Impact and predictors of acute exacerbation of interstitial lung diseases after pulmonary resection for lung cancer

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Objective: The study objective was to examine the incidence, risk factors, and mortality rate of acute exacerbation of interstitial lung diseases in patients with lung cancer undergoing pulmonary resection in a large-scale multi-institutional cohort.

Methods: We retrospectively analyzed 1763 patients with non-small cell lung cancer who had undergone pulmonary resection and presented with a clinical diagnosis of interstitial lung diseases between January 2000 and December 2009 at 61 hospitals in Japan. The incidence and outcomes of acute exacerbation within 30 days from the operation were investigated. Univariate and multivariate logistic regression analyses were used to identify independent risk factors of acute exacerbation.

Results: Acute exacerbation occurred in 164 patients (9.3%; 95% confidence interval, 8.0-10.8), with a mortality rate of 43.9%, and was the top cause of 30-day mortality (71.7%). The following 7 independent risk factors of acute exacerbation were identified: surgical procedures, male sex, history of exacerbation, preoperative steroid use, serum sialylated carbohydrate antigen KL-6 levels, usual interstitial pneumonia appearance on computed tomography scan, and reduced percent predicted vital capacity. Surgical procedures showed the strongest association with acute exacerbation (using wedge resection as the reference, lobectomy or segmentectomy: odds ratio, 3.83; 95% confidence interval, 1.94-7.57; bi-lobectomy or pneumonectomy: odds ratio, 5.70; 95% confidence interval, 2.38-13.7; $P < .001$). The effect of perioperative prophylactics, such as steroids and sivelestat, was not confirmed in this study.

Conclusions: Pulmonary resection for patients with lung cancer with interstitial lung diseases may provoke acute exacerbation at a substantially high rate and has high associated mortality. Surgical procedures that proved to be a risk factor for acute exacerbation should be chosen cautiously for these high-risk patients. (J Thorac Cardiovasc Surg 2014;147:1604-11)

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Interstitial lung diseases (ILDs) are associated with an increased risk of lung cancer.^{1,2} Therapeutic modalities for patients with lung cancer with ILDs should be selected carefully because interventions may provoke exacerbation of ILDs.^{3,4} Pulmonary resection has been shown to be associated with high postoperative morbidity and mortality in these patients. Postoperative acute exacerbation (AE) of interstitial pneumonia is one such possible comorbidity and is associated with mortality rates between 33.3% and 100%.⁵⁻⁸ In addition to treatment-related morbidity and mortality, the prognosis of ILDs itself—particularly in patients with idiopathic pulmonary fibrosis (IPF)—can be a life-limiting factor. Several retrospective studies suggest a median survival time of patients with IPF from 2 to 3 years after diagnosis.⁹⁻¹³ Whether

Abbreviations and Acronyms

AE	= acute exacerbation
ALI	= acute lung injury
ARDS	= acute respiratory distress syndrome
CI	= confidence interval
CRP	= C-reactive protein
CT	= computed tomography
DLCO	= diffusing capacity for carbon monoxide
FEV1	= forced expiratory volume in 1 second
FEV1%	= percent forced expiratory volume in 1 second
ILD	= interstitial lung disease
IPF	= idiopathic pulmonary fibrosis
OR	= odds ratio
Paco ₂	= partial pressure of carbon dioxide
%DLCO	= percent predicted diffusing capacity for carbon monoxide
%VC	= percent vital capacity
UIP	= usual interstitial pneumonia
VC	= vital capacity

pulmonary resections are indicated for patients with lung cancer with fibrosis remains a matter of debate.^{8,14-16}

To determine the most appropriate treatment strategy, a reliable assessment of the risks and benefits of the various interventions is required. However, no cohort study of a sufficiently large scale for this purpose has been conducted. The purpose of this study was therefore to clarify the incidence, risk factors, and outcomes of postoperative AE in patients with lung cancer with ILDs who had undergone pulmonary resection. At the initiative of the Japanese Association for Chest Surgery, we have conducted a large-scale multi-institutional retrospective cohort study to inform the decision-making process for these patients.

MATERIALS AND METHODS**Study Design and Patients**

The design of the study was planned by Drs Sato, Teramukai, and Date with assistance from the advisory board of the Japanese Association for Chest Surgery and the Project Team for Diffuse Lung Diseases, organized by the Japanese Ministry of Health, Labour and Welfare. The study protocol was approved by the institutional review boards of all participating hospitals, including that of the Ethics Committee, Kyoto University Graduate School and Faculty of Medicine (Approval Number: E-982).

The original data for analysis were obtained from patients with non-small cell lung cancer who had undergone pulmonary resection and presented with a clinical diagnosis of ILD between January 2000 and December 2009 at 64 institutions throughout Japan.

The primary end point for outcomes analysis was postoperative AE of interstitial pneumonitis within 30 days after pulmonary resection. Medical records of the patients were reviewed for age; sex; comorbidities, including collagen and respiratory diseases; smoking history; blood work and physiologic data, including white blood cells, C-reactive protein (CRP), lactate dehydrogenase, KL-6 (sialylated carbohydrate antigen KL-6), carcinoembryonic antigen, partial pressure of oxygen, partial pressure of carbon

dioxide (Paco₂), vital capacity (VC), percent vital capacity (%VC), forced expiratory volume in 1 second (FEV1), percent FEV1 (FEV1%), percent predicted FEV1, diffusing capacity for carbon monoxide (DLCO), and percent predicted DLCO (%DLCO); operation time; bleeding amount; perioperative prophylactics, including steroids, sivelestat sodium hydrate, ulinastatin, and combinations thereof; surgical procedures; tumor location; pathologic diagnosis; and cancer pTNM stages based on the 6th edition of the American Joint Committee on Cancer lung cancer staging.

Inclusion Criteria for Patients With Interstitial Lung Diseases

Diagnoses of ILDs were confirmed on the basis of a combination of clinical and radiologic findings according to the clinical criteria proposed by the Japanese Respiratory Society,¹⁷ which are consistent with the guidelines of the American Thoracic Society in 2011.¹² The cases were categorized into 2 groups according to their radiologic appearance on computed tomography (CT) scan: (1) usual interstitial pneumonia (UIP) pattern: characterized by the presence of basal-dominant reticular opacities and predominantly basal and subpleural distribution of honeycomb lesions, with multiple equal-sized cystic lesions of 2 to 10 mm diameter with a thick wall; and (2) non-UIP pattern: characterized by the presence of basal-predominant ground glass opacities and infiltrative shadows inconsistent with UIP patterns.

Definition of Postoperative Acute Exacerbation

AE caused by pulmonary resection was defined on the basis of criteria proposed by the American Thoracic Society Guidelines¹² and Yoshimura and colleagues.¹⁸ These criteria were (1) onset within 30 days after pulmonary resection, (2) intensified dyspnea, (3) increase in the interstitial shadow on chest radiograph and chest CT scan, (4) decrease in arterial oxygen tension of more than 10 mm Hg under similar conditions, (5) no evidence of pulmonary infection, and (6) exclusion of alternative causes, such as cardiac failure, pulmonary embolism, or other identifiable causes of lung injury. Exacerbations occurring from 31 days onward were defined as chronic exacerbations.

Patient Characteristics

Data were initially obtained from 41,742 consecutive patients with lung cancer who had undergone pulmonary resections in 64 institutions; 2418 of these patients presented with ILDs. Because of poor quality of data, 404 cases from 3 institutions were excluded from the study. In addition, 135 cases were excluded because their fibrotic changes were pathologically confirmed, but there were no apparent fibrotic changes detected on CT scans. After reviewing all data for eligibility, completeness, and consistency, 116 more cases were excluded, leaving 1763 cases with ILDs deemed eligible for final analysis in this study.

The demographics of the cohort used in this study are shown in Table 1. The majority of patients were men (90.4%) and ex- or current smokers (93.8%). History of AE of interstitial pneumonia treated before the index pulmonary resection was observed in 1.1% of patients. Approximately 6.2% of patients had been treated preoperatively with steroids and other immunosuppressant drugs, 4.2% of patients had induction chemotherapy, and 1.8% of patients had radiation therapy. UIP diagnoses were made in 73.7% of patients by CT scan, and 45.7% of patients were confirmed pathologically with resected specimens as having UIP. Squamous cell carcinoma was the most common type of lung cancer.

Statistical Analyses

Univariate logistic regression analysis was performed to preliminarily evaluate the associations between the incidence of AE and the following candidate patient characteristics: age, sex, body mass index, smoking history, Brinkman index, comorbidities (asthma, emphysema, and collagen disease), neoadjuvant chemotherapy, neoadjuvant radiation therapy, white blood cells, CRP, lactate dehydrogenase, KL-6, carcinoembryonic antigen,

TABLE 1. Patient characteristics

Characteristics	No. of patients (%)	Median (range)
Age, y	1763	71 (36-88)
Sex		
Male/female	1593 (90.4)/170 (9.6)	
BMI, kg/m ²	1746	23.0 (13.7-37.0)
Smoking history		
Never smoker	109 (6.2)	
Ex-smoker	1006 (57.6)	
Current smoker	632 (36.2)	
Brinkman index	1742	1000 (0-5760)
Comorbidity		
Asthma		
−/+	1724 (98.1)/33 (1.9)	
Emphysema		
−/+	1167 (66.5)/589 (33.5)	
Collagen disease		
−/+	1654 (94.2)/102 (5.8)	
History of AE*		
−/+	1741 (98.9)/20 (1.1)	
Preoperative medication for IP		
None/steroids/others	1638 (93.8)/103 (5.9)/6 (0.3)	
Neoadjuvant chemotherapy		
−/+	1686 (95.8)/73 (4.2)	
Neoadjuvant radiation		
−/+	1728 (98.2)/32 (1.8)	
Radiologic diagnosis		
UIP/non-UIP pattern	1300 (73.7)/463 (26.3)	
Histology		
Squamous cell carcinoma	816 (46.9)	
Adenocarcinoma	721 (41.4)	
Large cell carcinoma	64 (3.7)	
Others	139 (8.0)	
pTNM stage		
1a	547 (31.6)	
1b	481 (27.8)	
2a	70 (4.0)	
2b	241 (13.9)	
3a	244 (14.1)	
3b	114 (6.6)	
4	34 (2.0)	
Surgical procedure		
Wedge resection	275 (15.7)	
Segmentectomy	150 (8.5)	
Lobectomy	1236 (70.4)	
Bilobectomy	61 (3.5)	
Pneumonectomy	33 (1.9)	

(Continued)

TABLE 1. Continued

Characteristics	No. of patients (%)	Median (range)
Tumor location		
Upper lobe	670 (39.2)	
Middle lobe	77 (4.5)	
Lower lobe	958 (56.0)	
Multiple	5 (0.3)	
VATS		
−/+	964 (54.7)/798 (45.3)	
Node dissection		
0/1/2	331 (17.7)/339 (19.3)/1104 (63.0)	

The pTNM staging was based on the 6th edition of the American Joint Committee on Cancer lung cancer staging. *AE*, Acute exacerbation; *BMI*, body mass index; *IP*, interstitial pneumonia; *UIP*, usual interstitial pneumonia; *VATS*, video-assisted thoracoscopic surgery. *History of treated AE before pulmonary resection.

partial pressure of oxygen, P_{aCO_2} , VC, %VC, FEV1, FEV1%, %FEV1, DLCO, %DLCO, radiologic findings, pathologic findings, history of AE, preoperative steroid use, pTNM stage, operation time, bleeding amount, transfusion, surgical procedures, tumor location, video-assisted thoracoscopic surgery, and node dissection.

Risk factors for inclusion in the multivariate analysis were selected on the basis of the results of the univariate analyses, statistical independence, and clinical significance for preoperative patient evaluation of AE risk.

Surgical procedures were categorized into 3 groups on the basis of the results of multivariate analyses that adjusted for the other covariates. These groups were wedge resection, lobectomy and segmentectomy, and bilobectomy and pneumonectomy. Multivariate logistic regression analysis using backward elimination was used to identify independent risk factors for AE and to estimate the respective odds ratios (ORs) and their 95% confidence intervals (CIs) of the various risk factors. All reported *P* values were 2-sided. The cutoff value for %VC was set at 80%, which is the widely accepted clinical criteria for restrictive change of pulmonary fibrosis, and is correlated to disease progression and patient survival.¹⁹ For KL-6, 1000 U/mL was determined as the cutoff value on the basis of the results of a preliminary receiver operating characteristic analysis, which showed 1040 U/mL to be the optimal cutoff value with a c-index of 0.583. Data management and statistical analyses were conducted in the Department of Clinical Trial Design and Management, Translational Research Center, Kyoto University Hospital. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Inc, Cary, NC).

RESULTS

Incidence of Acute Exacerbation

Postoperative AE developed within 30 days after the operation in approximately 9.3% of patients (95% CI, 8.0-10.8) who had undergone pulmonary resection. AE developed within 10 days after operation in the majority of the patients (64.6%), with postoperative day 4 showing the highest frequency of AE. The mortality rate of each postoperative day varied from 0% to 100%, and showed no particular tendency or trend (Figure 1 and Table 2).

Risk Factor Analysis for Acute Exacerbation

Univariate and multivariate analyses were carried out to identify possible risk factors for AE. The univariate analysis identified sex, KL-6, P_{aCO_2} , %VC, FEV1.0%, DLCO, radiologic findings, history of AE, preoperative use of steroids,

FIGURE 1. Histogram of AE incidence within 30 days after pulmonary resection (n = 164). *Black columns* represent patient death (72 cases, 43.9%), and *white columns* represent patient survival (92 cases, 56.1%). AE developed in the majority of the patients (64.6%) within 10 days after operation, with post-operative day 4 showing the highest frequency of AE. AE, Acute exacerbation.

and surgical procedures as candidate risk factors for AE (Table E1). VC and FEV1 were excluded as candidates because these variables were highly correlated with %VC (Spearman’s $r = 0.796$ and 0.603 , respectively). Multivariate analysis further identified the following risk factors for AE: sex, KL-6, %VC, radiologic findings, history of AE, preoperative steroid use, and surgical procedures (Table 3).

The lobectomy/segmentectomy and the bilobectomy/pneumonectomy groups were both more likely to develop AE than the wedge resection group, with ORs of 3.83 and 5.70, respectively. AE was 3 times more likely to develop in male patients than in female patients. Preoperative steroid use, history of AE, UIP pattern on CT scans, elevated levels of KL-6, and reduced %VC were identified as independent risk factors for AE. Neoadjuvant treatment and video-assisted thoracoscopic surgery showed no association with AE in our study (Table E1).

Surgical Procedures and Acute Exacerbation Risk

Multivariate analysis of surgical procedures adjusting for KL-6, preoperative steroid use, sex, CT findings, %VC, and history of AE was carried out. The associated risk of AE gradually increased according to resected lung volume. By using the wedge resection group as the referent category, the OR for AE in the segmentectomy group was 3.675 (95% CI, 1.586-8.519; $P = .0024$); the OR in the lobectomy group was 3.861 (95% CI, 1.946-7.660; $P < .001$); the OR in the bilobectomy group was 5.055 (95% CI, 1.871-13.660; $P = .001$); and the OR in the pneumonectomy group was 6.953 (95% CI, 2.260-21.390; $P < .001$).

Risk Factor Analysis for Acute Exacerbation in Patients With Usual Interstitial Pneumonia Patterns on Computed Tomography Scan

Subgroup analyses were carried out for the patients with UIP patterns on CT scans. To ensure only patients with UIP/IPF were included in this subgroup analysis, we excluded 65 patients with collagen diseases; a total of 1235 cases were analyzed. Sex, CRP, KL-6, %VC, FEV1, history of

TABLE 2. Incidence of acute exacerbation, its outcomes, and 30-day mortality of patients undergoing pulmonary resection

Categories	No. of patients (%)	Median (range)
30-d mortality	46 (2.6)	
30-d mortality by cause of death		
AE	33 (71.7)	
Infection	3 (6.5)	
Pulmonary embolism	1 (2.1)	
Others	9 (19.5)	
AE		
—	1599 (90.7)	
+	164 (9.3)*	
Days from operation to AE		7 (0-29)
Outcome of AE		
Alive	92 (56.1)	
Death	72 (43.9)	
Days from AE to death		20 (1-82)
Side of AE		
Operation side	22 (14.2)	
Contralateral	39 (25.2)	
Bilateral	94 (60.6)	

AE, Acute exacerbation (occurring within 30 days after pulmonary resection). *9.3%; 95% CI, 8.0-10.8.

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TABLE 3. Results of multivariate logistic regression analyses of acute exacerbation in all patients and in the usual interstitial pneumonia subgroup

Factors	All patients (n = 1763)					UIP subgroup (n = 1235)*				
	Patients (n)	AE (%)	OR	95% CI	P value	Patients (n)	AE (%)	OR	95% CI	P value
Surgical procedures					.0005†					.0005†
Wedge resection	275	10 (3.6)	1.000	—	—	202	10 (5.0)	1.000	—	—
Lobectomy/segmentectomy	1386	138 (10.0)	3.83	1.941-7.567	.0001	955	100 (10.5)	2.91	1.453-5.847	.0026
Bilobectomy/pneumectomy	94	15 (16.0)	5.7	2.381-13.66	.0001	70	14 (20.0)	5.96	2.413-14.74	.0001
N/A	8	1 (12.5)				8	1 (12.5)			
KL-6 (U/mL)										
<1000‡	834	68 (8.2)	1.000	—	—	571	56 (9.8)	1.000	—	—
≥1000	209	34 (16.3)	2.14	1.344-3.394	.0013	151	27 (17.9)	2.02	1.199-3.408	.0083
N/A	720	62 (8.6)				513	42 (8.2)			
Sex										
Male	1593	158 (9.9)	1.000	—	—	1138	123 (10.8)	1.000	—	—
Female	170	6 (3.5)	0.3	0.126-0.688	.0047	97	2 (2.1)	0.18	0.043-0.737	.0172
%VC										
<80	263	36 (13.7)	1.000	—	—	191	30 (15.7)	1.000	—	—
≥80	1478	126 (8.5)	0.63	0.417-0.959	.0308	1033	94 (9.1)	0.57	0.350-0.884	.0131
N/A	22	2 (9.1)				11	1 (9.1)			
History of AE										
—	1741	158 (9.1)	1.000	—	—	1223	120 (9.8)	1.000	—	—
+	20	6 (30.0)	3.24	1.063-9.897	.0387	10	5 (50.0)	7.67	1.997-29.42	.0030
N/A	2	0 (0.0)				2	0 (0.0)			
Preoperative steroid use										
—	1651	144 (8.7)	1.000	—	—					
+	103	20 (19.4)	2.46	1.356-4.454	.0031					
N/A	9	0 (0.0)								
CT findings										
UIP pattern	1300	134 (10.3)	1.000	—	—					
Non-UIP pattern	463	30 (6.5)	0.59	0.386-0.900	.0143					

AE, Acute exacerbation; CI, confidence interval; CT, computed tomography; N/A, not available; OR, odds ratio; %VC, percent vital capacity; UIP, usual interstitial pneumonia.

*Cases with collagen diseases were excluded (n = 65). †P value among 3 surgical procedure categories. ‡The cutoff value of 1000 U/mL was determined on the basis of the result of the receiver operating characteristic analysis.

AE, preoperative steroid use, and surgical procedures were identified as possible risk factors of AE in the univariate analyses. Multivariate analysis using these factors identified surgical procedures, history of AE, KL-6, %VC, and male sex as independent risk factors (Table 3).

Prophylactics and Acute Exacerbation

During the perioperative period, 31% of the patients were administered prophylactics. Steroids were the most common drug for this purpose (11.4%), followed by sivelestat (6.7%) and a combination of steroid and sivelestat (5.4%). The results of multivariate analyses adjusted with the aforementioned AE risk factors (surgical procedures, sex, KL-6, preoperative steroid use, %VC, radiologic findings, and history of AE) are shown in Table 4. Drug administration, whether given individually or in combinations, did not show any positive effects in preventing AE.

Morbidity and Mortality of Pulmonary Resection

Outcomes involving the morbidity and mortality of pulmonary resections are summarized in Table 2. The 30-day

mortality rate was 2.6%, and the most frequent cause of death was AE. In patients with an AE, the mortality rate was 43.9%. Days from AE to death varied from 1 to 82 days (median, 20 days).

TABLE 4. Use of prophylactics and acute exacerbation

Factors	No. of patients (%)	OR	95% CI	P value
Prophylactics				
—	1216 (69)	1.000	—	—
+	544 (31)	1.047	0.724-1.513	.808
Steroid	194 (11.4)	0.862	0.491-1.514	.605
Sivelestat	115 (6.7)	1.397	0.752-2.596	.290
Sivelestat + steroid	92 (5.4)	0.749	0.338-1.661	.477
Ulinastatin	69 (4.0)	2.488	1.266-4.887	.008
Sivelestat + ulinastatin	5 (0.3)	1.302	0.109-15.49	.835
Steroid + ulinastatin	11 (0.6)	0.000	N/A	N/A
Sivelestat + steroid + ulinastatin	4 (0.2)	1.035	0.089-12.03	.978

Adjusted for surgical procedures, KL-6, preoperative steroid use, sex, CT findings, %VC, and history of AE. CI, Confidence interval; OR, odds ratio.

DISCUSSION

AE of interstitial pneumonia is a rapidly progressive disorder often observed in patients with ILDs. Its clinical course is specific and distinguishable from infectious pneumonia. The criteria for identifying AE of pulmonary fibrosis include an unexplained rapid worsening of dyspnea, severely impaired gas exchange, new radiographic diffuse alveolar infiltrates, and the absence of alternate causes, such as infectious pneumonia, pulmonary embolism, pneumothorax, and heart failure.²⁰ Thoracic surgery for patients with ILDs, including open lung biopsy and bronchoalveolar lavage, may trigger this decompensating acute respiratory failure.^{6,21} The mortality rate of AE is reportedly high⁵⁻⁸ and has been shown to be the major cause of death for patients with lung cancer after pulmonary resection in a report cumulating more than 10,000 cases from the Japanese Joint Committee for Lung Cancer Registration and in the 2009 annual report of the Japanese Association for Thoracic Surgery.^{22,23} In light of these circumstances, identifying the possible risk factors for AE and enabling the stratification of patients according to risk are relevant for chest surgeons to reduce operation-related mortality and improve the outcomes of pulmonary resection in patients with lung cancer. To address these issues, we focused on patients with ILDs with lung cancer and found that the incidence of AE was 0.4% in patients with non-small cell lung cancer and 9.3% in similar patients with ILDs; to the best of our knowledge, these are the first such figures reported with high statistical reliability in a large-scale multi-institutional study. These figures were comparable to the incidences documented in past reports, including those of the aforementioned studies,²¹⁻²⁶ and indicate the difficulties in the treatment of patients with lung cancer with ILDs. The similarities observed in incidences have important implications for further comparisons with other anticancer therapies, such as chemotherapy and radiotherapy, which have been shown to be associated with this fatal complication at the rate of 20% to 42.9%.^{3,4}

We identified 7 risk factors for AE: surgical procedures, elevated KL-6, sex, reduced %VC, history of AE, preoperative steroid use, and UIP pattern on CT scan. Surgical procedures showed the strongest association with the incidence of AE. Anatomic resection would result in more serious insult to patients' lungs when compared with wedge resection, because the former requires longer operation time and increased hilar vascular procedures and node dissection, which may hinder the lymphatic flow. In addition to damage caused by perioperative patient management (eg, fluid overload, 1-lung ventilation, positive pressure ventilation, and high concentration oxygen exposure), the resection of larger lung volume likely gives greater stress to the endothelium, which may result in AE. Likewise, the effect of a reduced vascular bed is substantial in patients with lower

%VC because their residual lung volume is relatively small, which may result in a higher incidence of AE. These speculations are supported by our findings that the risk of AE gradually increased according to the volume of lung removed (wedge resection < segmentectomy < lobectomy < bilobectomy < pneumonectomy). The less-invasive video-assisted thoracoscopic surgery procedures did not reduce the risk of AE.

The possible effects of blood transfusions on AE also were considered. We conducted a risk-adjusted evaluation using transfusions and the other 7 covariates, which showed a significant association between transfusion and AE (OR, 2.04; 95% CI, 1.22-3.40; $P = .006$). However, transfusion also was observed to be highly correlated to the operative procedures, which may bring about possible effects of multicollinearity if included in the same model. Furthermore, the need for transfusions and operation time are to a large degree unpredictable before surgery, which reduces their potential effectiveness for preoperative identification of patients at high risk of developing AE. However, general operation time and the risk of bleeding can be grouped within the types of surgical procedures. The inclusion of surgical procedures in the regression models may therefore adjust for operation time and transfusions.

There are limited data on the value of serum biomarkers in patients with ILDs. Among the clinical laboratory variables, only KL-6 was identified as an independent risk factor for AE, where patients with KL-6 levels more than 1000 IU had an AE incidence twice that of patients with lower levels. KL-6, a circulating glycoprotein expressed from type 2 alveolar pneumocytes and bronchiolar epithelial cells, has been established as an indicator of damage to alveolar cells.^{27,28} Elevated KL-6 levels have been documented in patients who had developed acute lung injury (ALI) or acute respiratory distress syndrome (ARDS), and this relationship may be used to predict patient outcomes. In interstitial pneumonia, KL-6 is an independent factor reflecting the degree of clinical disease activity, confirmed by Ga-citrate scintigraphy and clinical course.²⁷ Our observations in which KL-6 was identified as a risk factor have clinical significance because the elevated level of serum KL-6 indicates increased alveolar-capillary permeability, which can lead to diffuse alveolar damage—the initial and essential aspect of AE.

Our results indicated that men had 3 times the risk of developing AE than women. An additional analysis showed that smoking history and the Brinkman index were higher in men than in women; however, the results did not show any significant association between a smoking habit and AE incidence. Ruffini and colleagues documented that ALI/ARDS developed in male patients at approximately 4 times the rate of female patients,²⁴ so the male lung may be more susceptible to the insult of surgical intervention.

Although %DLCO and %VC have been considered reliable indicators of fibrotic change,^{12,13,17} an analysis of lung function (including FEV1, FEV1%, %DLCO, and %VC) showed that only %VC had a significant and independent association with AE incidence, which was congruent with the results reported by Kushibe and colleagues²⁹ and Shintani and colleagues.³⁰

Our analysis showed that preoperative steroid use and history of AE were independent risk factors for AE, which is consistent with clinical expectations. These findings represent the first time that the statistical associations between these factors have been documented.

The findings in which patients with UIP patterns in CT scans had a higher risk of developing AE also are consistent with clinical expectations, because honeycomb lesions have been reported to be associated with IPF and act as a prognostic factor.³¹⁻³³ Our own data corroborate this, because patients with distinct honeycomb lesions had a higher risk of developing AE (OR, 1.800; 95% CI, 1.157-2.800; $P = .009$). Further evaluation of the relationship between the extent and the prevalence of honeycomb lesions in CT scans and AE is required, which we were unable to do in our large retrospective cohort study.

There is no current consensus among the numerous studies regarding the relationship between prophylactic use and postoperative AE.⁵ Prophylactic steroids are a common agent with an anti-inflammatory and stabilizing effect on alveolar cells. However, previous studies with comparatively large cohorts also have revealed no preventive effects from the perioperative administration of steroids.^{16,25} Neutrophil elastase is known to cause endothelial cell injury and increase epithelial permeability, thereby playing an important role in ALI or ARDS. Sivelestat sodium hydrate is a neutrophil elastase inhibitor, and although its clinical efficacy has yet to be clearly demonstrated,³⁴ it is widely used for the treatment of ALI in Japan. In our cohort, up to 216 patients (12%) had been administered sivelestat in the perioperative period, ostensibly for its prophylactic effects on AE. In our retrospective study, these prophylactics showed no positive effect on AE prevention. A randomized prospective study on the effects of prophylactics, such as macrolides, N-acetylcysteine, and pirfenidone, is required to gain a clearer understanding of this relationship.

Study Limitations

This study has several limitations that should be considered in the interpretation of the results. First, this was a retrospective cohort study, which may not necessarily reflect the characteristics of the entire population with this disease entity. Second, the primary inclusion criterion was CT appearance of ILDs. Although radiologic diagnoses were made by each individual institute following criteria based on widely used guidelines,^{12,17} UIP diagnosis may

vary among the institutes. We were unable to conduct a centrally controlled review of this aspect of the diagnosis, particularly of the extent and area of honeycomb lesion, which are putative risk factors for the AE.

CONCLUSIONS

In this study, we have clarified the incidence, risk factors, and outcomes of postoperative AE in patients with lung cancer with ILDs who had undergone pulmonary resection. These results provide essential information for comparisons with other anticancer therapies, such as chemotherapy and radiotherapy. We identified 7 risk factors for AE onset. By evaluating the presence and degree of the identified risk factors before surgery, we can stratify patients and identify those at high risk for pulmonary resection. Surgical procedures were found to be the strongest risk factor and may represent a crucial step in reducing the incidence of this potentially fatal complication. The findings in this study provide essential information to support fair and objective decision-making by oncologists in the treatment of this difficult entity.

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APPENDIX E1. PARTICIPATING CENTERS AND INVESTIGATORS

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TABLE E1. Univariable analysis for acute exacerbation

Factors	Categories	Numbers	OR	95% CI	P value
Age		1763	1.017	0.994-1.041	.141
Sex	Male	1593	1.000	—	—
	Female	170	0.332	0.145-0.763	.009
BMI		1746	0.980	0.930-1.031	.434
Smoking history	Never smoker	109	1.000	—	—
	Ex-smoker	1006	1.336	0.657-2.720	.424
	Current smoker	632	0.893	0.424-1.879	.765
Brinkman index		1742	1.000	1.000-1.000	.413
Comorbidities					
Asthma	—	1742	1.000	—	—
	+	33	0.971	0.293-3.217	.962
Emphysema	—	1167	1.000	—	—
	+	589	0.778	0.546-1.109	.165
Collagen disease	—	1654	1.000	—	—
	+	102	0.936	0.463-1.892	.854
Neoadjuvant chemotherapy	—	1686	1.000	—	—
	+	73	1.207	0.569-2.562	.624
Neoadjuvant radiation	—	1728	1.000	—	—
	+	32	1.401	0.485-4.044	.533
WBC (/μL)		1737	1.000	1.000-1.000	.111
CRP (g/dL)	<2.0	1462	1.000	—	—
	>2.0	231	1.425	0.923-2.201	.110
LDH (IU/L)		1730	1.002	1.000-1.004	.064
KL-6 (U/mL)	<1000	834	1.000	—	—
	>1000	209	2.189	1.405-3.409	<.001
CEA (ng/mL)		1664	1.000	0.997-1.004	.883
Pao ₂ (torr)		1552	0.996	0.981-1.011	.609
Paco ₂ (torr)		1547	0.954	0.914-0.995	.030
VC (L)		1750	0.566	0.441-0.728	<.001
%VC	<80	263	1.000	—	—
	>80	1478	0.588	0.395-0.873	.009
FEV1 (L)		1748	0.683	0.496-0.941	.020
FEV1%	<70	460	1.000	—	—
	>70	1289	1.500	1.003-2.243	.048
%FEV1		1742	0.995	0.987-1.002	.176
DLCO (mL/min/torr)		1121	0.957	0.916-0.999	.047

(Continued)

TABLE E1. Continued

Factors	Categories	Numbers	OR	95% CI	P value
%DLCO		1128	0.997	0.989-1.006	.532
Radiologic findings	UIP pattern	1300	1.000	—	—
	Non-UIP pattern	463	0.603	0.400-0.909	.016
Pathologic findings	UIP pattern	709	1.000	—	—
	Non-UIP pattern	418	0.904	0.608-1.343	.616
	No IP diagnosis	426	0.635	0.411-0.981	.041
History of AE	—	1741	1.000	—	—
	+	20	4.295	1.628-11.33	.003
Preoperative steroid use	—	1651	1.000	—	—
	+	103	2.522	1.504-4.231	<.001
pTNM stage	1a	547	1.000	—	—
	1b	481	1.349	0.858-2.120	.195
	2a	70	1.488	0.638-3.474	.358
	2b	241	1.832	1.101-3.049	.020
	3a	244	2.022	1.230-3.323	.006
	3b	114	1.011	0.459-2.229	.979
	4	34	2.309	0.846-6.307	.103
Operation time (min)		1753	1.003	1.002-1.005	<.001
Bleeding (mL)		1744	1.001	1.000-1.001	<.001
Transfusion	—	1629	1.000	—	—
	+	124	2.276	1.392-3.723	.001
Surgical procedures	Wedge Resection	275	1.000	—	—
	Segmentectomy/lobectomy	1386	2.930	1.521-5.644	.001
	Bilobectomy/pneumonectomy	94	5.032	2.175-11.64	<.001
Tumor location	Upper lobe	670	1.000	—	—
	Middle lobe	77	0.963	0.445-2.083	.924
	Lower lobe	958	0.705	0.502-0.991	.044
	Multiple	5	0.000	N/A	
VATS	—	964	1.000	—	—
	+	798	1.199	0.869-1.654	.268
Node dissection	0	311	1.000	—	—
	1	339	2.979	1.559-5.694	.001
	2	1104	2.587	1.436-4.661	.002

AE, Acute exacerbation; BMI, body mass index; CEA, carcinoembryonic antigen; CI, confidence interval; CRP, C-reactive protein; DLCO, diffusing capacity for carbon monoxide; FEV1, forced expiratory volume in 1 second; IP, interstitial pneumonia; LDH, lactate dehydrogenase; OR, odds ratio; Paco₂, partial pressure of carbon dioxide; Pao₂, partial pressure of oxygen; UIP, usual interstitial pneumonia; VATS, video-assisted thoracic surgery; VC, vital capacity; WBC, white blood cell; %VC, percent vital capacity; FEV1%, percent forced expiratory volume in 1 second; %DLCO, percent predicted diffusing capacity for carbon monoxide.