

Prognostic value of the advanced lung cancer inflammation index in early-stage non-small cell lung cancer patients undergoing video-assisted thoracoscopic pulmonary resection

Yan Wang, Lin Lin, Yanli Ji, Xiaoli Mei, Chunlin Zhao, Yu Chen, Guowei Che

Department of Thoracic Surgery, West China Hospital, Sichuan University, Chengdu, 610041, China

Contributions: (I) Conception and design: G Che; (II) Administrative support: G Che; (III) Provision of study materials or patients: Y Wang, L Lin, Y Ji; (IV) Collection and assembly of data: X Mei, C Zhao, Y Chen; (V) Data analysis and interpretation: Y Wang, L Lin; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Guowei Che. Department of Thoracic Surgery, West China Hospital, Sichuan University, Guoxuexiang No. 37, Chengdu 610041, China. Email: hx_guowei_che@foxmail.com.

Background: The aim of this study was to assess the prognostic value of the preoperative advanced lung cancer inflammation index (ALI) in early stage non-small lung cancer (NSCLC) patients who received video-assisted thoracoscopic surgery (VATS) pulmonary surgery as their only therapy.

Methods: We retrospectively reviewed the medical records of patients who were diagnosed with earlystage NSCLC and received a VATS pulmonary resection from January 2014 to June 2016 in the Department of Thoracic Surgery, West China Hospital. A receiver operating characteristic (ROC) curve analysis was conducted to determine the optimal cut-off values, and patients were divided into low and high ALI groups. The Kaplan-Meier method and Cox proportional hazards model were used to evaluate potential predictors of overall survival (OS) and disease-free survival (DFS).

Results: A total of 292 patients were enrolled in our analysis. Then, 155 and 137 patients were assigned to the low ALI (ALI <50) and high (ALI >50) groups, respectively. The multivariate analyses revealed that preoperative ALI <50 was an independent prognostic factor for both OS [hazard ratio (HR) =2.603, 95% confidence interval (95% CI): 1.128–6.006, P=0.025] and DFS (HR =2.372, 95% CI: 1.141–4.935, P=0.021), and patients with a low preoperative ALI had worse OS (P<0.001) and DFS (P <0.001) compared with those with a high preoperative ALI.

Conclusions: A low preoperative ALI was significantly correlated with poor survival, and the ALI might serve as a promising marker of prognosis in early-stage NSCLC patients who received a VATS pulmonary resection as their only therapy.

Keywords: Advanced lung cancer inflammation index; early stage non-small cell lung cancer; video-assisted thoracoscopic surgery (VATS); prognosis

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Introduction

Lung cancer remains the leading cause of tumor-related deaths worldwide, and non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases (1,2). With the advances in video-assisted thoracoscopic surgery (VATS), surgery has been the major treatment for

early-stage NSCLC patients, and the prognosis of these patients has improved to a certain extent (3). However, to date, the tumor-node-metastasis (TNM) stage is still the most common indicator for predicting the survival of NSCLC patients. More valuable and reliable prognostic biomarkers are urgently needed.

Inflammation status has been proven to play a key role in cancer development and long-term clinical outcomes of cancer patients (4-6). As previously reported, there are several inflammation biomarkers that have high prognostic value in NSCLC patients undergoing lung resection, including the neutrophil-lymphocyte ratio (NLR) (7), the platelet-lymphocyte ratio (PLR) (8), the lymphocytemonocyte ratio (LMR) (9) and C-reactive protein (CRP) (10). On the other hand, nutritional status has also been demonstrated to show a strong linkage with survival after surgery in NSCLC (11,12). Tewari et al. (12) and Nakagawa et al. (13) showed that low body mass index (BMI), which represented impaired nutrition, was significantly associated with worse long-term survival in patients with resected NSCLC. Albumin (ALB) is also a promising indicator for nutritional status, and hypoalbuminemia is correlated with poor prognosis in patients with NSCLC (14). In 2013, Jafri et al. (15) developed a novel prognostic index named the advanced lung cancer inflammation index (ALI) and evaluated its value for prognosis in patients with metastatic NSCLC. The ALI consists of BMI, ALB and NLR, which incorporate both inflammatory and nutritional factors. Subsequently, its usefulness has been reported in malignant lymphoma (16), esophageal carcinoma (17), small cell lung cancer (SCLC) (18) and NSCLC (19). However, no study has focused on earlystage NSCLC patients who undergo VATS pulmonary operation as the only treatment.

Therefore, the aim of this study was to explore the prognostic value of preoperative ALI in patients who were diagnosed with limited-stage NSCLC and received only VATS pulmonary resection (either lobectomy or segmentectomy).

Methods

Study design

This was a retrospective single-center study.

Patient selection

Patients with NSCLC who underwent VATS pulmonary surgery from January 2014 to June 2016 in the Department of Thoracic Surgery, West China Hospital, Sichuan University, were reviewed retrospectively. The inclusion criteria were as follows: (I) pathologically diagnosed with NSCLC in TNM stage I or II; (II) VATS pulmonary

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resection with lymph node dissection was the only treatment; (III) available preoperative BMI, serum ALB and NLR values; (IV) adequate clinicopathologic and followup data; (V) no acute or chronic inflammatory diseases preoperatively, such as active infection or rheumatoid arthritis; (VI) normal liver function; and (VII) no second malignancies or recurrent NSCLC. Patients were excluded according to the exclusion criteria: (I) received neoadjuvant, postoperative adjuvant or immunological therapies; (II) intraoperative conversion to thoracotomy; or (III) concomitant hepatic or inflammatory diseases.

Data collection

All preoperative clinicopathological data were extracted from the medical records of our hospital. They included age, gender, BMI, smoking history, preoperative comorbidity, lung function, tumor location, size, pathology, type of resection, TNM stage, serum ALB, NLR and platelet-lymphocyte ratio (PLR) levels. BMI was calculated as weight in kilograms divided by height in square meters. NLR and PLR were defined as a simple ratio between the neutrophil and lymphocyte counts and a simple ratio between the platelet and lymphocyte counts, respectively. The ALI was calculated as BMI × ALB/NLR.

Overall survival (OS) was defined as the date of surgery to the date of death from any cause or last follow-up, and disease-free survival (DFS) was defined as the date of surgery to the date of local recurrence, distant metastasis or last follow-up. The follow-up time was from the date of surgery to September 2018 or the date of last followup. During the follow-up period, patients received routine follow-up tests, such as computed tomography (CT) scans, every two months or/and telephone contacts to assess the patient's current conditions.

Statistical analysis

The thresholds for BMI, ALB, NLR and ALI were determined by receiver operating characteristic (ROC) curve analyses for the prediction of death from any cause. The thresholds for other continuous variables were determined using their median values. The chi-square test or Fisher's exact test was performed to compare differences between ALI groups. Univariate and multivariate analyses were conducted using the Cox proportional hazard model to identify independent predictors for OS and DFS, and all variables with a P value <0.10 in the univariate analysis were

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Table 1 Baseline clinicopathological characteristics

Characteristics	Value
Patients, n	292
Age (median, range), years	62 [18–81]
Male/Female	158/134
BMI (median, range), kg/m ² 23.48 (15.62–32	
Smoking history, n	134
Preoperative comorbidity	
COPD	39
Emphysema	44
Tumor location (left/right)	100/192
Tumor size (median, range), cm	2.4 (0.5–5.0)
Pathology (AC/SC/others)	197/71/24
Extent of resection (lobectomy/segmentectomy)	204/88
TNM stage (I/II)	197/95

BMI, body mass index; COPD, chronic obstructive pulmonary disease; AC, adenocarcinoma; SC, squamous carcinoma; TNM, tumor-node-metastasis.



Figure 1 ROC curves for survival prediction (overall survival). BMI, body mass index; NLR, neutrophil to lymphocyte ratio; Alb, albumin; ALI, advanced lung cancer inflammation index; ROC, receiver operating characteristic.

included in the multivariate analysis. Survival curves were calculated by the Kaplan-Meier method, and differences between groups were analyzed by the log-rank test. All analyses were performed using the IBM SPSS statistics software program, version 22.0. A P value <0.05 was considered statistically significant.

Results

Characteristics of the study population

A total of 292 patients were included in the current research. The baseline clinicopathological characteristics of these patients are summarized in *Table 1*. The median age, BMI and tumor size were 62 years (range, 18–81 years), 23.48 kg/m² (15.62–32.27 kg/m²) and 2.4 cm (0.5–5.0 cm), respectively. Of all cases, 158 patients were male, 134 patients were current or ex-smokers, 39 patients had chronic obstructive pulmonary disease, 44 patients had emphysema, 100 cases were located on the left, 197 cases were adenocarcinoma (AC), 204 patients received lobectomy and 197 patients were in TNM stage I.

Cut-off values defined by ROC curve analyses

The critical values of BMI, ALB, NLR and ALI were 24.79 (sensitivity 68.8% and specificity 35.1%), 4.32 (sensitivity 76.0% and specificity 44.6%), 1.67 (sensitivity 82.3% and specificity 41.6%) and 50.0 (sensitivity 67.7% and specificity 64.5%), respectively (*Figure 1*).

Association between ALI and patient characteristics

The correlation of ALI with the clinicopathological characteristics of patients is shown in *Table 2*. Patients in the low ALI group (ALI <50) had a significantly higher proportion of men (P=0.002), lower BMI (P=0.004), a higher proportion of cigarette smoking history (P<0.001), lower forced vital capacity (FVC) (P=0.007), larger tumors (P=0.002), a lower proportion of AC (P=0.032), higher NLR (P<0.001) and higher PLR (P <0.001).

Predictive factors for OS

The univariate analysis suggested that male sex (P=0.008), smoking history (P<0.001), larger tumors (P=0.018), TNM stage II (P=0.047), an ALB level <4.32 g/dL (P=0.004), NLR \geq 1.67 (P=0.001) and ALI <50 (P<0.001) were potential independent factors for OS. The multivariate analysis showed that only the ALI was significantly correlated with OS (HR =2.603, 95% CI: 1.128–6.006, P=0.025) (*Table 3*). Patients with an ALI <50 had a

Table 2 Comparison of clinicopathological characteristics between low and high ALI groups

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Characteristics	ALI <50 (n=155) (%)	ALI ≥50 (n=137) (%)	P value	
Age ≥62 years	80 (51.61)	72 (52.55)	0.872	
Male	97 (62.58)	61 (44.53)	0.002	
BMI <24.79 kg/m ²	91 (58.71)	57 (41.61)	0.004	
Smoking history	88 (56.77)	46 (33.58)	<0.001	
Preoperative comorbidity				
COPD	20 (12.90)	19 (13.87)	0.809	
Emphysema	26 (16.77)	18 (13.14)	0.386	
Lung function				
FEV1 ≥2.2 L	76 (49.03)	70 (51.82)	0.725	
FVC ≥3.0 L	66 (42.58)	80 (58.39)	0.007	
FEV1/FVC ≥76.4%	81 (52.26)	65 (47.45)	0.412	
Tumor location (left)	54 (34.84)	46 (33.58)	0.821	
Tumor size ≥2.4 cm	91 (58.71)	55 (40.15)	0.002	
Pathology (AC)	96 (61.94)	101 (73.72)	0.032	
Resection (lobectomy)	113 (72.90)	91 (66.42)	0.228	
TNM stage				
la	35 (22.58)	39 (28.47)	0.248	
lb	64 (41.29)	59 (43.06)	0.759	
lla	20 (12.90)	19 (13.87)	0.809	
llb	36 (23.23)	20 (14.60)	0.062	
Alb <4.32 g/dL	101 (65.16)	74 (54.01)	0.052	
NLR ≥1.67	153 (98.71)	54 (39.42)	<0.001	
PLR ≥97	105 (67.74)	41 (29.93)	<0.001	

ALI, advanced lung cancer inflammation index; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; AC, adenocarcinoma; TNM, tumor-node-metastasis; Alb, albumin; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

significantly worse OS than patients with an ALI \geq 50 (P<0.001) (*Figure 2*).

in the high ALI group had significantly better survival than patients in the low ALI group (P<0.001) (*Figure 3*).

Predictive factors for DFS

The univariate analysis revealed that smoking status (P=0.009), tumor size (P<0.001), TNM stage (P=0.037), NLR (P=0.009) and ALI values (P<0.001) were significantly associated with DFS. Tumor size \geq 2.4 cm (HR =1.860, 95% CI: 1.108–3.121, P=0.019) and ALI <50 (HR =2.372, 95% CI: 1.141–4.935, P=0.021) were demonstrated to be independent risk factors for poorer DFS (*Table 4*). Patients

Discussion

Nutrition and inflammation status are well known to be correlated with the prognosis of malignancies (4-6,11,12). BMI and ALB level are valuable parameters for the evaluation of nutritional status. A decreased muscle and fat burden caused by cancer progression results in body weight loss and a higher risk of mortality (20). Although the detailed mechanism remains unclear, malnutrition

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Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age ≥62 years	1.566 (0.950–2.584)	0.079	1.338 (0.787–2.275)	0.282
Male	2.018 (1.205–3.378)	0.008	0.729 (0.266–1.994)	0.538
BMI <24.79 kg/m ²	0.809 (0.492–1.329)	0.402		
Smoking history	2.589 (1.556–4.309)	<0.001	2.299 (0.849–6.224)	0.101
Preoperative comorbidity				
COPD	1.254 (0.620–2.537)	0.53		
Emphysema	1.689 (0.933–3.057)	0.083	1.371 (0.722–2.603)	0.335
Lung function				
FEV1 ≥2.2 L	1.516 (0.922–2.490)	0.101		
FVC ≥3.0 L	0.775 (0.475–1.265)	0.308		
FEV1/FVC ≥76.4%	1.632 (0.990–2.691)	0.055	1.120 (0.659–1.905)	0.675
Tumor location (left)	1.236 (0.752–2.032)	0.402		
Tumor size ≥2.4 cm	1.833 (1.112–3.022)	0.018	1.195 (0.697–2.046)	0.518
Pathology (AC)	0.962 (0.659–1.406)	0.843		
Resection (lobectomy)	1.501 (0.843–2.673)	0.168		
TNM stage II	1.644 (1.006–2.687)	0.047	1.411 (0.834–2.387)	0.199
Alb <4.32 g/dL	2.331 (1.308–4.152)	0.004	1.717 (0.941–3.134)	0.078
NLR ≥1.67	3.652 (1.667–8.002)	0.001	1.391 (0.488–3.966)	0.537
PLR ≥97	1.553 (0.945–2.551)	0.082	0.916 (0.524–1.600)	0.757
ALI <50	3.783 (2.059–6.950)	<0.001	2.603 (1.128-6.006)	0.025

Table 3 Univariate and multivariate Cox regression analyses to assess the prognostic factors for overall survival in all patients

BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; AC, adenocarcinoma; TNM, tumor-node-metastasis; Alb, albumin; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; ALI, advanced lung cancer inflammation index.



Figure 2 Kaplan-Meier overall survival curves stratified by ALI. ALI, advanced lung cancer inflammation index.

may cause the deterioration of the immune system (19). However, the utility of BMI is usually limited due to its inaccurate representation of body compositions, and body weight loss is indistinct in patients with pleural effusion or body edema. Furthermore, the concentration of ALB can be affected by many factors, such as illness, dehydration and fluid retention (21,22), which greatly restricts its utility in clinical practice.

Previous studies have demonstrated that lymphocytes play a crucial role in killing tumor cells and regulating apoptosis, angiogenesis, proliferation and metastasis of tumors by secreting cytokines (11,23). On the other hand, neutrophils can inhibit lymphocyte-mediated immune activity consisting of activated T cells and natural killer T cells by producing

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Table 4 Univariate and multivariate Cox regression analyses to assess the prognostic factors for disease-free survival in all patients

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% Cl)	P value
Age ≥62 years	1.244 (0.775–1.998)	0.366		
Male	1.474 (0.913–2.378)	0.112		
BMI <24.79 kg/m ²	1.373 (0.859–2.194)	0.185		
Smoking history	1.885 (1.174–3.029)	0.009	1.440 (0.882–2.353)	0.145
Preoperative comorbidity				
COPD	1.459 (0.766–2.779)	0.25		
Emphysema	1.584 (0.882–2.847)	0.124		
Lung function				
FEV1 ≥2.2 L	0.919 (0.575–1.468)	0.722		
FVC ≥3.0 L	0.847 (0.530–1.354)	0.487		
FEV1/FVC ≥76.4%	1.438 (0.895–2.309)	0.133		
Tumor location (left)	0.994 (0.607–1.628)	0.981		
Tumor size ≥2.4 cm	2.434 (1.478–4.011)	<0.001	1.860 (1.108–3.121)	0.019
Pathology (AC)	0.828 (0.557–1.233)	0.353		
Resection (lobectomy)	1.425 (0.825–2.461)	0.204		
TNM stage II	1.655 (1.031–2.658)	0.037	1.324 (0.813–2.158)	0.259
Alb <4.32 g/dL	1.449 (0.880–2.386)	0.145		
NLR ≥1.67	2.293 (1.231–4.270)	0.009	0.934 (0.393–2.219)	0.876
PLR ≥97	1.439 (0.896–2.311)	0.132		
ALI <50	2.821 (1.665–4.780)	<0.001	2.372 (1.141–4.935)	0.021

BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; AC, adenocarcinoma; TNM, tumor-node-metastasis; Alb, albumin; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; ALI, advanced lung cancer inflammation index.



Figure 3 Kaplan-Meier disease-free survival curves stratified by ALI. ALI, advanced lung cancer inflammation index.

cytokines (18,24). A meta-analysis including 7,219 patients reported that an elevated NLR was a negative predictor of survival in patients with lung cancer (25).

Nevertheless, a single marker or ratio often fails to assess the prognosis of patients precisely. In 2003, Forrest *et al.* (26) proposed the Glasgow prognostic score (GPS), which combined CRP and ALB levels, and a number of studies have reported its prognostic value in several cancers (26-30). Subsequently, McMillan *et al.* (31) proposed the modified Glasgow prognostic score (mGPS), which was more sensitive than the GPS, and a meta-analysis involving 5,817 patients revealed that it was a good predictor for the survival of lung cancer patients (32). Thus, a combination of multiple indexes may perform better than single biomarkers in predicting prognosis in patients with lung cancer. In 2013, Jafri *et al.* (15) described a novel index called the ALI, and several studies have proven its high prognostic value in patients with NSCLC (18,19). However, none of them focused on early-stage patients who received VATS pulmonary resection as the only treatment. Therefore, we conducted this research to explore the association between preoperative ALI and prognosis in this population.

Compared with previous relevant studies, our research has several advantages or highlights. Only early stage (TNM I-II) patients were enrolled in the analysis. In addition, all of the included patients received the VATS pulmonary operation as their only treatment; as chemoradiotherapy and immunotherapy can significantly affect the inflammatory immune status, this significantly reduced the bias caused by therapy methods. Patients with hepatic diseases were excluded because ALB is produced by the liver and abnormal liver function may cause a decreased ALB level. No significant difference in the proportion of patients at different disease stages was observed between the high and low ALI groups; to some extent, this may indicate that the TNM stage had no effect on the prognostic role of ALI in our study. In addition, the endpoint outcomes in our research included OS and DFS, while most previous studies only reported OS. The cut-off value for the ALI was 50 in our study, which is much higher than the thresholds reported in previous studies including all-stage patients; meanwhile, compared with these previous studies, the median values of the ALB level and NLR of our study were significantly higher and lower, respectively. This indicates that the optimal critical value of ALI should be different for patients with different stages and that limited stage patients may have a relatively higher ALI threshold.

There are still some limitations that should be addressed. First, this was a retrospective single-center study with a small sample size. Second, there were some significant differences in the clinicopathological characteristics between the high and low ALI groups, and the influence of these factors on survival and the prognostic role of the ALI should not be ignored. Third, as mentioned above, the critical value of the ALI that maximized the Youden index in our study was 50; whether 50 is the optimal cutoff point still needs be tested in future studies. Fourth, the ALI lacks tumor specificity and does not include other important biomarkers, such as CRP, platelet-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), etc.

In conclusion, our research demonstrated that the

preoperative ALI may serve as a promising prognostic index in early-stage NSCLC patients who receive only pulmonary resection by VATS. More well-designed multicenter studies with larger samples are needed to verify our findings.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi. org/10.21037/apm.2020.03.18). The authors have no conflicts of interest to declare.

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. All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethics Committee of West China Hospital, Sichuan University, the national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the regional committee of Sichuan University West China Hospital (ID: 2018-571). Written informed consent for the use and storage of information from the hospital database was obtained from each patient.

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