Prognostic Value of Neutrophil-to-lymphocyte Ratio and Prognostic Nutrition Index in Patients with Non-small Cell Lung Cancer Receiving Pulmonary Resection

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Abstract

Background: The prognostic value of neutrophil-to-lymphocyte ratio (NLR) and prognostic nutritional index (PNI) for patients with early-stage non-small cell lung cancer (NSCLC) has not been elucidated. In the present study, we retrospectively evaluated the prognostic value of NLR and PNI for patients with NCSLC received pulmonary resection, even early-stage patients.

Methods: The clinical data of 739 patients who underwent pulmonary resection for NSCLC were collected, and the prognostic value of NLR and PNI were analyzed.

Results: Coexistence of interstitial lung disease (ILD) ($p<0.01$), coexistence of arrhythmia ($p=0.04$), smoking status ($p=0.02$), carcinoembryonic antigen (CEA) ($p=0.04$), NLR>1.75 ($p=0.01$), and pathological stage ($p<0.01$) were revealed as significant factors for progression free survival (PFS) in the multivariate analysis. Coexistence of ILD ($p=0.03$), smoking status ($p<0.01$), CEA ($p<0.04$), PNI<47.97 ($p=0.01$), and pathological stage ($p<0.01$) were revealed as significant factors for overall survival in the multivariate analysis. Furthermore, smoking status ($p=0.01$), CEA ($p=0.03$), NLR>4.04 ($p<0.01$), pathological stage ($p=0.01$), and lobectomy ($p<0.01$) were revealed as significant factors for PFS in pathological stage I NSCLC patients. Smoking status ($p<0.01$), PNI<49.19 ($p=0.02$), pathological stage ($p=0.01$), and wedge resection ($p=0.01$) were revealed as significant factors for OS in pathological stage I NSCLC patients.

Conclusions: NLR was revealed as the significant factor for PFS in NSCLC patients received surgical treatment, even patients with pathological stage I. Furthermore, PNI was revealed as a significant factor of OS for NSCLC patients received surgical treatment.

Trial registration: The Institutional Review Board of Kanazawa Medical University approved the protocol of this retrospective study (approval number: I392), and written informed consent was obtained from all patients.

Introduction

The survival rate for lung cancer remains low because approximately 60% of patients with lung cancer have metastatic disease at the time of diagnosis [1]. Because the 5-year survival rate for patients with localized stage lung cancer is only 59%, it is considered that poor prognostic factors are involved. Although the neutrophil-to-lymphocyte ratio (NLR) is defined as the ratio of neutrophil-to-lymphocyte count, as a parameter of systemic inflammation and stress in critically ill surgical and medical patients [2], it has been shown to play a major role in cell-mediated destruction of cancer cells [3]. In previous studies, NLR has been reported as a prognostic factor for patients with non-small cell lung cancer (NSCLC) who underwent pulmonary resection [4–10].

The prognostic nutritional index (PNI), calculated by combining serum albumin levels with total peripheral lymphocyte count in peripheral blood, is a widely used nutritional and immunological index. Although PNI was reported as a prognostic factor for patients who underwent surgery for various cancers in several studies [11–14], only a few studies have reported that preoperative PNI is a prognostic factor in patients with NSCLC [9, 15, 16]. However, the prognostic value of PNI in patients with early-stage NSCLC has not yet been elucidated.

In this study, we retrospectively evaluated the prognostic value of NLR and PNI in patients with NCSLC who underwent pulmonary resection, even patients in the early stage.

Methods

Patients

A total of 739 patients with NSCLC who underwent pulmonary resection at Kanazawa Medical University between January 2010 and March 2019 were enrolled in this retrospective study.

Data including clinical factors, such as sex, age, comorbidities, smoking history, body mass index (BMI), carcinoembryonic antigen (CEA) levels, respiratory function, PNI, NLR, tumor diameter on computed tomography (CT), lobe involvement in lung cancer, clinical and pathological stage, and histology were collected. The following comorbidities were included: malignant disease, hypertension, diabetes mellitus, angina pectoris, chronic obstructive pulmonary disease (COPD), cerebral infarction, arrhythmia, interstitial lung disease (ILD), asthma, autoimmune disease, and chronic renal failure. Furthermore, comorbidities were evaluated using the Charlson comorbidity index [17]. Respiratory function parameters, such as percent-predicted vital capacity (%VC) and forced expiratory volume in 1 s as a percentage of forced vital capacity (FEV1%), were collected. PNI, calculated from serum albumin levels and total lymphocyte count, is a simple and useful indicator of individual immune-nutritional status [18]. Smoking history was assessed using the Brinkman index, calculated by multiplying the number of cigarettes smoked per day by the number of years the patients have been smoking [19].

Operative factors

The operative approach was divided into three categories: video-assisted thoracic surgery (VATS), robot-assisted thoracic surgery (RATS), and thoracotomy. The operative procedure was divided into eight categories: wedge resection, segmentectomy, lobectomy, sleeve lobectomy, lobectomy combined with segmentectomy, lobectomy combined with chest wall resection, bilobectomy, and pneumonectomy.

Postoperative complications

Postoperative complications were classified into five grades according to the Clavien-Dindo classification system. Established in 1992, it is a simple and feasible grading system for all types of postoperative complications [20]. In 2004, it was modified to allow for the grading of life-threatening complications and

long-term disability caused by complications [21]. This revised version defined five grades of severity with subgrades (grades I, II, IIIa, IIIb, IVa, IVb, and V), and the suffix “d” (for “disability”) is used to denote any postoperative impairment. This modified version of the Clavien-Dindo classification has been widely used in clinical practice. Operative mortality was defined as death within 30 days after surgery. Severe morbidity was defined according to the Society of Thoracic Surgeons General Thoracic Database risk model and included the following: respiratory failure, interstitial pneumonia, tracheobronchial fistula, pulmonary thromboembolism, pneumonia, redo surgery, myocardial infarction, arrhythmia that requires therapy, renal failure, postoperative bleeding, and chylothorax [22, 23]. Furthermore, we added air leakage that requires therapy, atelectasis, asthma attacks, and cerebral infarction as postoperative morbidity.

Statistical analyses

Pearson’s chi-squared test of independence was used to compare the frequencies of the variables. Pearson’s product-moment correlation coefficient was used to evaluate the correlation between the variables. The cut-off values of factors associated with recurrence were calculated using ROC curve analysis, and prognostic analyses were performed based on these cut-off values. The risk factors related to postoperative complications were analyzed using logistic regression analysis. All statistical analyses were two-sided, and statistical significance was set at $p < 0.05$. Statistical analyses were performed using the JMP software (version 13.2; SAS Institute Inc., Cary, NC, USA).

This study was conducted following the principles of the Declaration of Helsinki. The Institutional Review Board of Kanazawa Medical University approved the protocol (approval number: I392), and written informed consent was obtained from all patients.

Results

Patient characteristics

The clinical characteristics of the 739 patients are shown in Table 1. Among these, 457 were males, and the median age was 70 years. A total of 460 patients had comorbidities, including 135 patients with malignant disease (25 with colon cancer, 10 with rectal cancer, 27 with gastric cancer, three with esophageal cancer, 16 with breast cancer, 12 with prostate cancer, 10 with bladder cancer, three with gallbladder cancer, 10 with thyroid cancer, five with renal cancer, six with laryngeal cancer, five with pharyngeal cancer, two with tongue cancer, and eight with lymphoma; duplication occurred in some patients), 127 patients had hypertension, 115 had diabetes mellitus, 50 had angina pectoris, 45 had COPD, 34 had cerebral infarction, 27 had arrhythmia (25 with atrial fibrillation, one with paroxysmal supraventricular tachycardia, and one with atrioventricular block), 23 with interstitial lung disease, 23 with asthma, 21 with autoimmune disease, and nine with chronic renal failure. The median BMI was 22.6, the median CEA was 3.4 ng/ml, the median Brinkman index was 600, the median %VC was 110%, and the median FEV1% was 73.2%. The median PNI was 49.8, and the median NLR was 2.16. Pathological stages were as follows: stage 0, 46; IA, 388; IB, 131; IIA, 47; IIB, 65; IIIA, 51; IIIB, 3; IV, 2; yield to treatment, 5; and

IIA, 1. Histological types were as follows: adenocarcinoma, 556; squamous cell carcinoma, 139; large cell neuroendocrine carcinoma, 19; adenosquamous cell carcinoma, 11; pleomorphic carcinoma, 8; large cell carcinoma, 3; and carcinoid, 3.

Table 1
Patient characteristics

Variables	
Sex (man / woman)	457 / 282
Age, medial, range (y)	70 (33–92)
Comorbidity	460 (62.2%)
Malignant disease	135 (18.2%)
Diabetes mellitus	115 (15.5%)
Angina pectoris	50 (6.8%)
COPD	45 (6.1%)
Cerebral infarction	34 (4.6%)
Arrhythmia	27 (3.6%)
Interstitial lung disease	23 (3.1%)
Asthma	23 (3.1%)
Autoimmune disease	21 (2.8%)
Chronic renal failure	9 (1.2%)
Charlson comorbidity index	0 (0–6)
Body mass index, median (range)	22.6 (14.3–36.6)
CEA, median, range (ng/ml)	3.4 (0.5–306)
Brinkman index, median (range)	600 (0–3600)
%VC, median (range)	110 (45.7–184.2)
FEV1%, median (range)	73.2 (30.5–108.8)
PNI, median (range)	49.8 (26.9–67.5)
NLR, median (range)	2.16 (0.53–12.65)

COPD; chronic obstructive pulmonary disease, CEA; carcinoembryonic antigen, VC; vital capacity, FEV_1%; forced expiratory volume % in one second, PNI; prognostic nutritional index, NLR; neutrophil-to-lymphocyte ratio, y; yield to treatment, Ad; adenocarcinoma, Sq; squamous cell carcinoma, LCNEC; large cell neuroendocrine carcinoma, AdSq; adenosquamous cell carcinoma, Large; large cell carcinoma, Carci; carcinoid. Open; open thoracotomy, VATS; video-assisted thoracic surgery, RATS; robotic-assisted thoracic surgery, RU; right upper, RM; right middle, RL; right lower, LU; left upper, LL; left lower, Wedge; wedge resection, Seg; segmentectomy, Lob; lobectomy, CW; chest wall resection, Bilob; bi-lobectomy, Pneumo; pneumonectomy.

Variables	
Pathological stage (0 / IA / IB / IIA / IIB / IIIA / IIIB / IV / yIA / yIIA)	46 / 388 / 131 / 47 / 65 / 51 / 3 / 2 / 5 / 1
Histological type (Ad / Sq / LCNEC / AdSq / Pleo / Large / Carci)	556 / 139 / 19 / 11 / 8 / 3 / 3
Operative approach (Open / VATS / RATS)	71 / 662 / 6
Operation time, median (range) (min)	161 (27–1149)
Wound length, median (range) (cm)	6 (2–36)
Operative procedure (Wedge / Seg / Lob / Lob + CW / Lob + Seg / Sleeve Lob / Bilob / Pneumo)	154 / 68 / 473 / 9 / 3 / 4 / 10 / 18
Morbidity	193 (26.1%)
Air leakage	93 (12.6%)
Arrhythmia	45 (6.1%)
Atelectasis	19 (2.5%)
Pneumonia	15 (2.0%)
Attack of asthma	4 (0.5%)
Cerebral infarction	3 (0.4%)
Chylothorax	2 (0.3%)
Broncho-pleural fistula	2 (0.3%)
Clavien-Dindo grade (0 / 1 / 2 / 3a / 3b)	546 / 1 / 76 / 111 / 5
Mortality	1 (0.1%)
Mortality or severe morbidity	72 (9.7%)

COPD; chronic obstructive pulmonary disease, CEA; carcinoembryonic antigen, VC; vital capacity, FEV_1%; forced expiratory volume % in one second, PNI; prognostic nutritional index, NLR; neutrophil-to-lymphocyte ratio, y; yield to treatment, Ad; adenocarcinoma, Sq; squamous cell carcinoma, LCNEC; large cell neuroendocrine carcinoma, AdSq; adenosquamous cell carcinoma, Large; large cell carcinoma, Carci; carcinoid. Open; open thoracotomy, VATS; video-assisted thoracic surgery, RATS; robotic-assisted thoracic surgery, RU; right upper, RM; right middle, RL; right lower, LU; left upper, LL; left lower, Wedge; wedge resection, Seg; segmentectomy, Lob; lobectomy, CW; chest wall resection, Bilob; bi-lobectomy, Pneumo; pneumonectomy.

Correlation coefficient

The correlation between PNI or NLR and the variables is shown in Table 2. Age showed a slightly negative correlation, BMI was positively correlated, and NLR was negatively correlated with PNI. In contrast, BMI was negatively correlated with NLR.

Table 2
Correlation between variables and PNI or NLR

Variables	Correlation coefficient	*p* value
Correlation with PNI		
Age	-0.0723	0.04
BMI	0.2088	< 0.01
Smoking status	-0.0412	0.26
CEA	0.0181	0.62
NLR	-0.3507	< 0.01
Correlation with NLR		
Age	0.0583	0.11
BMI	-0.1263	< 0.01
CEA	0.0512	0.16
Smoking status	0.0326	0.37

PNI; prognostic nutritional index, NLR; neutrophil-to-lymphocyte ratio, BMI; body mass index, CEA; carcinoembryonic antigen.

Operative factors, postoperative morbidity, and mortality

The operative factors, postoperative morbidities, and mortality rates are shown in Table 1. Thoracotomy, VATS, and RATS were performed in 71, 662, and six patients, respectively. The median operation time was 161 min, and the median wound length was 6 mm. The pulmonary lobes removed during lobectomy were the right upper lobe in 175 patients, the right middle lobe in 36, the right lower lobe in 106, the left upper lobe in 108, and the left lower lobe in 76. Regarding the operative procedures, wedge resection was performed in 154 patients, segmentectomy in 68, lobectomy in 473, lobectomy with chest wall resection in 9, lobectomy combined with segmentectomy in 3, sleeve lobectomy in 4, bilobectomy in 10, and pneumonectomy in 18.

Postoperative morbidities were observed in 193 patients (26.1%). Clavien-Dindo grade I complications were observed in one patient, grade II in 76, grade IIIa in 111, and grade IIIb in five patients. Air leakage occurred in 93 patients, arrhythmia in 45 patients (atrial fibrillation, 38; paroxysmal supraventricular tachycardia, 3; ventricular tachycardia, 3; and sick sinus syndrome, 1), atelectasis in 19 patients, pneumonia in 15 patients, asthma attacks in four patients, cerebral infarction in three patients, chylothorax in two patients, and bronchopleural fistula in two patients. Minor but serious postoperative complications included postoperative bleeding in one patient and right middle lobe torsion in another patient. All complications were resolved surgically. Postoperative death was observed in one patient, and the mortality rate was 0.1%. Mortality and severe morbidity were observed in 72 patients (9.7%), including

respiratory failure in four patients, tracheobronchial fistula in two patients, pneumonia in 15 patients, redo surgery in two patients (postoperative bleeding in one patient), arrhythmia requiring therapy in 45 patients (atrial fibrillation, 38; paroxysmal supraventricular tachycardia, 3; ventricular tachycardia, 3; and sick sinus syndrome, 1), and chylothorax in two patients.

Cut-off values calculated from ROC curves

The cut-off values of factors associated with recurrence were calculated using ROC curve analysis. The following cut-off values were determined: PNI, 47.97 and NLR, 1.75.

Univariate and multivariate analysis

The relationships between patient characteristics, operative factors, and progression-free survival (PFS) were analyzed (Table 3). The coexistence of ILD ($p < 0.01$), coexistence of arrhythmia ($p < 0.01$), smoking status ($p < 0.01$), CEA ($p < 0.04$), PNI, < 47.97 ($p < 0.01$), NLR, > 1.75 ($p < 0.01$), and pathological stage ($p < 0.01$) were significant factors for PFS in the univariate analysis. The coexistence of ILD ($p < 0.01$), coexistence of arrhythmia ($p = 0.04$), smoking status ($p = 0.02$), CEA ($p = 0.04$), NLR > 1.75 ($p = 0.01$), and pathological stage ($p < 0.01$) were significant factors for PFS in the multivariate analysis. The relationships between patient characteristics, operative factors, and overall survival (OS) were analyzed (Table 4). Coexistence of ILD ($p < 0.01$), coexistence of arrhythmia ($p < 0.01$), smoking status ($p < 0.01$), CEA ($p < 0.04$), PNI < 47.97 ($p < 0.01$), NLR > 1.75 ($p = 0.01$), FEV1% <70 ($p = 0.01$), pathological stage ($p < 0.01$), histological type ($p < 0.01$), extended lobectomy ($p < 0.01$), and mortality or severe morbidity ($p = 0,02$) were significant factors for OS in the univariate analysis. The coexistence of ILD ($p = 0.03$), smoking status ($p < 0.01$), CEA ($p < 0.04$), PNI < 47.97 ($p = 0.01$), and pathological stage ($p < 0.01$) were significant factors for OS in the multivariate analysis.

Table 3
Univariate analysis and multivariate analysis of risk factor for progression free survival

Univariate analysis					**Multivariate analysis**		
Variables		Hazard ratio	95% CI	*p* value	Hazard ratio	95% CI	*p*-value
Sex	man	1.19	0.842–1.731	0.31			
Age	≥ 75	1.15	0.766–1.687	0.48			
Comorbidity							
Interstitial lung disease	present	4.09	2.074–7.268	< 0.01	2.98	1.449–5.603	< 0.01
Asthma	present	0.84	0.259–2.008	0.73			
Arrhythmia	present	2.88	1.412–5.230	< 0.01	2.15	1.002–4.154	0.04
Charlson comorbidity index	≥ 3	1.60	0.718–3.083	0.22			
Smoking status	BI ≥ 600	2.12	1.494–3.068	< 0.01	1.50	1.045–2.186	0.02
BMI	≥ 25.1	0.79	0.517–1.183	0.26			
CEA	> 5	2.46	1.752–3.471	< 0.01	1.66	1.165–2.366	< 0.01
PNI	< 47.97	1.59	1.133–2.245	< 0.01	1.17	0.818–1.674	0.38
NLR	> 1.75	1.93	1.301–2.955	< 0.01	1.67	1.110–2.611	0.01
%VC	< 80	1.50	0.587–3.120	0.36			
FEV_1%	< 70	1.38	0.970–1.950	0.07			
Pathological stage	II-IV	4.47	3.177–6.297	< 0.01	3.43	2.396–4.928	< 0.01
Histological type	SCC	1.41	0.928–2.101	0.10			

CI; confidence interval, BI; Brinkman index BMI; body mass index, CEA; carcinoembryonic antigen, PNI; prognostic nutritional index, NLR; neutrophil-to-lymphocyte ratio, VC; vital capacity, FEV_1%; forced expiratory volume % in one second, SCC; squamous cell carcinoma.

Univariate analysis					Multivariate analysis
Operative approach	open thoracotomy	1.45	0.853–2.320	0.16	
Operative procedure	wedge resection	1.48	0.991–2.167	0.05	
	segmentectomy	0.59	0.231–1.227	0.17	
	lobectomy	0.71	0.503–1.015	0.06	
	extend-lobectomy	2.09	0.941–4.022	0.06	
Clavian-Dindo grade	> 3	1.52	0.982–2.299	0.05	
Mortality or severe morbidity	present	1.29	0.760–2.069	0.32	

CI; confidence interval, BI; Brinkman index BMI; body mass index, CEA; carcinoembryonic antigen, PNI; prognostic nutritional index, NLR; neutrophil-to-lymphocyte ratio, VC; vital capacity, FEV_1%; forced expiratory volume % in one second, SCC; squamous cell carcinoma.

Table 4
Univariate analysis and multivariate analysis of risk factor for overall survival

Univariate analysis					**Multivariate analysis**		
Variables		Hazard ratio	95% CI	*p*-value	Hazard ratio	95% CI	*p*-value
Sex	man	1.19	0.774–1.897	0.42			
Age	≥ 75	0.75	0.405–1.299	0.32			
Comorbidity							
Interstitial lung disease	present	4.21	1.760–8.544	< 0.01	2.76	1.093–6.080	0.03
Asthma	present	1.26	0.387–3.048	0.65			
Arrhythmia	present	2.09	0.734–5.230	< 0.01	1.59	0.545–3.751	0.35
Charlson comorbidity index	≥ 3	1.04	0.254–2.789	0.94			
Smoking status	BI ≥ 600	4.14	2.544-7.100	< 0.01	2.79	1.629–4.989	< 0.01
BMI	≥ 25.1	0.67	0.378–1.131	0.14			
CEA	> 5	2.81	1.843–4.296	< 0.01	1.82	1.172–2.832	< 0.01
PNI	< 47.97	2.29	1.505–3.535	< 0.01	1.82	1.149–2.907	0.01
NLR	> 1.75	1.75	1.096–2.912	0.01	1.23	0.741–2.122	0.42
%VC	< 80	1.81	0.639–4.050	0.23			
FEV_1%	< 70	1.69	1.101–2.593	0.01	1.04	0.660–1.632	0.86
Pathological stage	II-IV	3.24	2.245–5.225	< 0.01	2.19	1.384–3.453	< 0.01
Histological type	SCC	2.22	1.394–3.474	< 0.01	1.11	0.659–1.834	0.68

CI; confidence interval, BI; Brinkman index BMI; body mass index, CEA; carcinoembryonic antigen, PNI; prognostic nutritional index, NLR; neutrophil-to-lymphocyte ratio, VC; vital capacity, FEV_1%; forced expiratory volume % in one second, SCC; squamous cell carcinoma.

Univariate analysis					Multivariate analysis		
Operative approach	open thoracotomy	1.67	0.906–2.871	0.09			
Operative procedure	wedge resection	1.29	0.755–2.105	0.33			
	segmentectomy	0.89	0.465–1.782	0.24			
	lobectomy	0.65	0.426–1.024	0.06			
	extend-lobectomy	3.43	1.523–6.716	< 0.01	1.45	0.628–2.969	0.35
Clavian-Dindo grade	> 3	1.36	0.765–2.287	0.27			
Mortality or severe morbidity	present	1.89	1.093–3.114	0.02	1.14	0.632–1.964	0.64

CI; confidence interval, BI; Brinkman index BMI; body mass index, CEA; carcinoembryonic antigen, PNI; prognostic nutritional index, NLR; neutrophil-to-lymphocyte ratio, VC; vital capacity, FEV_1%; forced expiratory volume % in one second, SCC; squamous cell carcinoma.

Sub-analysis

We analyzed the prognostic factors for patients with pathological stage I as a sub-analysis. The clinical characteristics of the 519 patients who underwent lobectomy are shown in Table 5.

Table 5
Patient characteristics of pathological stage I

Variables	
Sex (man / woman)	323 / 196
Age, medial, range (y)	70 (33–92)
Comorbidity	460 (62.2%)
Malignant disease	106 (20.4%)
Diabetes mellitus	84 (16.2%)
Angina pectoris	34 (6.5%)
COPD	26 (5.0%)
Cerebral infarction	22 (4.2%)
Arrhythmia	13 (2.5%)
Interstitial lung disease	18 (3.5%)
Asthma	16 (3.1%)
Autoimmune disease	17 (3.3%)
Chronic renal failure	4 (0.7%)
Charlson comorbidity index	0 (0–6)
Body mass index, median (range)	22.4 (14.3–36.0)
CEA, median, range (ng/ml)	3.2 (0.5–269)
Brinkman index, median (range)	435 (0–2700)
%VC, median (range)	110 (45.7–173.1)
FEV1%, median (range)	73.2 (30.5–108.8)
PNI, median (range)	50.5 (34.7–67.5)
NLR, median (range)	2.06 (0.53–9.35)
Pathological stage (IA / IB)	388 / 131

COPD; chronic obstructive pulmonary disease, CEA; carcinoembryonic antigen, VC; vital capacity, FEV_1%; forced expiratory volume % in one second, PNI; prognostic nutritional index, NLR; neutrophil-to-lymphocyte ratio, y; yield to treatment, Ad; adenocarcinoma, Sq; squamous cell carcinoma, LCNEC; large cell neuroendocrine carcinoma, AdSq; adenosquamous cell carcinoma, Large; large cell carcinoma, Carci; carcinoid. Open; open thoracotomy, VATS; video-assisted thoracic surgery, RATS; robotic-assisted thoracic surgery, RU; right upper, RM; right middle, RL; right lower, LU; left upper, LL; left lower, Wedge; wedge resection, Seg; segmentectomy, Lob; lobectomy, CW; chest wall resection, Bilob; bi-lobectomy, Pneumo; pneumonectomy.

Variables	
Histological type (Ad / Sq / LCNEC / AdSq / Pleo / Large / Carci)	406 / 84 / 14 / 5 / 4 / 3 / 3
Operative approach (Open / VATS / RATS)	36 / 478 / 5
Operation time, median (range) (min)	158 (27–580)
Wound length, median (range) (cm)	5 (2–22)
Operative procedure (Wedge / Seg / Lob / Lob + CW / Lob + Seg / Sleeve Lob / Bilob / Pneumo)	128 / 51 / 331 / 1 / 2 / 1 / 0 / 1
Morbidity	131 (25.3%)
Air leakage	66 (12.7%)
Arrhythmia	30 (5.8%)
Atelectasis	15 (2.9%)
Pneumonia	8 (1.5%)
Attack of asthma	2 (0.4%)
Cerebral infarction	2 (0.4%)
Chylothorax	2 (0.4%)
Broncho-pleural fistula	0 (0%)
Clavien-Dindo grade (0 / 1 / 2 / 3a / 3b)	388/ 0 / 49 / 80 / 2
Mortality	1 (0.2%)
Mortality or severe morbidity	44 (8.5%)

COPD; chronic obstructive pulmonary disease, CEA; carcinoembryonic antigen, VC; vital capacity, FEV_1%; forced expiratory volume % in one second, PNI; prognostic nutritional index, NLR; neutrophil-to-lymphocyte ratio, y; yield to treatment, Ad; adenocarcinoma, Sq; squamous cell carcinoma, LCNEC; large cell neuroendocrine carcinoma, AdSq; adenosquamous cell carcinoma, Large; large cell carcinoma, Carci; carcinoid. Open; open thoracotomy, VATS; video-assisted thoracic surgery, RATS; robotic-assisted thoracic surgery, RU; right upper, RM; right middle, RL; right lower, LU; left upper, LL; left lower, Wedge; wedge resection, Seg; segmentectomy, Lob; lobectomy, CW; chest wall resection, Bilob; bi-lobectomy, Pneumo; pneumonectomy.

The relationships between patient characteristics, operative factors, and PFS were analyzed (Table 6). The cut-off values of the factors associated with recurrence in pathological stage I were calculated using ROC curve analysis. The following cut-off values were determined: PNI, 49.19; and NLR, 4.04. The coexistence of ILD ($p < 0.01$), smoking status ($p < 0.01$), CEA ($p < 0.04$), PNI < 49.19 ($p = 0.02$), NLR > 4.04 ($p < 0.01$), FEV1% <70 ($p = 0.02$), pathological stage ($p < 0.01$), histological stage ($p = 0.03$), and lobectomy ($p < 0.01$) were significant factors for PFS in the univariate analysis. Smoking status ($p = 0.01$), CEA ($p = 0.03$), NLR > 4.04 ($p < 0.01$), pathological stage ($p = 0.01$), and lobectomy ($p < 0.01$) were significant

factors for PFS in multivariate analysis. The relationships between patient characteristics, operative factors, and OS were analyzed (Table 7). The coexistence of ILD ($p < 0.01$), smoking status ($p < 0.01$), CEA ($p < 0.04$), PNI < 49.19 ($p < 0.01$), pathological stage ($p < 0.01$), histological type ($p < 0.01$), wedge resection ($p < 0.01$), and lobectomy ($p = 0.03$) were significant factors for OS in the univariate analysis. Smoking status ($p < 0.01$), PNI < 49.19 ($p = 0.02$), pathological stage ($p = 0.01$), and wedge resection ($p = 0.01$) were significant factors for OS in the multivariate analysis.

Table 6. Univariate analysis and multivariate analysis of risk factor for progression free survival in pathological stage I

Univariate analysis					Multivariate analysis		
Variables		Hazard ratio	95% CI	*p*-value	Hazard ratio	95% CI	*p*-value
Sex	man	1.10	0.668-1.893	0.69			
Age	≥ 75	1.51	0.859-2.575	0.14			
Comorbidity							
Interstitial lung disease	present	5.72	2.362-11.842	< 0.01	1.96	0.739-4.653	0.16
Asthma	present	0.91	0.149-2.933	0.89			
Arrhythmia	present	2.05	0.501-5.576	0.27			
Charlson comorbidity index	≥ 3	2.38	0.830-5.431	0.09			
Smoking status	BI ≥ 600	2.56	1.537-4.385	< 0.01	2.10	1.173-3.851	0.01
BMI	≥ 25.1	1.04	0.572-1.800	0.88			
CEA	> 5	2.62	1.581-4.311	< 0.01	1.62	0.948-2.765	0.07
PNI	< 49.19	1.75	1.070-2.921	0.02	1.41	0.846-2.373	0.18
NLR	> 4.04	3.33	1.692-6.066	< 0.01	2.56	1.278-4.744	< 0.01
%VC	< 80	2.00	0.488-5.424	0.28			
FEV_1%	< 70	1.77	1.059-2.953	0.02	1.31	0.756-2.283	0.32
Pathological stage	IB	2.26	1.359-3.714	< 0.01	2.06	1.183-3.568	0.01
Histological type	SCC	1.91	1.033-3.329	0.03	0.90	0.470-1.645	0.74
Operative approach	open thoracotomy	1.05	0.368-2.385	0.16			
Operative procedure	wedge resection	2.67	1.607-4.387	< 0.01			

	segmentectomy	1.30	0.502-2.798	0.54			
	lobectomy	0.37	0.227-0.618	< 0.01	0.36	0.215-0.627	< 0.01
	extend-lobectomy	1.48	0.083-6.782	0.71			
Clavian-Dindo grade	> 3	1.04	0.498-1.961	0.90			
Mortality or severe morbidity	present	1.17	0.486-2.403	0.69			

CI; confidence interval, BI; Brinkman index BMI; body mass index, CEA; carcinoembryonic antigen, PNI; prognostic nutritional index, NLR; neutrophil-to-lymphocyte ratio, VC; vital capacity, FEV_1%; forced expiratory volume % in one second, SCC; squamous cell carcinoma.

Table 7
Univariate analysis and multivariate analysis of risk factor for overall survival in pathological stage I

Univariate analysis					**Multivariate analysis**		
Variables		Hazard ratio	95% CI	*p*-value	Hazard ratio	95% CI	*p*-value
Sex	man	1.49	0.788–3.031	0.22			
Age	≥ 75	1.45	0.692–2.848	0.30			
Comorbidity							
Interstitial lung disease	present	7.90	2.958–17.762	< 0.01	1.87	0.639–4.890	0.23
Asthma	present	0.64	0.036–2.965	0.64			
Arrhythmia	present	3.40	0.820–9.453	0.08			
Charlson comorbidity index	≥ 3	0.69	0.039–3.202	0.70			
Smoking status	BI ≥ 600	4.55	2.323–9.765	< 0.01	3.39	1.641–7.565	< 0.01
BMI	≥ 25.1	0.67	0.378–1.131	0.14			
CEA	> 5	2.89	1.571–5.289	< 0.01	1.56	0.809–2.979	0.18
PNI	< 49.19	2.30	1.250–4.436	< 0.01	2.00	1.075–3.891	0.02
NLR	> 4.04	1.43	0.430–3.576	0.51			
%VC	< 80	3.01	0.727–8.310	0.11			
FEV_1%	< 70	1.85	0.994–3.424	0.05			
Pathological stage	IB	2.68	1.470–4.929	< 0.01	2.20	1.161–4.199	0.01
Histological type	SCC	2.68	1.353–5.053	< 0.01	1.28	0.623–2.507	0.48

CI; confidence interval, BI; Brinkman index BMI; body mass index, CEA; carcinoembryonic antigen, PNI; prognostic nutritional index, NLR; neutrophil-to-lymphocyte ratio, VC; vital capacity, FEV_1%; forced expiratory volume % in one second, SCC; squamous cell carcinoma, NA; not available.

Univariate analysis					Multivariate analysis		
Operative approach	open thoracotomy	1.49	0.512–3.456	0.42			
Operative procedure	wedge resection	2.63	1.413–4.803	< 0.01	2.32	1.159–4.524	0.01
	segmentectomy	NA	NA	NA			
	lobectomy	0.56	0.278–0.942	0.03			
	extend-lobectomy	2.51	0.141–11.693	0.42			
Clavian-Dindo grade	> 3	0.96	0.366–2.132	0.94			
Mortality or severe morbidity	present	1.31	0.499–2.901	0.54			

CI; confidence interval, BI; Brinkman index BMI; body mass index, CEA; carcinoembryonic antigen, PNI; prognostic nutritional index, NLR; neutrophil-to-lymphocyte ratio, VC; vital capacity, FEV_1%; forced expiratory volume % in one second, SCC; squamous cell carcinoma, NA; not available.

Discussion

In this study, we analyzed the prognostic value of NLR in patients with NCSLC who underwent pulmonary resection. NLR was revealed as a significant factor for PFS in patients with NSCLC who received surgical treatment, even in patients with pathological stage I. Although the cut-off value of NLR for patients who underwent pulmonary resection was 1.5–5 in the previous study, NLR 5 was often used as the cut-off value of NLR [4–10]. Although the cut-off value of NLR was 1.75 in all patients and 4.04 in pathological stage I in this study, NLR was revealed as a significant factor for PFS, and NLR could be the criterion for indication of adjuvant chemotherapy in patients with early stage NSCLC who received surgical treatment. However, NLR was not a significant factor in OS in patients with NSCLC in this study. In a previous study, NLR was reported to be a significant factor in OS [4–10]. Furthermore, NLR has been reported as a prognostic marker in patients with NSCLC treated with systemic therapy, including an immune checkpoint inhibitor [24–27]. Considering why NLR was revealed as a significant factor in OS in univariate analysis, it is possible that the other significant factors of OS affect and NLR was not revealed as significant factor in multivariate analysis.

The PNI was initially designed to assess the nutritional and immunological status of patients undergoing gastrointestinal surgery [28]. PNI has been reported as a prognostic factor for patients who have undergone surgery for various cancers [11–14]. PNI was found to be a significant factor for OS in patients with NSCLC in this study. PNI was reported as a prognostic factor for OS in NSCLC patients who received surgical treatment, even in a previous study [9, 29, 30]. The cut-off value of PNI was reported to be range 48

to 50 in the previous study, and the cut-off value of PNI (47.97) in this study was similar. Although PNI was revealed as a significant factor for OS in pathological stage I - III NSCLC patients who received surgical treatment in a previous study, it was not reported whether PNI is a significant factor for OS in pathological stage I NSCLC [9, 29, 30]. In this study, we revealed that PNI is a significant factor in OS in patients with pathological stage I NSCLC. Meanwhile, PNI was not revealed as a significant factor for PFS in this study. Because PNI was correlated with NLR, NLR might be a significant factor in PFS in multivariate analysis. Although there have been reports that PNI is a significant factor for OS in patients with NSCLC who received surgical treatment [29, 30], a report revealed that PNI is a significant factor for PFS in patients with NSCLC who received surgical treatment [9]. It is necessary to reveal why PNI affects OS but not PFS in patients with NSCLC who will receive surgical treatment in the future.

This study has several limitations. The study had a retrospective design, and there was a possibility of unobserved confounding and selection bias. Another limitation is that this study was conducted in a single institution.

Conclusions

We analyzed the prognostic value of NLR and PNI in patients with NSCLC who received surgical treatment. NLR was revealed as a significant factor for PFS in patients with NSCLC who received surgical treatment, even in patients with pathological stage I. Furthermore, PNI was revealed as a significant factor for OS in patients with NSCLC who received surgical treatment but was not revealed as a significant factor for PFS. In the future, it is necessary to reveal why PNI affects OS but not PFS in patients with NSCLC who receive surgical treatment.

Abbreviations

NLR; neutrophil-to-lymphocyte ratio, NSCLC; non-small cell lung cancer, PNI; prognostic nutritional index, COPD; chronic obstructive pulmonary disease, VC; vital capacity, FEV1%; forced expiratory volume % in one second, VATS; video-assisted thoracic surgery, RATS; robotic-assisted thoracic surgery, CEA; carcinoembryonic antigen, CT; computed tomography, ILD; interstitial lung disease, PFS; progression free survival, OS; overall survival.

Declarations

Ethics approval and consent to participate

The present study was conducted in accordance with the amended Declaration of Helsinki. The Institutional Review Boards of Kanazawa Medical University approved the protocol (approval number: I392), and written informed consent was obtained from all of the patients.

Consent to publish

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to [our institutional restrictions e.g. them containing information that could compromise research participant privacy/consent], but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

N. M. performed the research, collected and analyzed the data and wrote the paper. M.I., S. I., and Y. I. contributed to sample collection. H. U. contributed to supervision of this study and revision of the manuscript. All authors have read and approved the manuscript, and ensure that this is the case.

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Competing interests

The authors declare that they have no competing interests.

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