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Original Article

Advanced Lung Cancer Inflammation Index Predicts Outcomes of Patients with Pathological Stage IA Lung Adenocarcinoma Following Surgical Resection

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Purpose: The correlation of advanced cancer with inflammation and/or nutrition factors is well known. Recently, the advanced lung cancer inflammation index (ALI) was developed as a new prognostic tool for patients with advanced lung cancer. In this study, we examined whether ALI results are correlated with prognosis of patients with early stage lung adenocarcinoma who undergo lung resection.

Methods: From January 2009 to December 2014, 544 patients underwent lung resection due to primary lung cancer at Dokkyo Medical University Hospital, of whom 166 with pathological stage IA lung adenocarcinoma were retrospectively investigated in this study. ALI was calculated as follows: Body Mass Index (BMI; kg/m^2) × albumin (g/dL)/neutrophil-to-lymphocyte ratio (NLR).

Results: Multivariate analysis revealed that gender, red cell distribution width (RDW), NLR, and ALI were parameters significantly correlated with overall survival (OS). Patients with an ALI value less than 22.2 had an inferior 5-year OS rate as compared to those with a value of 22.2 or higher ($p < 0.001$) as well as an inferior 5-year recurrence-free survival (RFS) rate ($p < 0.001$).

Conclusion: Low ALI was correlated with poor prognosis in patients with stage IA lung adenocarcinoma. Those with an ALI value less than 22.2 should be carefully followed regardless of cancer stage.

Keywords: outcome, thoracic, nutrition

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Introduction

Inflammation status is well known to correlate with cancer growth and long-term patient outcome.[1–4] Several inflammation markers, including red cell distribution width (RDW),[5] neutrophil to lymphocyte ratio (NLR),[6] and platelet to lymphocyte ratio (PLR),[7] have been reported as useful prognostic factors for patients with non-small-cell lung cancer (NSCLC) who undergo lung resection. In 2003, Forrest and colleagues[8] presented a scoring system termed Glasgow Prognostic Score (GPS) that uses

the combination of C-reactive protein (CRP) as an inflammation marker and albumin as a nutritional marker, and found that the score was correlated with prognosis of patients with inoperable NSCLC. Thereafter, several reports indicating the correlation of GPS with the prognosis of patients who underwent surgery for NSCLC have been presented.[9)]

In 2013, Jafri et al.[10)] developed a new prognostic index termed advanced lung cancer inflammation index (ALI) for patients with advanced lung cancer including small-cell lung cancer. ALI incorporates both inflammation and nutrition factors, the same as GPS, and consists of Body Mass Index (BMI), albumin, and NLR. Its utility has been reported for patients with esophageal cancer, small-cell lung cancer, and malignant lymphoma.[11–14)] Furthermore, Tomita et al.[15)] recently reported the utility of ALI for patients with NSCLC who undergo surgical treatment.

The correlation of inflammation and/or nutrition factors with advanced cancer is well known. In this study, we examined whether ALI correlates with prognosis of patients with early stage NSCLC. We analyzed several prognostic factors, including ALI and GPS, as well as others, in patients with pathological stage (p-stage) IA lung adenocarcinoma who underwent a lung resection procedure. Most previous similar reports were based on version 7 of the Union International Contre Cancer (UICC) TNM classification or a former version. Here, we used UICC TNM classification version 8 for analysis, which excludes adenocarcinoma *in situ*.

Methods

From January 2009 to December 2014, a total of 544 patients underwent lung resection due to primary lung cancer at Dokkyo Medical University Hospital, of whom 166 with p-stage IA lung adenocarcinoma were retrospectively investigated. Patients with acute and/or chronic inflammatory disease during the preoperative period, such as active infection or collagen vascular disease including rheumatoid arthritis, were excluded. The Ethical Committee of Dokkyo Medical University Hospital approved this retrospective study (#28080).

Routine laboratory measurements, including CRP, albumin, carcinoembryonic antigen (CEA), RDW, NLR, and PLR, were performed prior to the operation. ALI was calculated as follows: BMI (kg/m^2) × albumin (g/dL)/NLR.[10)] GPS was determined according to the following scoring system. Patients with both increased CRP (>1.0 mg/dL) and hypoalbuminemia (3.5 g/dL) received a score of 2 while those with only one of those parameters received a score of 1 and those with neither of those findings received a score of 0.[8)]

Cutoff values for ALI, RDW, NLR, and PLR were determined using receiver operating characteristic (ROC) curve analysis to estimate optimal sensitivity, specificity, and area under the curve (AUC) for prediction of death from all causes. Statistical analysis was performed using a chi-square test or Fisher's exact test for a contingency table. Univariate and multivariate analyses with a COX proportional hazards regression model were used to identify independent risk factors for survival, as well as to estimate the respective hazard ratio (HR) and 95% confidence interval (CI) values for the various factors. When parameters were confounding factors, those analyses were separately performed. The Kaplan–Meier method and a log-rank test were used to compare survival of patients in relation to each parameter. Differences were considered to be significant at $p < 0.05$. All calculations were done using the IBM SPSS statistics software program, version 22.0 (IBM Corporation, Armonk, NY, USA).

Results

The characteristics of the 166 enrolled patients are shown in **Table 1**. The median observation period was 1653 days (range: 100–3143 days). In all, 25 patients died during the observation period, eight patients due to lung cancer and the others due to other causes such as pneumonia. In total, 18 patients had lung cancer recurrence, 9 loco-regional, 7 distant metastasis (brain 4, bone 2, and multiple organs 1), and 2 unknown. Nine of the 18 patients with recurrence died, 8 from lung cancer and 1 from pneumonia. The cutoff values for ALI, RDW, NLR, and PLR shown by ROC curve analysis were 22.2 (AUC 0.610), 13.3 (AUC 0.695), 3.43 (AUC 0.574), and 120 (AUC 0.566), respectively.

The relationships between ALI and patient characteristics are shown in **Table 2**. Patients with an ALI value less than 22.2 were older, had the lower performance status (ECOG-PS) and BMI values, higher Hugh Jones classification, serum CEA, and CRP, lower albumin level, higher GPS, PLR, and NLR, less vital capacity (%), and the higher rate of death.

As shown in **Table 2**, 18 patients had an ALI value less than 22.2. During postoperative follow-up, two had the recurrence of lung cancer. Nine of the 18 patients died, one from lung cancer and eight from other cause

Table 1 Patient characteristics (n = 166)

	Baseline	No.
Age (years)	<75	117
	≥75	49
Gender	Male	74
	Female	92
Brinkman index	0	89
	<600	37
	≥600	40
Performance status (ECOG)	0	158
	1	4
	2	4
Body Mass Index	<18.5	15
	18.5 to <25	111
	≥25	40
Hugh-Jones classification	1	154
	2	9
	3	2
Surgical procedure	Wedge resection	22
	Segmentectomy	29
	Lobectomy	115
Lymphatic permeation	Absent	149
	Present	17
Vascular invasion	Absent	146
	Present	20
Pathological stage IA (T factor)	1 (mi)	36
	(1a)	38
	2 (1b)	56
	3 (1c)	36
Pathological subtype	Minimally invasive adenocarcinoma	36
	Lepidic	70
	Papillary	38
	Acinar	12
	Solid	6
	Others	4
EGFR mutation	Negative	57
	Positive	47
	Not recorded	62
CEA (ng/mL)	≤5	151
	>5	15
CRP (mg/dL)	≤1	160
	>1	6
Albumin (g/dL)	≥3.5	159
	<3.5	7
GPS	0	156
	1	7
	2	3
RDW	<13.3	97
	≥13.3	69
PLR	<120	69
	≥120	97
NLR	<3.43	143
	≥3.43	23
ALI	≥22.2	148
	<22.2	18
%VC (%)	≥80	150
	<80	12
	not recorded	4
%FEV1.0 (%)	≥80	136
	<80	26
	Not recorded	4
%DLCO (%)	≥80	150
	<80	12
	Not recorded	4

ECOG: eastern cooperative oncology group; EGFR: epidermal growth factor receptor; CEA: carcinoembryonic antigen; CRP: C-reactive protein; GPS: glasgow prognostic score; RDW: red cell distribution width; PLR: platelet-to-lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio; ALI: advanced lung cancer inflammation index; VC: vital capacity; FEV: forced expiratory volume; DLCO: diffusing capacity of lung carbon monoxide

Table 2 Relationship between patient characteristics and ALI

	Baseline characteristic	ALI ≥22.2	ALI <22.2	p value
		n = 148	n = 18	
Age (years)	<75	109	8	0.01
	≥75	39	10	
Gender	Male	82	10	0.99
	Female	66	8	
Brinkman index	0	80	9	0.839
	<600	32	5	
	≥600	36	4	
Performance status (ECOG)	0	143	15	<0.001
	1	4	0	
	2	1	3	
Body Mass Index (kg/m^2)	<18.5	9	6	0.001
	≥18.5 to <25	101	10	
	≥25	38	2	
Hugh-Jones classification	1	140	14	0.016
	2	6	3	
	3	1	1	
Surgical procedure	Wedge resection	18	4	0.49
	Segmentectomy	26	3	
	Lobectomy	101	11	
Lymphatic permeation	Absent	134	15	0.341
	Present	14	3	
Vascular invasion	Absent	132	14	0.16
	Present	16	4	
T factor	1 (mi)	35	1	0.197
	(1a)	31	7	
	2 (1b)	50	6	
	3 (1c)	32	4	
Pathological subtype	Minimally invasive Adenocarcinoma	35	1	0.074
	Lepidic	61	9	
	Papillary	35	3	
	Acinar	10	2	
	Solid	5	1	
	Others	2	2	
CEA (ng/mL)	≤5	138	13	0.003
	>5	10	5	
CRP (mg/dL)	≤1	147	13	<0.001
	>1	1	5	
Albumin (g/dL)	≥3.5	145	14	<0.001
	<3.5	3	4	
GPS	0	145	11	<0.001
	1	2	5	
	2	1	2	
RDW	<13.3	89	8	0.202
	≥13.3	59	10	
PLR	<120	68	1	0.001
	≥120	80	17	
NLR	<3.43	140	3	<0.001
	≥3.43	8	15	
%VC (%)	≥80	137	13	<0.001
	<80	7	5	
	Not recorded	4	0	
%FEV1.0 (%)	≥80	119	17	0.198
	<80	25	1	
	Not recorded	4	0	
%DLCO (%)	≥80	135	15	0.112
	<80	9	3	
	Not recorded	4	0	
Status	Alive	132	9	<0.001
	Dead	16	9	
Cause of death	Cancer	7	1	0.093
	Other disease	9	8	

ECOG: eastern cooperative oncology group; CEA: carcinoembryonic antigen; CRP: C-reactive protein; GPS: glasgow prognostic score; RDW: red cell distribution width; PLR: platelet-to-lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio; ALI: advanced lung cancer inflammation index; VC: vital capacity; FEV: forced expiratory volume; DLCO: diffusing capacity of lung carbon monoxide

Table 3 Univariate analysis

	p value	HR	95% CI
Age (years) (<75/≥75)	0.062	2.13	0.96–4.69
Gender (male/female)	0.003	0.25	0.1–0.63
Brinkman index (<600/≥600)	0.088	2.03	0.9–4.57
ECOG-PS (0/1-2)	0.061	3.17	0.95–10.6
Hugh-Jones classification (1/2–3)	0.066	3.16	0.93–10.78
BMI, kg/m^2 (≤18.5/>18.5)	0.217	1.97	0.67–5.76
Surgical procedure (Sublobar resection/lobectomy or greater)	0.608	1.27	0.51–3.19
Lymphatic permeation (absent/present)	0.519	1.42	0.49–4.15
Vascular invasion (absent/present)	0.096	2.18	0.87–5.46
Stage IA (1-2/3)	0.713	0.83	0.31–2.22
Histological subtype (lepidic/non-lepidic)	0.454	1.35	0.62–2.97
CEA, ng/mL, (≤5/>5)	0.007	3.55	1.41–8.92
GPS (0/1-2)	0.023	3.47	1.19–10.12
RDW (<13.3/≥13.3)	0.017	2.8	1.2–6.5
NLR (<3.43/≥3.43)	0.002	3.87	1.66–9.03
PLR (<120/≥120)	0.063	1.01	1.0–1.01
ALI (≥22.2/<22.2)	<0.001	6.81	2.97–15.59
%VC (<80/≥80)	0.075	2.66	0.91–7.8
%FEV1 (<80/≥80)	0.635	0.75	0.22–2.5
%DLCO (<80/≥80)	0.213	2.16	0.64–7.28

ECOG: eastern cooperative oncology group; PS: performance status; CEA: carcinoembryonic antigen; GPS: glasgow prognostic score; RDW: red cell distribution width; PLR: platelet-to-lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio; ALI: advanced lung cancer inflammation index; VC: vital capacity; FEV: forced expiratory volume; DLCO: diffusing capacity of lung carbon monoxide; BMI: body mass index; HR: hazard ratio; CI: confidence interval

(pneumonia in two, myocardial infarction in one, chronic heart failure in one, other malignancy in three, and unknown in one).

Univariate analysis of each factor was performed in regard to overall survival (OS) (**Table 3**). Gender, CEA, GPS, RDW, NLR, and ALI were each significantly correlated with OS. Since NLR and GPS are confounding factors for ALI, we conducted a separate multivariate analysis, which showed that gender, RDW, NLR, and ALI were significantly correlated with OS (**Table 4**).

Patients with an ALI value less than 22.2 had an inferior 5-year OS rate as compared to those with a value of 22.2 or higher (46.5% vs. 90.9%, p <0.001) (**Fig. 1A**) while those with an RDW value less than 13.3 and those with an NLR value less than 3.43 had superior 5-year OS rates as compared to those with values of 13.3 or higher and 3.43 or higher, respectively (RDW: 93.1% vs. 76.8%, p = 0.005; NLR: 89.6% vs. 62.6%, p = 0.001).

We also conducted analyses of recurrence-free survival (RFS) using the same cutoff values. Patients with an ALI value less than 22.2 had an inferior 5-year RFS rate as compared to those with a value of 22.2 or higher (47.7% vs. 85.6%, p <0.001) (**Fig. 1B**) while those with an RDW value less than 13.3 and those with an NLR value less than 3.43 had superior 5-year RFS rates as compared to those with values of 13.3 or higher and 3.43 or higher, respectively (RDW: 88.6% vs. 71.5%, p = 0.005; NLR: 84.1% vs. 64.7%, p = 0.001).

Discussion

When cancer advances, muscle and fat burden are decreased, resulting in body weight loss, which increases the risk of mortality.[16] BMI[17,18] and serum albumin level[19] have been shown to be useful parameters for evaluation of nutritional condition while malnutrition evaluated with those parameters is a risk factor for NSCLC.[19] Although the detailed mechanism remains unclear, malnutrition likely causes deterioration of the immune system.[15] An increase in NLR is due to increased neutrophils or a decrease in lymphocytes. Neutrophils produce cytokines, which inhibit lymphocyte-mediated immune activity comprised of natural killer T cells or activated T cells.[12,13] Previous meta-analysis findings revealed that an increase in NLR is correlated with inferior prognosis in NSCLC patients,[20,21] with a similar

Table 4 Multivariate analysis

	GPS-NLR model			ALI model		
	p value	HR	95% CI	p value	HR	95% CI
Gender (male/female)	0.007	0.27	0.1–0.7	0.002	0.22	0.09–0.58
CEA, ng/mL (≤5/>5)	0.109	2.23	0.84–5.93	0.235	1.8	0.68–4.72
GPS (0/1-2)	0.754	1.24	0.32–4.77			
RDW (<13.3/≥13.3)	0.012	3.11	1.28–7.55	0.023	2.78	1.15–6.69
NLR (<3.43/≥3.43)	0.011	3.91	1.36–11.26			
ALI (≥22.2/<22.2)				<0.001	7.55	3.03–18.8

CEA: carcinoembryonic antigen; GPS: Glasgow prognostic score; RDW: red cell distribution width; NLR: neutrophil-to-lymphocyte ratio; ALI: advanced lung cancer inflammation index; HR: hazard ratio; CI: confidence interval

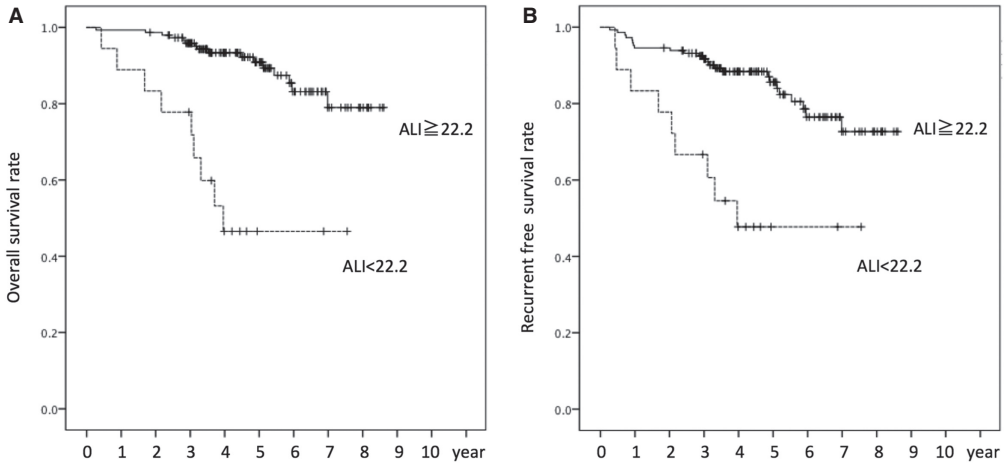

Fig. 1 Overall (**A**) and recurrence-free (**B**) survival following surgery. ALI: advanced lung cancer inflammation index

result reported in cases of surgically resected NSCLC.[22] The ALI consists of BMI, serum albumin, and NLR; thus, a correlation of decrease in ALI with poor prognosis in patients with advanced cancer is considered reasonable. We investigated early stage cancer cases (stage IA) in the present study and found that ALI was correlated with prognosis shown by OS as well as RFS. Our findings indicate the importance of malnutrition and inflammatory status in regard to prognosis, even in early stage cases because of a possible latent malignant potential.

Based on our findings of GPS and NLR as confounding factors with ALI, we conducted separate multivariate analyses. Those revealed that male gender, high RDW, and high NLR, the same as low ALI, were significantly associated with poor prognosis, which are findings consistent with previous investigations of patients with resected NSCLC.[5,7,15] RDW changes are due to iron metabolism deterioration, inhibition of response to erythropoietin, and shortened turnover of red blood cells, which are induced by inflammatory conditions.[23] Furthermore, high RDW has been reported to be a parameter of poor prognosis in NSCLC cases.[23]

Using ROC curve analysis, we determined a cutoff value of 22.2 for ALI. Jafri and colleagues[10] reported a cutoff value of 18 in analysis of 173 cases with advanced NSCLC and systemic metastasis while Tomita et al.[15] demonstrated a cutoff value of 37.66 in their report of resected NSCLC, and Kim et al. [13] reported that of 31.1 and He et al. [12] that of 19.5 in patients with small-cell lung cancer. Thus, our present analysis resulted in a value within the range of those found in other studies.

Age, performance status, Hugh-Jones score, serum CEA level, GPS, PLR, percentage of vital capacity (%VC), and alive status were different between patients with high and low ALI. Elevated CEA may represent the potential of lung adenocarcinoma malignancy even in a pathological early stage. Since GPS and PLR are also parameters representing nutritional and inflammatory status, their elevated levels may highlight patients with the poor prognosis from others, such as with ALI. In this

study, only 2 of the 18 patients with an ALI value less than 22.2 had the recurrence of lung cancer. Nine of the 18 patients died, 5 from benign disease and 1 from lung cancer and 3 in other malignancy. During the postoperative follow-up, we should pay attention to other disease control for the patients with an ALI value less than 22.2. Unfortunately, we do not have postoperative data of ALI, but our data suggested that preoperative ALI might predict postoperative death in all causes. In fact, Proctor et al.[24] reported that albumin and CRP are prognostic markers for cardiovascular and neurovascular diseases. ALI, consisting of BMI, albumin, and NLR, will be a prognostic factor of not only lung cancer but all causes of death as well as other inflammation or nutrition markers, such as GPS. Furthermore, there is no known report describing the relationship between %VC and ALI. We speculated that some types of inflammation may decrease vital capacity because of 5 of our patients with ALI lower than 22.2 and %VC lower than 80%, a history of pneumonia was noted in one patient and another was complicated with interstitial lung disease.

Limitations of this study include its nature as a single institute retrospective examination and the small patient population. Accumulation of additional cases is necessary to clarify the utility of ALI as a prognostic factor in patients with stage IA lung adenocarcinoma.

Conclusion

Low ALI was correlated with poor prognosis of stage IA lung adenocarcinoma patients. Those with an ALI less than 22.2 should be carefully followed, regardless of stage. During the postoperative follow-up for the patients with an ALI value less than 22.2, we should pay attention to other disease control.

Disclosure Statement

None was declared.

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