, 73% (n = 232) of patients accepted chemotherapy, and 12.6% of patients (n = 40) were treated with radiotherapy. The level of LDH in 74.5% of the patients was lower than 274.4, and the ALI level of most patients was low, ALI <32.6. The median survival time and 95% confidence interval of patients in different groups were obtained by univariate survival analysis. Among them, patients who received chemotherapy tended to have a longer survival time ($p = 0.003$). The difference in survival time between patients with different levels of LDH and ALI was considered to be statistically significant; furthermore, patients with low levels of LDH ($p = 0.013$) and a high ALI ($p = 0.003$) had longer survival times.
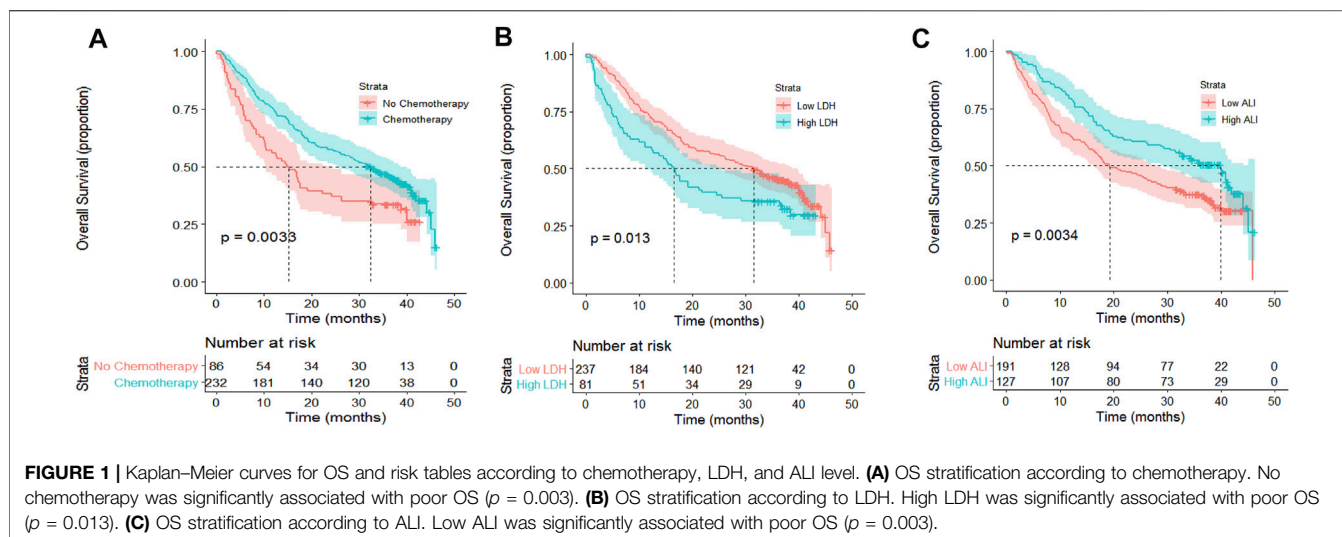
FIGURE 1 | Kaplan–Meier curves for OS and risk tables according to chemotherapy, LDH, and ALI level. **(A)** OS stratification according to chemotherapy. No chemotherapy was significantly associated with poor OS ($p = 0.003$). **(B)** OS stratification according to LDH. High LDH was significantly associated with poor OS ($p = 0.013$). **(C)** OS stratification according to ALI. Low ALI was significantly associated with poor OS ($p = 0.003$).

TABLE 3 | Multivariable Cox regression model (adjusted for gender, chemotherapy, LDH, and ALI).

Variables	Hazard Ratio	95% CI	p
Gender			
Male	—	—	—
Female	0.90	0.67–1.22	0.50
Chemotherapy			
No	—	—	—
Yes	0.67	0.49–0.91	0.01
LDH			
<274.4	—	—	—
≥274.4	1.33	0.96–1.83	0.08
ALI			
≥32.6	—	—	—
<32.6	1.39	1.03–1.89	0.03

Relationship Between Baseline Characteristic Variables and Advanced Lung Cancer Inflammation Index Analysed by Chi-Square Test or Fisher's Exact Test

According to X-tile software, the optimal cut-off value of ALI was determined to be 32.6. Then, all patients were divided into two groups: ALI<32.6 (n = 191) and ALI ≥32.6 (n = 127). The optimal cut-off value of LDH was determined to be 274.4. The relationship between demographic and clinical variables and ALI was analyzed by the chi-square test or Fisher's exact test, as shown in **Table 2**. The results indicated that gender ($p = 0.045$) and LDH ($p < 0.001$) were significantly associated with ALI.

Univariate Survival Analysis and Survival Curves

Some factors were recognized as associated with poor OS according to the results of univariate survival analysis (**Figure 1**), including no chemotherapy ($p = 0.003$; Figure A), high LDH ($p = 0.013$; Figure B), and low ALI ($p = 0.003$; Figure

C). According to the Kaplan–Meier survival curve, the median survival times in the no chemotherapy and chemotherapy groups were 14.83 months (95% CI: 9.96–19.71 months) and 32.40 months (95% CI: 25.61–39.20 months), respectively, signifying a marked difference, as revealed by the log-rank test ($p = 0.003$). Moreover, the high LDH group had a shorter median OS period than the low LDH group (16.60 vs 31.53 months, $p = 0.013$). The OS of patients with a high ALI (≥32.6) was longer than that of patients with a low ALI (<32.6) (39.97 vs 19.23 months, respectively).

Multivariate Cox Regression Model

A multivariate Cox proportional hazard model was used to analyze the influence of variables on OS and estimated its HR with 95% CI. Gender, chemotherapy, LDH, and ALI were included in the multivariate Cox regression model (**Table 3**). Chemotherapy ($p = 0.01$) and ALI ($p = 0.03$) were independent prognostic factors in terms of OS. Furthermore, the risk of death in patients with low ALI was 1.39 times higher than that in patients with high ALI (HR: 1.39; 95% CI: 1.03–1.89; $p = 0.03$).

DISCUSSION

Inflammation is an automatic defense response against pathogens, and inflammatory cytokines contribute to reactive oxygen species production, DNA damage, cell proliferation, and tumor-related angiogenesis in the tumor microenvironment. Inflammation contributes to the occurrence, development, and immune escape of tumors and even affects the treatment response.

The NLR and C-reactive protein (CRP) level have been proven to be prognostic factors for NSCLC and other tumors, including hepatocellular carcinoma (Liao et al., 2018), colorectal cancer (Tsai et al., 2016), and esophageal cancer (Otowa et al., 2019). It has been reported that patients with NSCLC whose NLR returned to normal after one cycle of systematic treatment had a better prognosis than those whose NLR was still not in the normal range (Cedrés et al.,

2012). However, in a study of advanced renal cell carcinoma, it was found that the remission rate of NLR after treatment was not related to the survival rate (Keizman et al., 2012). An increase in neutrophil count or a decrease in lymphocyte count can lead to an increase in the NLR. Neutrophils can produce cytokines and inhibit lymphocyte-mediated immune activity, thus affecting the prognosis of tumor patients.

Another study confirmed that hypoalbuminemia is related to a poor prognosis in NSCLC patients who are treated with erlotinib (Fiala et al., 2016). The correlation between hypoalbuminemia and shorter survival after tumor resection is statistically significant and has been confirmed in resectable colon cancer. It is well known that Alb is one of the indicators for assessing nutritional status. In addition, albumin is an acute phase protein that can indicate inflammatory activity; it can bind to other laboratory indicators, such as C-reactive protein, lymphocytes, and globulins, and its predictive value has been evaluated.

Moreover, as a nutritional status assessment indicator, BMI is also associated with the prognosis of cancer patients. Both underweight and morbidly obese statuses are associated with poor survival in NSCLC and SCLC (Shepshelovich et al., 2019). Similarly, Masaaki et al. explained that both low BMI and high BMI are related to an increased risk of poor survival in breast cancer (Kawai et al., 2012). For thyroid cancer, patients who have a high BMI might have a higher risk of suffering from cancer (Son et al., 2018; Abdel-Rahman, 2019).

As a metric reflecting BMI, Alb, and NLR, ALI provides a more comprehensive assessment of inflammation than these indicators alone. A low ALI value means higher systemic inflammatory activity and plays an important role in the prognosis of patients. A high ALI suggests low activity systemic inflammation in cancer patients, which may result from moderately increased BMI, increased albumin, and decreased NLR. These factors can be involved in the inhibition of tumor occurrence, invasion, and metastasis, promoting a good prognosis. Conversely, a low ALI is usually associated with a poor prognosis. In the univariate survival analysis, there was a significant correlation between a low ALI and poor OS ($p = 0.003$). In the multivariate Cox regression analysis, we adjusted for gender, chemotherapy, and LDH, and the results proved that a low ALI is an independent risk factor for OS in NSCLC patients. (HR = 1.39; $p = 0.03$). Therefore, we proposed that ALI can serve as an effective prognostic factor for NSCLC patients.

CONCLUSION

Our study confirms that the difference in survival time of metastatic NSCLC patients with different ALI statuses is statistically significant, and tumor patients with a low ALI have lower OS. Due to the clinical feasibility of assessing the ALI, it can be used to help distinguish patients with different prognoses.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during this study are available from the corresponding authors upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethical Committee of the Hubei Cancer Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors made a significant contribution to the work reported in one or more of the following aspects: conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas. All authors took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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