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ORIGINAL RESEARCH

Advanced Lung Cancer Inflammation Index is a Prognostic Factor of Patients with Small-Cell Lung Cancer Following Surgical Resection

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Purpose: Advanced lung cancer inflammation index (ALI) has been shown to predict overall survival (OS) in advanced non small-cell lung cancer (NSCLC), small-cell lung cancer (SCLC) and operable NSCLC. However, there were no studies of the correlation between ALI and operable SCLC. Therefore, this study is aimed to explore the relationship between ALI and the prognosis of operable SCLC.

Patients and Methods: A total of 48 patients with SCLC who underwent surgery at Hebei General Hospital and Zigong First People's Hospital were screened between 2016 and 2020. ALI was calculated as follows: body mass index (BMI, kg/m^2)×serum albumin (ALB, g/dL)/ neutrophil to lymphocyte ratio (NLR). Receiver operating characteristic (ROC) curve was used to determine the optimal cutoff value of ALI. Patients were divided into two groups according to the cutoff point of ALI: low ALI group with ALI<48.2 and high ALI group with ALI≥48.2. Kaplan-Meier and Cox regression analysis were performed to assess the potential prognostic factors associated with OS.

Results: The optimal cutoff value of ALI was determined as 48.2. The low ALI group displayed more adverse clinical characteristics and poorer survival rates. Multivariate analysis revealed that ALI and Charlson comorbidity index (CCI) were significantly correlated with OS.

Conclusion: Low ALI was correlated with poor prognosis in patients with SCLC who underwent surgery. Preoperative ALI might serve as a potential prognostic marker for patients with operable SCLC.

Keywords: ALI, SCLC, surgery, prognosis

Introduction

Lung cancer remains the leading cause of cancer-related deaths in China, and small-cell lung cancer (SCLC) accounts for approximately 15% of all cases.[1,2] SCLC, highly responsive to initial chemotherapy and radiotherapy, is highly aggressive and poor in prognosis.[3,4] Therefore, it is important to explore accurate prognostic factors for SCLC. The dichotomized staging system and TNM Classification of Malignant Tumors (TNM) are the most important predictors of overall survival (OS).[5] In addition, a number of clinical indicators such as gender, age, smoking status and performance status (PS) are reported to be related to prognosis in patients with SCLC.[4,6,7] There is increasing evidence that inflammation status is correlated with cancer growth and can be used for prognosis in operable cancers.[8–12] Jafri et al[13] developed a prognostic index based on systemic inflammation called advanced lung

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cancer inflammation index (ALI), which was calculated as body mass index (BMI, kg/m^2)×serum albumin (ALB, g/dL)/neutrophil to lymphocyte ratio (NLR). Although the prognostic effect of ALI has been tested in patients with SCLC, esophageal cancer, and malignant lymphoma,[14–16] the prognostic significance of ALI in operable SCLC has not yet been investigated. Operable SCLC refer to patients with SCLC that can be cured by local resection. In this study, we explored whether ALI is associated with the prognosis of patients with operable SCLC.

Patients and Methods

From January 2016 to August 2020, a total of 48 patients with SCLC who underwent curative surgery at Hebei General Hospital and Zigong First People's Hospital were enrolled. Curative surgery refers to local resection of lung tissue of SCLC patients to reach a cure. No patients received preoperative chemoradiotherapy. Patients with acute or chronic inflammatory disease during the preoperative period were excluded. All patients were pathologically diagnosed as SCLC with no clinical evidence of infection or other inflammatory conditions and no other malignancies.

End point of assessment was patient OS, which was defined as the time from operation to the time of death from any cause. For subjects who had missed their follow-up visits prior to death, the last follow-up was counted as the time of death. The clinicopathological variables including age, gender, height, weight, smoking status, PS and Charlson comorbidity index (CCI) were recorded by the electronic medical record system. Laboratory parameters including C-creative protein (CRP), neutrophil count, lymphocyte count, white blood cell count (WBC), red blood cell count (RBC), platelet count (PLT), monocyte count (MONO), eosinophil count (EO), basophil count (BASO), ALB and lactate dehydrogenase (LDH) were performed before operation. The preoperative serum carcinoembryonic antigen (CEA), squamous cell carcinoma antigen (SCC), cytokeratin-19 fragment (CYFRA 21–1), progastrin releasing peptide (Pro-GRP) and neuron-specific enolase (NSE) levels were measured in all patients by enzyme immunoassay in single laboratory at both hospitals. The median postoperative follow-up was 26 months. Ethical Committee of Hebei General Hospital and Zigong First People's Hospital approved this retrospective study. Informed consent was waived due to the retrospective nature of the study. We confirm the confidentiality of the data maintained and compliance with the "Declaration of Helsinki".

ALI was calculated by the following formula: BMI (kg/m^2) ×ALB (g/dL)/NLR.[13] Cutoff value for ALI, ALB, WBC, RBC, PLT, MONO, EO, BASO, NLR, platelet to lymphocyte ratio (PLR) and lymphocyte to monocyte ratio (LMR) were determined using receiver operating characteristic (ROC) curve analysis to estimate optimal sensitivity, specificity, and the area under the curve (AUC) for prediction of death from all causes. Pearson correlation, Chi-square test and Fisher exact test were used to compare continuous and categorical variables. Cumulative cancer-specific survival curves after surgery were calculated using the Kaplan–Meier method, and differences were assessed using Log rank test. The Cox proportional hazard model was used to evaluate the predictive power of potential prognostic variables, and the hazard ratios (HR) estimated from the Cox analysis reported as relative risks with corresponding 95% confidence intervals. Statistical analyses were performed using the IBM SPSS statistics software program, version 21.0 (IBM Corporation, Armonk, NY, USA). $P<0.05$ indicated statistical significance.

Results

In total, 48 patients with SCLC receiving surgical resection were analyzed, according to available clinical information and baseline laboratory parameters (Table 1). The median age was 60.5 years (range: 27 to 80 years). Thirty-four patients (70.8%) were male and 28 patients (58.3%) were current or ever smokers. Thirty-three patients (68.8%) scored

Table 1 Clinical Characteristics of Patients

	Baseline	No.
Age	<65 years ≥65 years	31 17
Gender	Male Female	34 14
Smoking	Never Current/ever	23 25
BMI	<18.5 ≥18.5 to <25 ≥25	2 23 23
PS	0–1 2	33 15

(*Continued*)

Table 1 (Continued).

	Baseline	No.
CCI	0 1–2 ≥3	19 13 16
ALB (g/dL)	<4.13 ≥4.13	23 25
WBC (×10^9/L)	<6.47 ≥6.47	23 25
RBC (×10^{12}/L)	<4.30 ≥4.30	15 33
PLT (×10^9/L)	<231.50 ≥231.50	24 24
MONO (×10^9/L)	<0.38 ≥0.38	31 17
EO (×10^9/L)	<0.12 ≥0.12	28 20
BASO (×10^9/L)	<0.05 ≥0.05	38 10
NLR	<2.08 ≥2.08	20 28
LMR	<10.86 ≥10.86	46 2
PLR	<124.27 ≥124.27	22 26
Pro-GRP	Normal High	3 21
NSE	Normal High	28 20
Postoperative chemotherapy	Yes No	33 15

Abbreviations: BMI, body mass index; PS, performance status; CCI, Charlson comorbidity index; ALB, albumin count; WBC, white blood cell count; RBC, red blood cell count; PLT, platelet count; MONO, monocyte count; EO, eosinophil count; BASO, basophil count; NLR, neutrophil to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; PLR, platelet to lymphocyte ratio; ALI, advanced lung cancer inflammation index; CEA, carcinoembryonic antigen; LDH, lactate dehydrogenase; SCC, squamous cell carcinoma antigen; CYFRA 21-1, cytokeratin-19 fragment; Pro-DRP, pro-gastrin releasing peptide; NSE, neuron-specific enolase; CRP, C-reactive protein.

PS as 0 or 1 while 15 patients (31.3%) scored CCI as 0. Thirty-three patients (68.8%) received postoperative chemotherapy (Etoposide-based combination chemotherapy). Nine patients had lung cancer recurrence, and 6 of them died. In total, 15 patients died during the observation period.

The median value of ALI was 46.8 (16.8 to 77.4). The optimal cutoff point shown by ROC curve analysis of ALI for the layering of OS in SCLC was determined to be 48.2 (Figure 1A). Optimal cutoff points of RBC (×10^{12}/L), WBC (×10^9/L), PLT (×10^9/L), MONO (×10^9/L), EO (×10^9/L), BASO (×10^9/L), LMR, PLR, NLR and ALB (g/dL) were 4.30, 6.47, 231.50, 0.38, 0.12, 0.45, 10.86, 124.27, 2.08 and 4.13, respectively (Figure 1B). Patients were divided into two groups according to the ALI value based on the cutoff point: low ALI group with ALI<48.2 (n=25) and high ALI group with ALI≥48.2 (n=23). The relationship between baseline characteristics and ALI are shown in Table 2. Comparison of postoperative survival curves of the two groups showed a significant difference in the rates of patient survival (Figure 2, P<0.05). Patients with high ALI had longer OS than those in low ALI group (34 vs 19 months, P<0.05).

The low ALI group displayed more adverse clinical characteristics. OS, PFS, PS, CCI, LDH, CRP, NLR and CYFRA21-1 were significantly different between the two groups (P<0.05). In univariable analysis of OS, lowALI, smoking, PS=2, CCI≥3, high MONO, high EO, high BASO and high LDH were significant factors for poor survival (P<0.05) (Table 3). In multivariable analyses using Cox hazard model (Table 3), CCI≥3 and low ALI were independent predictors of poor prognosis (P<0.05). In addition, MONO and EO might be independent prognostic factors for operable SCLC (p<0.1).

Discussion

Inflammation and immune response can affect angiogenesis and cellular proliferation, which play key roles in carcinogenesis.[8,17] Epidemiological observation has implicated that systemic inflammation is important in cancer etiology as inflammatory markers were evident in tumor microenvironment, which indicated the prognostic significance of inflammation in different cancers. Furthermore, recent studies have shown the correlation between systematic inflammation and poor cancer outcomes.[6,12,14,18,19] Inflammation is widely involved in multiple pathological conditions including lymphocytopenia, neutrophilia, thrombocytosis and so on.[20] Previous studies have shown that absolute inflammatory cell counts in peripheral blood (neutrophils, WBC, lymphocytes and MONO) and ratios based on these cell counts (NLR, PLR and LMR) may provide valuable information in predicting the prognosis of patients with malignances including NSCLC.[21–23] Therefore, these inflammatory parameters may also predict the prognosis of operable SCLC.

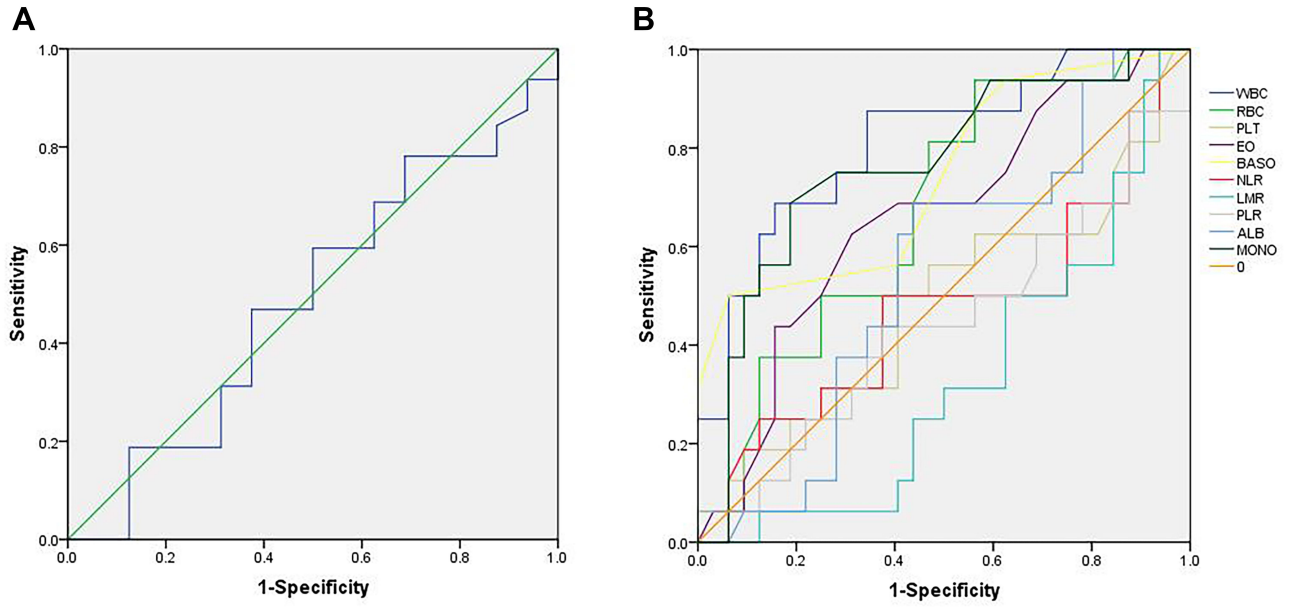

Figure 1 Receiver operating characteristic (ROC) curves. (**A**) shows the ROC curve of advanced lung cancer inflammation index (ALI). The maximum Youden index is 0.094, corresponding optimal cutoff value of ALI is 48.2. (**B**) shows the ROC curves of red blood cell count (RBC), white blood cell count (WBC), platelet count (PLT), monocyte count (MONO), eosinophil count (EO), basophil count (BASO), lymphocyte to monocyte ratio (LMR), platelet to lymphocyte ratio (PLR), neutrophil to lymphocyte ratio (NLR) and serum albumin (ALB). Maximum Youden indexes are as follows: 0.375 for RBC, 0.531 for WBC, 0.094 for PLT, 0.500 for MONO, 0.313 for EO, 0.438 for BASO, 0.063 for LMR, 0.063 for PLR, 0.125 for NLR and 0.250 for ALB. Optimal cutoff points of RBC ($\times 10^{12}$/L), WBC ($\times 10^{9}$/L), PLT ($\times 10^{9}$/L), MONO ($\times 10^{9}$/L), EO ($\times 10^{9}$/L), BASO ($\times 10^{9}$/L), LMR, PLR, NLR and ALB (g/dL) are 4.30, 6.47, 231.50, 0.38, 0.12, 0.45, 10.86, 124.27, 2.08 and 4.13.

Neutrophils, remodeling the extracellular matrix and releasing reactive oxygen species or nitric oxide, are thought to participate in the process of tumor proliferation and metastasis.[24] Platelets can affect the metastatic potential of tumor cells by secreting cellular growth factors which can stimulate tumor angiogenesis, thereby contributing to the stable adhesion and transmigration of tumor cells, promoting tumor stroma formation and tumor cell metastasis.[25,26] Therefore, an elevated neutrophil count and platelet count may be correlated with a poor prognosis of patients with cancer.[27] Lymphocytes play important roles in tumor immune surveillance, killing cancer cells and regulating the cancer progression. The cytotoxic activity of lymphocytes and their induction of apoptosis in tumor cells can control tumor growth.[28,29] Decrease in lymphocytes may count as a biomarker of poor outcome in patients with terminal cancer. Moreover, monocytes can facilitate the progression and dissemination of tumor cells. They can be recruited to the tumor microenvironment to promote tumor cell growth and survival. The differentiation of monocytes can be induced into tumor-associated macrophages, which can weaken the anti-tumor immune response and stimulate the migration and metastasis of tumor cells.[17,30] Peripheral monocyte levels were found to be negatively associated with prognosis in patients with various types of cancer.[27,31,32]

In addition, the significant prognostic effect of NLR, PLR and LMR on OS in cancer patients has been reported by various studies,[33–36] suggesting that elevated NLR, PLR and reduced MLR may predict poor prognosis of SCLC. In this study, NLR, WBC, PLT, PLR and LMR have no significant effect on OS of operable SCLC patients. Univariable analysis showed that MONO has prognostic value while multivariable analysis showed no significant value. The results might due to small sample size in our study, and tumors in early-stage rarely show obvious inflammation and migration.

Tumor-associated blood eosinophilia, accounts for 1–7% of all clinical eosinophilia's diagnoses,[37] was described in various tumors.[38,39] In addition, basophils were reported to be accessory cells exerting clinically relevant tumor-promoting functions in pancreatic cancer.[40] However, these findings are not frequently observed in clinical practice. Our study demonstrated the prognostic value of EO and BASO while multivariable analysis showed no independent value. The mechanisms of the two factors in tumors may be related to immune response, which need further investigation.

Table 2 Relationship Between Patient Characteristics and ALI

	Baseline	ALI<48.2	ALI≥48.2	P value
		n=25	n=23	
Age	<65 years ≥65 years	15 10	16 7	0.349
Gender	Male Female	18 7	16 7	0.552
Smoking	Never Now or ever	10 15	13 10	0.196
PS	0–1 2	11 14	22 1	<0.001
CCI	0 1–2 ≥3	7 6 12	12 7 4	<0.05
BMI	<18.5 ≥18.5 to <25 ≥25	2 13 10	0 9 14	0.086
ALB (g/dL)	<4.13 ≥4.13	13 12	10 13	0.382
WBC ($\times 10^9$/L)	<6.47 ≥6.47	11 14	12 11	0.391
RBC ($\times 10^{12}$/L)	<4.30 ≥4.30	7 18	8 15	0.422
PLT ($\times 10^9$/L)	<231.50 ≥231.50	13 12	11 12	1
MONO ($\times 10^9$/L)	<0.38 ≥0.38	17 8	14 9	0.415
EO ($\times 10^9$/L)	<0.12 ≥0.12	13 12	15 8	0.263
BASO ($\times 10^9$/L)	<0.05 ≥0.05	22 3	16 7	0.112
NLR	<2.08 ≥2.08	13 12	7 16	0.111
LMR	<10.86 ≥10.86	24 1	22 1	0.734
PLR	<124.27 ≥124.27	14 11	8 15	0.118
CRP	Normal High	8 17	19 4	<0.001
CEA	Normal High	14 11	17 6	0.160
LDH	Normal High	13 12	19 4	<0.05
SCC	Normal High	12 6	11 6	0.592
CYFRA21-1	Normal High	9 7	16 16	<0.05
Pro-GRP	Normal High	1 15	2 6	0.249
NSE	Normal High	14 9	14 11	0.481
Postoperative chemotherapy	Yes No	9 16	6 17	0.335
Living status	Live Death	17 8	15 8	0.540

Abbreviations: BMI, body mass index; PS, performance status; CCI, Charlson comorbidity index; ALB, albumin; WBC, white blood cell; RBC, red blood cell; PLT, platelet; MONO, monocyte; EO, eosinophil; BASO, basophil; NLR, neutrophil to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; PLR, platelet to lymphocyte ratio; ALI, advanced lung cancer inflammation index; CEA, carcinoembryonic antigen; LDH, lactate dehydrogenase; SCC, squamous cell carcinoma antigen; CYFRA 21–1, cytokeratin-19 fragment; Pro-GRP, pro-gastrin releasing peptide; NSE, neuron-specific enolase; CRP, C-reactive protein.

Cancer cachexia is a multi-factorial syndrome, considered as the clinical consequence of interactions between tumor, metabolism and inflammatory factors, impairing quality of life and response to therapy.[41] Though cachexia rarely appear in early-stage oncologic patients, estimation of body composition is of widely considerable importance. Previous study has indicated that body weight loss in advanced cancer may increase the risk of mortality.[42] BMI and ALB have been demonstrated to be important parameters for evaluation of nutritional status.[43–45] The two factors were reported to be closely linked to survival in patients with not only advanced lung cancer, but also resected NSCLC.[44–47] Therefore, they might be prognostic factors in operable SCLC patients. Tomita et al[46] reported that hypoalbuminaemia might be an important marker of inflammation in addition to malnutrition in patients with operable NSCLC, and ALI might be a useful prognostic marker in patients with resected NSCLC. Zhou et al[6] demonstrated the correlation between systemic inflammatory

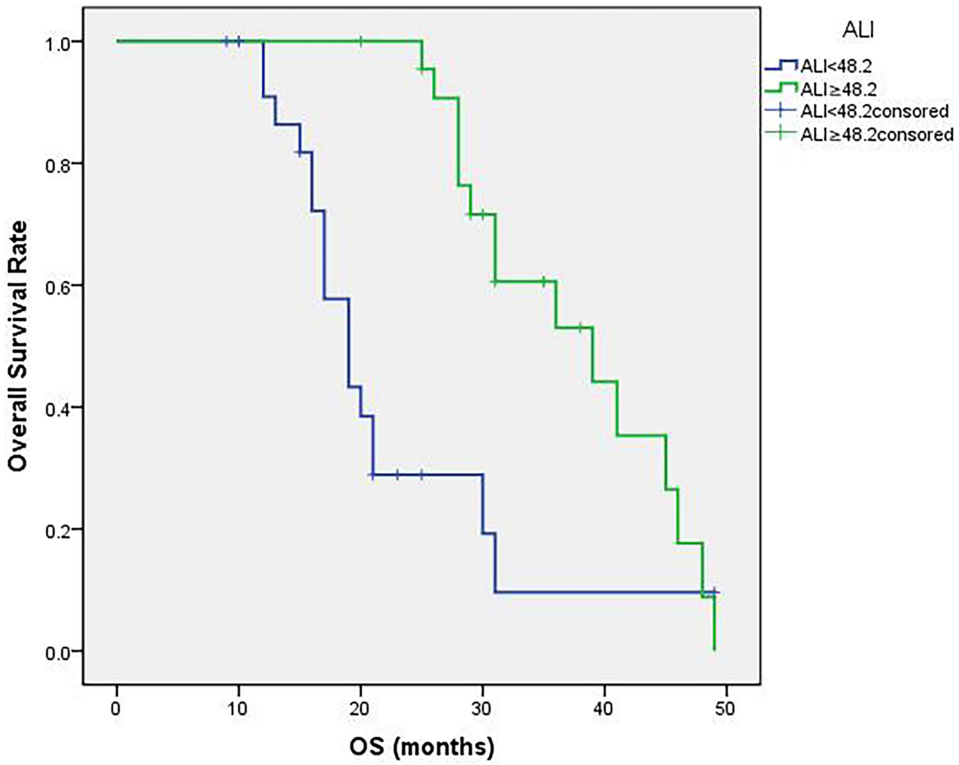

Figure 2 Patient overall survival (OS) curves following surgery. The curves indicate that high ALI group (ALI≥48.2) shows more survival rates and longer survival time (P<0.05).

response and cancer-specific survival in patients with SCLC. Since inflammation and malnutrition factors play important roles in many kinds of tumor including SCLC, it is likely that ALI, calculated from BMI, ALB and NLR, could be a prognostic marker in operable SCLC patients.

We investigated SCLC cases with radical resection in the present study and found the correlation between ALI and prognosis. Our findings indicate the importance of malnutrition and inflammatory status in prognosis of not only advanced lung cancer, but also early-stage operable SCLC. We determined a cutoff value of 48.2 for ALI with ROC curve analysis. In previous studies, different cutoff values such as 31.1 by Kim and colleagues,[48] 47.0 by Zhou et al[49] and 19.5 by He et al[14] have been reported in patients with small-cell lung cancer. Jafri et al[13] demonstrated a cutoff value of 18 in patients with advanced NSCLC, while Tomita et al[50] reported that of 37.66 in patients with resected NSCLC and Kobayashi et al[51] that of 22.2 in early-stage NSCLC. Our analysis resulted in a cutoff value within the range of those reported in other studies. OS, PFS, NLR, serum CYFRA21-1 level, PS and alive status were different between patients with high and low ALI. The analysis results strongly indicate that ALI could be a prognostic factor for operable SCLC patients.

Our data suggest that preoperative ALI, along with smoking, PS, CCI and LDH, is a prognostic factor for operable SCLC. Furthermore, ALI and CCI could be independent prognostic factors. Other inflammation indicators we evaluated are not of statistical significance for prognosis, which may due to small sample size and early-stage cancer that do not show obvious inflammation with significant increase. Radical resection is associated with significantly longer OS for early SCLC. Studies showed five-year OS for patients with clinical stages I and II after resection to be 51% and 25%.[52] However, due to poor OS in SCLC patients, postoperative treatment is suggested. Previous studies have shown the effect of targeted therapy[53] and immunotherapy[54] on reducing postoperative recurrence rates. By studying the prognostic factors of SCLC patients, we can better assess the prognostic risk and give appropriate postoperative adjuvant treatments to effectively extend patients' lifetime.

Limitations

The study has limitations in the following aspects. It is a retrospective study and we did not select postoperative

Table 3 Univariable and Multivariable Analysis

	Univariable Analysis				Multivariable Analysis			
	P value	HR	95% CI		P value	HR	95% CI	
			LL	UL			LL	UL
ALI	0.031	0.309	0.107	0.896	0.009	0.035	0.003	0.425
Gender	0.070	53.193	0.722	3918.139	0.952	260,285.584	0	
Age	0.505	1.454	0.484	4.370				
Smoking	0.005	6.280	1.750	22.534	0.538	0.492	0.051	4.704
PS	0.019	0.276	0.094	0.809				
CCI=0	0.011				0.137			
CCI=1-2	0.936	0.943	0.225	3.949	0.310	3.644	0.301	44.150
CCI≥3	0.006	7.011	1.739	28.267	0.046	9.355	1.037	84.381
ALB	0.675	1.236	0.458	3.336				
WBC	0.669	0.806	0.299	2.170				
RBC	0.093	43.222	0.534	3495.431	0.955	292,578.176	0	
PLT	0.487	1.421	0.528	3.826				
MONO	0.001	6.590	2.067	21.015	0.073	0.225	0.044	1.151
EO	0.023	3.562	1.194	10.632	0.094	5.371	0.750	38.493
BASO	0.012	3.711	1.335	10.314	0.475	0.567	0.120	2.685
NLR	0.069	0.384	0.137	1.079	0.323	2.090	0.484	9.022
LMR	0.567	0.045	0	1813.598				
PLR	0.393	0.650	0.242	1.747				
CEA	0.745	1.184	0.427	3.289				
LDH	0.046	2.867	1.017	8.079	0.826	0.783	0.089	6.881
SCC	0.556	1.533	0.370	6.359				
CYFRA21-1	0.127	2.284	0.790	6.599				
NSE	0.152	2.074	0.765	5.624	0.329	0.319	0.032	3.156
BMI<18.5	0.243							
BMI[18.5,25)	0.797	0.745	0.079	7.037				
BMI≥25	0.114	2.383	0.812	6.991				
CRP	0.926	1.053	0.357	3.103				
Pro-GRP	0.960	0.946	0.110	8.136				
Postoperative chemotherapy	0.644	0.775	0.263	2.283				

Abbreviations: ALI, advanced lung cancer inflammation index; PS, performance status; CCI, Charlson comorbidity index; ALB, albumin; WBC, white blood cell; RBC, red blood cell; PLT, platelet; MONO, monocyte; EO, eosinophil; BASO, basophil; NLR, neutrophil to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; PLR, platelet to lymphocyte ratio; CEA, carcinoembryonic antigen; LDH, lactate dehydrogenase; SCC, squamous cell carcinoma antigen; CYFRA 21–1, cytokeratin-19 fragment; NSE, neuron-specific enolase; BMI, body mass index; CRP, C-reactive protein; Pro-GRP, pro-gastrin releasing peptide.

data of ALI. Thus, there is potential of selection bias. Multivariate analysis showed that ALI could be an independent prognostic factor. Therefore, a large-scale multicenter prospective validation study is required to establish more reliable and independent findings.

Conclusion

Inflammation plays a vital role in cancer prognosis. Preoperative ALI, smoking, PS, CCI and LDH may be prognostic factors for SCLC patients receiving radical surgery. ALI, along with CCI, may be an independent and effective prognostic factor for patients with operable SCLC, which can be adapted in the clinical practice to stratify SCLC patients for future trials.

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Disclosure

The authors report no conflicts of interest in this work.

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