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The Postoperative Complication After Lung Cancer Surgery Does Not Affect for Survival: A Retrospective Study

Nozomu Motono*, Masahito Ishikawa, Shun Iwai, Yoshihito Iijima, Katsuo Usuda and Hidetaka Uramoto

Department of Thoracic Surgery, Kanazawa Medical University, 1-1 Daigaku, Uchinada, Ishikawa, 920-0293, Japan

***Corresponding author:**

Nozomu Motono,
Department of Thoracic Surgery, Kanazawa Medical University, 1-1 Daigaku, Uchinada, Ishikawa, 920-0293, Japan,
Tel: +81-76-286-2211; Fax: +81-76-286-1207;
E-mail: motono@kanazawa-med.ac.jp

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1. Abstract

1.1. Aims: The relationship between postoperative complications and prognosis in patients with non-small cell lung cancer (NSCLC) who have undergone surgery is unclear.

1.2. Materials and Methods: We analyzed clinical data from 355 NSCLC patients from January 2014 to December 2018. Comorbidities were assessed by the Charlson comorbidity index. Postoperative complications were classified into 5 grades according to the Clavien-Dindo classification. Univariate and multivariate analysis using the Cox proportional hazards model was performed to obtain progression-free survival (RFS) and overall survival (OS) risk factors.

1.3. Results: The RFS differed significantly based on the gender (p=0.04), carcinoembryonic antigen (CEA) (p=0.02), differentiation (p=0.01), lymphatic invasion (Ly) (p<0.01), vascular invasion (V) (p<0.01), histologic type (p<0.01), pathological stage (pStage) (p<0.01), and postoperative complication (p=0.02). The gender (p = 0.03), CEA (p = 0.02), differentiation p < 0.01), Ly p < 0.01), V (p < 0.01), histologic type (p < 0.01), pStage (p < 0.01), and postoperative complication (p = 0.02) were identified as significant prognostic factors in a univariate analysis. The multivariate analysis showed that only the pStage was a significant prognostic factor for the RFS (p < 0.01). The multivariate analysis showed that only V was a significant prognostic factor for the OS (p = 0.03).

1.4. Conclusions: The severity of postoperative complication classified by the Clavien-Dindo grade does not affect the long-term outcomes in patients who have undergone surgery for NSCLC.

2. Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide [1]. The incident of postoperative complication and 30-day postoperative mortality of pulmonary resection for non-small cell lung cancer (NSCLC) was reported to be 9%-37% and ≤3%, respectively [2-4]. Several studies have shown a poor prognosis due to postoperative complications after surgery for gastrointestinal cancers [5-9]. Furthermore, it was reported that systemic inflammation as a postoperative complication may carry a risk of inducing cancer recurrence [10, 11]. However, other studies have reported that the postoperative complication did not influence the prognosis [12, 13], so the actual situation is controversial.

The Clavien-Dindo classification, established in 1992, is a simple and feasible grading system for all types of postoperative complications [14]. In 2004, the Clavien-Dindo classification was changed to allow for grading of life-threatening complications and long-term disabilities caused by complications [15]. This revised edition defines five grades of severity (grades I, II, IIIa, IIIb, IVa, IVb, and V), with the suffix "d" (representing "disability") postoperative. Used to indicate a failure. This modified Clavien-Dindo classification is widely used in clinical practice. However, the relationship between the postoperative complication and prognosis in NSCLC patients who have undergone surgery has not been elu-

cidated.

In the present study, we evaluated the prognostic impact of postoperative complication classified by the Clavien-Dindo system after surgery for NCSLC patients.

3. Materials and Methods

3.1. Study patients

Six hundred and eighty-one NSCLC patients who underwent complete resection with the video-assisted thoracic surgery (VATS) technique in Kanazawa Medical University between January 2014 and December 2018 were identified. Among these, 355 patients with NSCLC had available data. These patients were therefore enrolled in the present retrospective study.

Regarding the data collected, the clinical factors were the gender, age, smoking history, comorbidity, carcinoembryonic antigen (CEA). The smoking history was assessed using the Brinkman index, which is calculated as the numbers of cigarettes smoked per day multiplied by the number of years for which the subject has smoked [16]. The comorbidity was evaluated by the Charlson comorbidity index [17]. Pathological factors were the histological type, differentiation, lymphatic invasion (Ly), vascular invasion (V), pathological stage (pStage). Perioperative factors were the operative procedure, postoperative complication. The postoperative complication was categorized into five grades according to the Clavien-Dindo classification.

3.2. Statistical analyses

The cumulative survival rates were calculated by the Kaplan–Meier methods, and survival curves were compared using the log-rank test. Univariate and multivariate analyses using the Cox proportional hazard model were conducted to obtain the risk factors for the relapse-free survival (RFS) and the overall survival (OS). All statistical analyses were two-sided, and statistical significance was defined as a p value of less than 0.05. The statistical analyses were conducted using the JMP software program (Version 13.2; SAS Institute Inc., Cary, NC, USA).

4. Results

4.1. Patients characteristics

The clinicopathologic characteristics of the 355 included patients are listed in Table 1. Two hundred and twenty-five patients were men, and the median age was 70 years. The median Brinkman index was 600, the median CEA was 3.6 ng/ml. Almost half of patients had a low comorbidity index (Charlson comorbidity index score of 0, n= 196; 55%). The pStage was IA in 228, IB in 56, IIA in 25, IIB in 27, and IIIA in 19. Adenocarcinoma was diagnosed in 266, squamous cell carcinoma in 65, and other types of lung cancer (adenosquamous cell carcinoma, pleomorphic carcinoma, large cell neuroendocrine carcinoma) in 24. Differentiation was divided into four categories: grade 1 (G1) in 115, grade 2 (G2) in 170, grade 3 (G3) in 55, and grade 4 (G4) in 15. Ly was present in 112 patients, and V was present in 163. Sublobar resection was performed in 119 patients, and lobectomy or more was performed in 236. Postoperative complication was present in 114 patients (32%), and almost half (60 patients) of cases showed air leakage. Clavien-Dindo grade I was noted in 22, II in 36, IIIa in 53, and IIIb in 3.

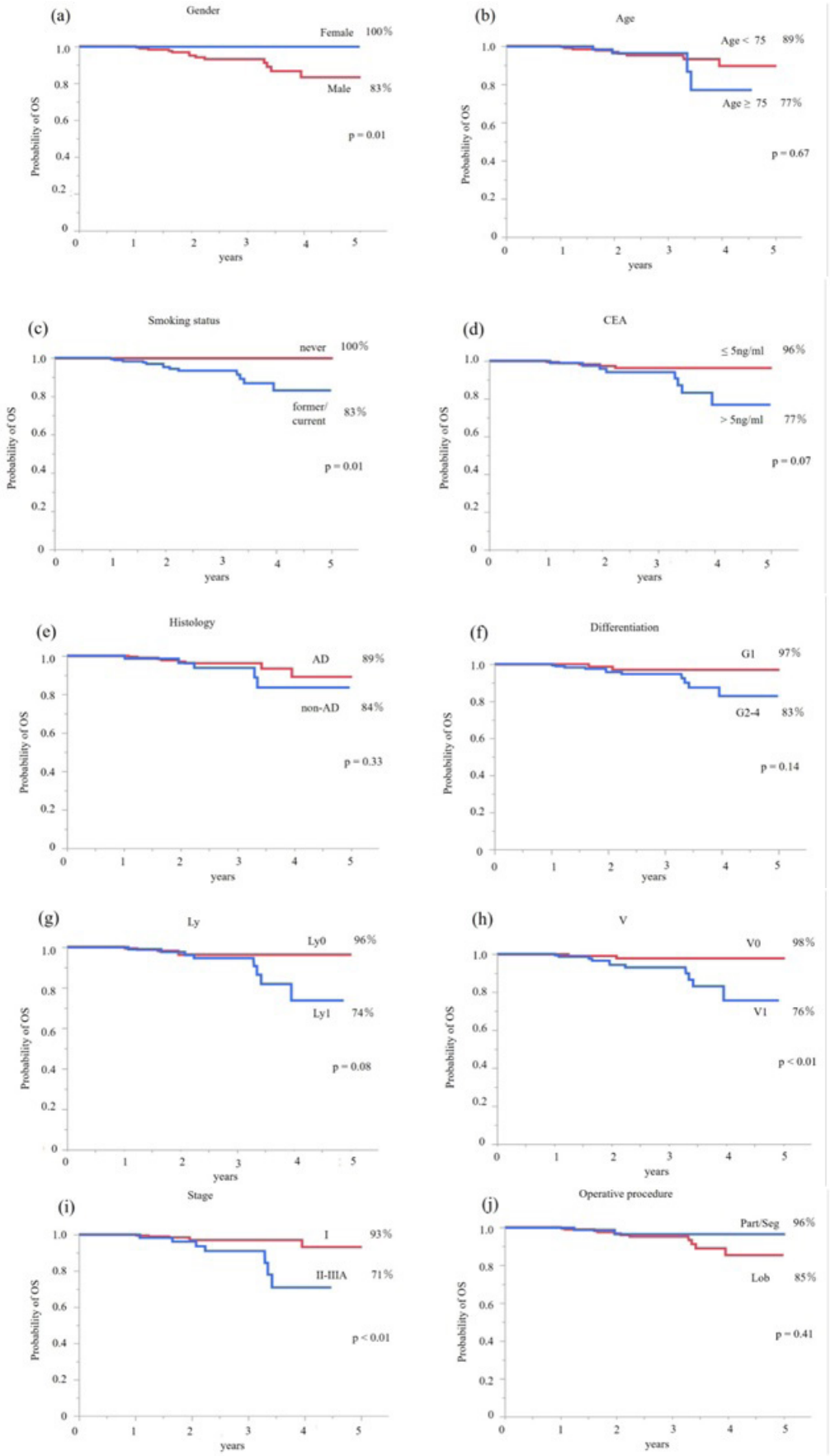
Table 1: Patients characteristics

Variables	
Gender (male/female)	225/130
Age, median, range (y.o.)	70(34-89)
charlson comorbidity index (0/1/2/3/4)	196/71/69/15/4
Smoking index, median, range	600 (0-3600)
CEA, median, range (ng/ml)	3.6 (0.5-306)
Differentiation (G1/2/3/4)	115/170/55/15
Ly (0/1)	243/112
V(0/1)	192/163
Histology (Ad/Sq/Others)	266/65/24
pStage (IA/IB/IIA/IIB/IIIA)	228/56/25/27/19
Operative Procedure (Part/ Seg/ Lob/ Bilob/ Pneum)	89/30/226/3/7
Postoperative Complication (absent/present)	241/114
Clavien-Dindo grade (I/II/IIIa/IIIb)	22/36/53/3

CEA: Carcinoembryonic antigen, Ly: lymphatic invasion, V: vascular invasion. Ad: adenocarcinoma, Sq: Squamous cell carcinoma, pStage: pathological stage, Part: partial resection, Seg: sementectomy, Lob: lobectomy, Bilob: bi-lobectomy, Pneum: pneumonectomy

4.2. Survival analyses

The RFS is shown in Figure 1. There were significant prognostic differences in the gender ($p<0.04$), CEA ($p=0.02$), differentiation ($p=0.01$), Ly ($p<0.01$), V ($p<0.01$), histologic type ($p<0.01$), pStage ($p<0.01$), and postoperative complication ($p=0.02$). The OS is shown in Figure 2. There were significant prognostic differences in the gender ($p=0.01$), smoking history ($p=0.02$), V ($p<0.01$), and pStage ($p<0.01$).


(a)
Gender
Female 100%
Male 83%
p = 0.01
(b)
Age
Age < 75 89%
Age ≥ 75 77%
p = 0.67
(c)
Smoking status
never 100%
former/ current 83%
p = 0.01
(d)
CEA
≤ 5ng/ml 96%
> 5ng/ml 77%
p = 0.07
(e)
Histology
AD 89%
non-AD 84%
p = 0.33
(f)
Differentiation
G1 97%
G2-4 83%
p = 0.14
(g)
Ly
Ly0 96%
Ly1 74%
p = 0.08
(h)
V
V0 98%
V1 76%
p < 0.01
(i)
Stage
I 93%
II-IIIA 71%
p < 0.01
(j)
Operative procedure
Part/Seg 96%
Lob 85%
p = 0.41
Probability of OS
years

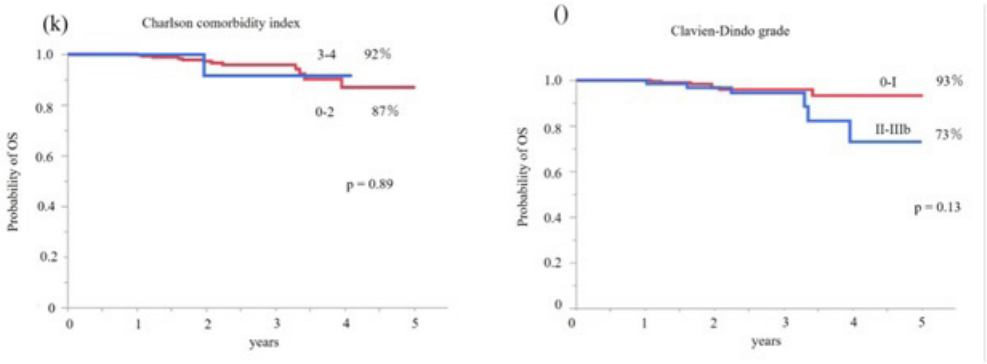
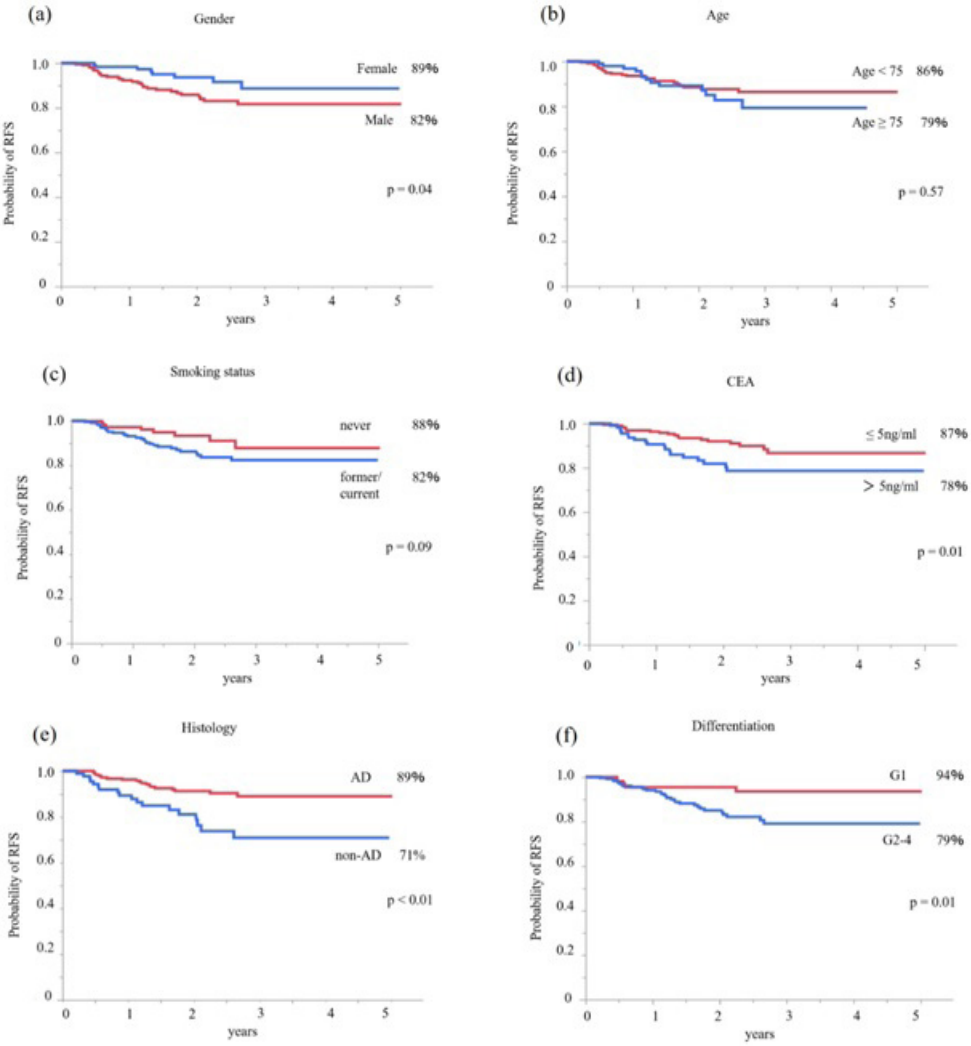


Figure 1: (a) The relapse-free survival is significantly higher in women than in men. (b) The relapse-free survival does not significantly differ by age. (c) The relapse-free survival does not significantly differ by smoking status. (d) The relapse-free survival is significantly higher in patients with CEA ≤5 ng/ml than in CEA > 5ng/ml. (e) The relapse-free survival is significantly higher in adenocarcinoma patients than in non-adenocarcinoma patients. (f) The relapse-free survival is significantly higher in patients with differentiation grade 1 than in grade 2 to 4. (g) The relapse-free survival is significantly higher in patients without lymphatic invasion than in those with it. (h) The relapse-free survival is significantly higher in patients without vascular invasion than in those with it. (i) The relapse-free survival is significantly higher in patients with pathological stage I than in pathological stage II to IIIA. (j) The relapse-free survival does not significantly differ by operative procedure. (k) The relapse-free survival does not significantly differ by comorbidity classified by the Charlson comorbidity index. (l) The relapse-free survival is significantly higher in patients with postoperative complications classified as Clavien-Dindo grade 0 or I than in grade II to IIIb.



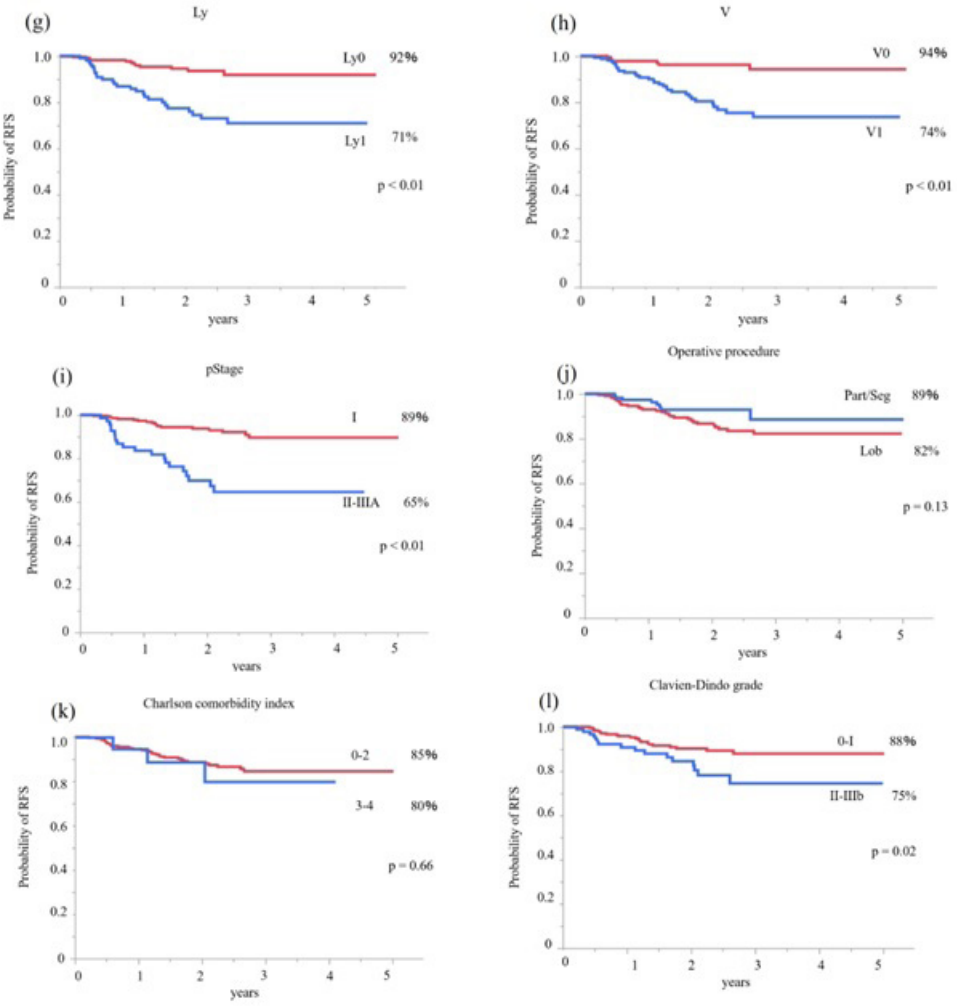


Figure 2: (a) The overall survival is significantly higher in women than in men. (b) The overall survival does not significantly differ by age. (c) The overall survival is significantly higher in never-smoking patients than in current or former smoker. (d) The overall survival does not significantly differ by CEA. (e) The overall survival does not significantly differ by histological type. (f) The overall survival does not significantly differ by differentiation. (g) The overall survival does not significantly differ by lymphatic invasion. (h) The overall survival is significantly higher in patients without vascular invasion than in those with it. (i) The overall survival is significantly higher in patients with pathological stage I than in pathological stage II to IIIA. (j) The overall survival does not significantly differ by operative procedure. (k) The overall survival does not significantly differ by comorbidity classified by the Charlson comorbidity index. (l) The overall survival does not significantly differ by postoperative complications classified the Clavien-Dindo grade.

Univariate and multivariate analyses

The univariate and multivariate analyses of the factors affecting the RFS are summarized in Table 2. The gender (hazard ratio [HR], 2.20; 95% confidence interval [CI], 1.06-5.16; p = 0.03), CEA (HR, 2.09; 95% CI, 1.10-3.97; p = 0.02), differentiation (HR, 2.95; 95% CI, 1.32-7.84; p < 0.01), Ly (HR, 4.38; 95% CI, 2.25-9.01; p < 0.01), V (HR, 5.17; 95% CI, 2.42-12.80; p < 0.01), histologic type (HR, 2.83; 95% CI, 1.48-5.37; p < 0.01), pStage (HR, 4.77; 95% CI, 2.52-9.11; p < 0.01), and postoperative complication (HR, 2.10; 95% CI, 1.08-3.98, p = 0.02) were identified as significant prognostic factors in the univariate analysis. The multivariate analysis showed that only the pStage was a significant prognostic factor for the RFS (HR, 2.64; 95% CI, 1.31-5.39, p < 0.01).

The univariate and multivariate analyses of the factors affecting the OS are summarized in Table 3. V (HR, 5.97; 95% CI, 1.59-38.67; p < 0.01) and pStage (HR, 4.10; 95% CI, 1.36-12.76; p = 0.01) were identified as significant prognostic factors in the univariate analysis. The multivariate analysis showed that only V was a significant prognostic factor for the OS (HR, 4.38; 95% CI, 1.08-29.38, p = 0.03).

Table 2: Cox proportional hazard analyses for factors affecting relapse free survival

	Univariate analysis				Multivariate analysis		
Variables		HR (95%CI)	p-value	Variables		HR (95%CI)	p-value
Gender	female	1		Gender	female	1	
	male	2.20 (1.06-5.16)	0.03		male	1.43 (0.61-3.64)	0.41
Age	< 75y	1					
	≥ 75y	1.21 (0.60-2.33)	0.57				
Charlson comorbidity index	0-2	1					
	3-4	1.29 (0.31-3.60)	0.67				
Smoking status	never	1					
	former/current	1.93 (0.93-4.54)	0.07				
CEA	≤ 5ng/ml	1		CEA	≤ 5ng/ml	1	
	> 5ng/ml	2.09 (1.10-3.97)	0.02		> 5ng/ml	1.52 (0.76-3.05)	0.23
Differentiation	G1	1		Differentiation	G1	1	
	G2/G3	2.95 (1.32-7.84)	<0.01		G2/G3	0.84 (0.31-2.56)	0.75
Ly	absent	1		Ly	absent	1	
	present	4.38 (2.25-9.01)	<0.01		present	1.70 (0.74-4.18)	0.21
V	absent	1		V	absent	1	
	present	5.17 (2.41-12.80)	<0.01		present	2.08 (0.74-6.46)	0.17
Histology	AD	1		Histology	AD	1	
	non-AD	2.83(1.48-5.37)	<0.01		non-AD	1.55 (0.76-3.19)	0.22
pStage	I	1		pStage	I	1	
	II-IIIA	4.77 (2.52-9.11)	<0.01		II-IIIA	2.65 (1.31-5.42)	<0.01
Procedure	Part/Seg	1					
	Lob	1.81 (0.87-4.25)	0.11				
Clavien-Dindo grade	0-I	1		Clavien-Dindo grade	0-I	1	
	II-IIIb	2.11 (1.08-3.98)	0.02		II-IIIb	1.31 (0.68-2.52)	0.42

CEA: carcinoembryonic antigen, Ly: lymphatic invasion, V: vascular invasion, pStage: pathological stage, Part: partial resection, Seg: segmentectomy, Lob: lobectomy or more

Table 3: Cox proportional hazard analyses for factors affecting overall survival

		Univiriate analysis		Multivariate analysis	
Variables		HR (95% CI)	p-value	HR (95% CI)	p-value
Gender	female	1			
	male	N.A.	N.A.		
Age	<75y	1			
	≥75y	1.29(0.34-4.04	0.67		
Charlson comorbidity index	0-2	1			
	3-Jan	1.15 (0.06-5.85)	0.89		
smoking status	never	1			
	former/current	N.A.	N.A.		
CEA	≤5ng/ml	1			
	>5ng/ml	2.71 (0.89-9.01)	0.07		
Differentiation	G1	1			
	G2/G3	2.94 (0.79-19.07)	0.11		
LY	absent	1			
	present	2.59 (0.86-8.59)	0.08		
V	absent	1		1	
	present	5.97 (1.59-38.67)	<0.01	4.38 (1.08-29.38)	0.03
Histology	AD	1			
	non-AD	1.72 (0.51-5.17)	0.35		
pStage	1	1		1	
	II-IIIA	4.10 (1.36-12.76)	0.01	2.68 (0.86-8.74)	0.08
Procedure	Part/Seg	1			
	Lob	1.85 (0.48-12.09)	0.39		
Clavien-Dindo grade	0-I	1			
	II-IIIb	2024 (0.72-6.77)	0.15		

N.A.: not available, CEA: carcinoembryonic antigen, LY: lymphatic invasion, V: vascular invasion, pStage: pathological stage, Part: partial resection, Seg: segmentectomy, Lob: lobectomy or more

5. Discussion

We showed that postoperative complications classified as Clavien-Dindo ≥ II tend to increase the possibility of the relapse in patients who have undergone surgery for NSCLC. The Clavien-Dindo classification has been used to evaluate the severity of postoperative complications in several fields of surgery, and the utility was reported in several reports [18-20]. A previous study reported that major infectious complications, such as pneumonia, empyema, and mediastinitis, influenced a poor prognosis in patients who had undergone lung cancer surgery [10]. Furthermore, postoperative complication was associated with the patient prognosis in gastrointestinal cancers [5-15, 17-22]. In these reports, it was suggested that an inflammatory reaction might promote tumor proliferation, avoidance of apoptosis, progression of metastasis, and resistance to drug therapy. Although inflammatory complications, such as pneumonia and urinary tract infection, developed in only 14 patients (4%) in the present study, the RFS in patients with postoperative complications classified as Clavien-Dindo ≥ II tended to be lower than in those without such complications. Postoperative complications classified as Clavien-Dindo ≥ II require additional treatment, which can cause inflammatory reactions. Although the severity of postoperative complication was reported to have a detrimental impact on the long-term outcomes, particularly cancer-specific outcomes, in patients undergoing surgery for colorectal cancer, the relationship between the severity of the postoperative complication and the prognosis in patients who have undergone surgery for NSCLC has not yet been revealed. Based on the present findings, the severity of postoperative complication classified by Clavien-Dindo grade might have some prognostic influence on the long-term outcomes in patients who have undergone surgery for NSCLC.

Previous studies reported that the presence of comorbidities was associated with a worse survival in lung cancer patients than their absence [23-28]. Although the Charlson comorbidity index has often been used to evaluate the severity of comorbidity, with a good utility reported, the severity boundary is not clear [23, 25, 26]. We found no significant prognostic difference between the patients with a Charlson comorbidity index ≤ 2 and those with an index > 2 in the present study. Furthermore, no significant difference was noted between the patients with a Charlson comorbidity index 0 and those with an index ≥1 on a univariate analysis for the RFS in present study (HR 0.84; 95% CI, 0.83, 0.43-1.58; p=0.58). Because the Charlson comorbidity index was not developed specifically for patients with NSCLC, it might not have adequately affected the prognosis in the present study. A VATS approach is low-invasive and can be performed safely in patients with severe comorbidities. The low-invasiveness and prognostic improvement associated with the VATS approach have been reported in recent studies [29-31]. In the future, when surgical procedures have become even less invasive, a new comorbidity index should be developed that emphasizes the different effects of certain comorbidities.

Several limitations associated with the present study warrant mention. First, the study is retrospective, and there is a possibility of unobserved cofounding and selection bias. Second, the present study was performed at a single institution, and the number of patients was small.

In conclusion, our findings suggested that the severity of postoperative complications classified by Clavien-Dindo grade does not affect a prognostic impact on the long-term outcomes in patients who have undergone surgery for NSCLC. In addition, a new comorbidity index should be developed with emphasize on the different effects of some specific comorbidities.

6. Declarations

6.1. 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.

6.2. Author's contributions

N. M. performed the research, collected and analyzed the data and wrote the paper. M.I., S. I., Y.I, and K. U. 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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