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Original Article

Associations between Comorbidities and Acute Exacerbation of Interstitial Lung Disease after Primary Lung Cancer Surgery

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Acute exacerbation (AE) of interstitial lung disease (ILD) is a severe complication of lung resection in lung cancer patients with ILD (LC-ILD). This study aimed to assess the predictive value of comorbidities other than ILD for postoperative AE in patients with LC-ILD. We retrospectively evaluated 68 patients with LC-ILD who had undergone lung resection. We classified them into two groups: those who had developed postoperative AE within 30 days after resection and those who had not. We analyzed patient characteristics, high-resolution computed tomography findings, clinical data, pulmonary function, and intraoperative data. The incidence of postoperative AEs was 11.8%. In univariate analysis, performance status (PS), honeycombing, forced vital capacity (FVC), and high hemoglobin A1c (HbA1c) levels without comorbidities were significantly associated with postoperative AE. Patients were divided into two groups according to cutoff levels of those four variables as determined by receiver operating characteristic curves, revealing that the rates of patients without postoperative AE differed significantly between groups. The present results suggested that preoperative comorbidities other than ILD were not risk factors for postoperative AE in patients with LC-ILD. However, a high preoperative HbA1c level, poor PS, low FVC, and honeycombing may be associated with postoperative AE of LC-ILD.

Key words: lung cancer, interstitial lung disease, acute exacerbation, comorbidity

Interstitial lung disease (ILD) often complicates lung cancer (LC), and acute exacerbation (AE) of ILD is a severe complication of pulmonary resection in patients with LC. In a large multicenter cohort study in Japan, the postoperative AE incidence was 9.3% and the mortality rate of LC-ILD was 43.9% [1]. Thus, it is clinically important to clarify the associated risk factors in order to prevent postoperative AE.

Several studies have identified the preoperative risk factors for postoperative AE of LC-ILD. Evaluating a Japanese cohort, Sato *et al.* reported seven predictors of postoperative AE (sex, history of AE, preoperative steroid use, high-resolution computed tomography (HRCT) pattern, surgical procedure, serum Krebs von den Lungen-6 (KL-6) level, and vital capacity (VC)) and assessed them to develop a simple risk score [2]. It has also been reported that serum levels of lactate dehydrogenase and C-reactive protein (CRP), intraoperative respiratory management, and water balance were associated with postoperative AE [3-5]. However, comorbidities other than ILD have not been investigated thoroughly. If several comorbidities are risk factors for postoperative AE in patients with LC-ILD, preoperative interventions for comorbidities may reduce postoperative AE risk.

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The study aimed to evaluate the ability of each of several comorbidities to predict AE in patients with LC-ILD.

Materials and Methods

Study population. This was a retrospective, case-control, single-center, observational study. Between July 2010 and March 2017, 534 patients underwent lung resection for primary LC at Ehime University Hospital. Subjects were excluded if they had had LC without ILD or had undergone thoracotomy. We classified the patients into two groups: those who had developed postoperative AE within 30 days after resection (Group A) and those who had not (Group N). In both groups, we collected the following data from medical records: patient characteristics, Eastern Cooperative Oncology Group performance status (PS) score, Charlson Comorbidity Index (CCI), preoperative steroid use, history of AE, HRCT pattern of ILD, presence of honeycombing on HRCT, preoperative blood test [including lactate dehydrogenase, CRP, KL-6, and hemoglobin A1c (HbA1c)], pulmonary function indices, and surgical and anesthesia procedures. Except for the surgical and anesthesia procedures, these data were obtained within 2 months before surgery.

Definition of ILD and HRCT pattern of ILDs. ILD was diagnosed in accordance with the clinical criteria established by the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association statement guidelines [6]. Two independent pulmonologists evaluated the HRCT pattern (UIP/Probable UIP/Indeterminate for UIP/Alternative Diagnosis) and the presence of honeycombing on HRCT. Secondary ILDs (such as collagen vascular disease-related ILD) were also included.

Definition of postoperative AE. We defined postoperative AE on the basis of three criteria with reference to international working group reports [6,7]: (1) dyspnea that appeared or worsened within 30 days after resection, (2) new bilateral ground-glass opacity on chest HRCT, and (3) unexplained worsening with alternative etiologies (infection, heart failure, and pulmonary embolism). Triggered AE was included because subclinical micro-aspiration, drugs, and mechanical stress during surgery could not be excluded.

CCI and gender, age, and physiology index. Preoperative comorbidity status was assessed by the CCI, which is the sum of the weighted scores of 19 comorbid conditions (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes, hemiplegia, moderate or severe renal disease, diabetes with end organ damage, any tumor, leukemia, lymphoma, moderate or severe liver disease, metastatic solid tumor, and acquired immunodeficiency syndrome) [8].

We also evaluated the gender, age, and physiology score, a quick and simple index for estimating mortality risk in patients with idiopathic pulmonary fibrosis. This score is based on four commonly measured variables: sex, age, % predicted forced vital capacity (FVC), and % predicted diffusing capacity of the lung for carbon monoxide (DLco) [9].

Spirometry. Pulmonary function indices (*i.e.*, VC, FVC, and forced expiratory volume in 1 sec) were measured via spirometry. DLco was measured using the single-breath method. These indices were calculated as percentages of the predicted normal values.

Statistical analyses. Continuous and categorical variables were expressed as medians with interquartile ranges and as numbers and percentages, respectively. We used the κ statistic to evaluate the degree of concordance between the two pulmonologists for the HRCT pattern and the presence of honeycombing. Comparisons between the two groups were performed using the Mann-Whitney *U* test for continuous variables to confirm non-normal distributions in the histogram and Fisher's exact test for categorical variables. Univariate analyses via logistic regression analysis were also performed to analyze predictors of postoperative AE. Receiver operating characteristic (ROC) curves were used to find an optimal cutoff level that could discriminate between patients with and without postoperative AE. Cutoff levels were set as the closest point to 100% sensitivity and specificity. The Kaplan-Meier method was used to evaluate the predictive value for AE, and comparisons were made using a log-rank test. *P*-values <0.05 in the two-tailed test were considered statistically significant. All statistical analyses were conducted using EZR version 1.54.

Ethics statement. This study complied with the standards of the Declaration of Helsinki and current ethics guidelines and was approved by the institutional ethics board (approval number 1808002). Informed patient consent was waived because this was a noninterventional and retrospective study. However, participants were allowed to opt out of the study and maintain patient confidentiality.

Results

Clinical characteristics of patients. Among the 534 patients, 72 were diagnosed with LC-ILD. We excluded 4 patients who had undergone thoracotomy. The remaining 68 patients were included in this study (Fig. 1). These were classified into two groups: those who had developed (Group A, n = 8) and those who had not developed (Group N, n = 60) AE within 30 days after resection.

Patient characteristics are shown in Table 1. In the present study, the median age was 76 years and most patients were men. Many patients had a PS < 1. The median values of blood test data and pulmonary function data were within normal limits. The HRCT pattern and the presence of honeycombing on HRCT were evaluated by two pulmonologists, between whom concordance was good (κ = 0.63 for HRCT pattern, and 0.76 for presence of honeycombing). The numbers of patients with UIP/probable UIP/indeterminate for UIP/alternative diagnosis on HRCT pattern were 13, 4, 45 and 6, respectively. The numbers of patients with and without honeycombing were 13 and 55, respectively. None of the patients received anti-fibrosis drugs or neoadjuvant therapy, including chemotherapy and radiation therapy. There were no statistically significant differences in HbA1c levels between patients with and without preoperative steroid use ($p = 0.485$).

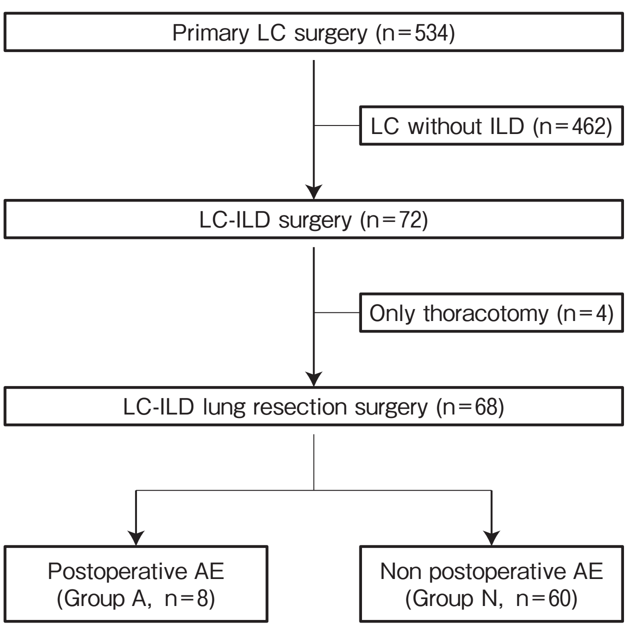

Fig. 1 Flow chart for study participants. LC, lung cancer; ILD, interstitial lung disease; AE, acute exacerbation.

The proportion of patients with honeycombing and the HbA1c levels were significantly higher in Group A than in Group N, while VC, FVC, and %FVC were significantly lower in Group A than in Group N (Table 1). In the other variables, including the CCI and patient ratio of each comorbidity, there were no significant differences between the two groups. Because no patients had dementia, hemiplegia, leukemia, lymphoma, or acquired immunodeficiency syndrome, and all patients had chronic pulmonary disease, these variables are not included in Table 1.

Analysis of predictive parameters for postoperative AE. Univariate logistic regression analysis showed that PS, honeycombing, HbA1c level, and FVC were significantly correlated with postoperative AE (Table 2).

We described the ROC curves for PS, HbA1c, and FVC and evaluated the areas under the curve (AUC) and cutoff levels (Table 3). The AUCs were similar among the variables. Sensitivity for HbA1c and specificity for PS were the highest among the four variables.

We classified patients according to the above cutoff level and used the Kaplan-Meier method to estimate postoperative AE. In all four variables, the rates of patients without postoperative AE differed significantly between the two groups (Fig. 2).

Clinical data of patients with postoperative AE. Clinical data of patients with postoperative AE are shown in Table 4. The median postoperative day until AE occurred was 6.5 days (2-14 days). Only one patient died of AE within 30 days after resection. This patient had a history of renal transplantation therapy and had been treated with methylprednisolone and azathioprine as graft rejection depressors for a long period.

Discussion

We investigated the predictive factors of postoperative AE after pulmonary resection for LC-ILD. The results suggested that postoperative AE of LC-ILD was

Table 1 Patient characteristics

Variables	Total (n=68)	Group A (n=8)	Group N (n=60)	*P*-value
Age (years)	76 [71, 81]	74 [73, 80]	76 [71, 81]	0.939
Sex (M/F)	62/6	7/1	55/5	0.543
BMI (kg/m^2)	24.5 [21.0, 26.6]	24.4 [20.7, 27.4]	24.6 [21.0, 26.5]	0.977
Smoking history (+/−)	63/5	8/0	55/5	1.000
Performance status (0/1/2/3/4)	54/10/3/1/0	3/3/2/0/0	51/7/1/1/0	0.003
Charlson Comorbidity Index	4 [3, 4]	4 [4, 4.25]	4 [3, 4]	0.322
Myocardial infarction (+/−)	5/63	0/8	5/55	1.000
Congestive heart failure (+/−)	1/67	1/7	0/60	0.118
Peripheral vascular disease (+/−)	4/64	1/7	3/57	0.401
Moderate or severe renal disease (+/−)	1/67	1/7	0/60	0.118
Ulcer disease (+/−)	7/61	0/8	7/53	0.587
Liver disease (+/−)	8/60	2/6	6/54	0.236
Diabetes mellitus (+/−)	23/45	4/4	19/41	0.429
Cerebrovascular disease (+/−)	10/58	0/8	10/50	0.593
Connective tissue disease (+/−)	4/64	0/8	4/56	1.000
Preoperative steroid use (+/−)	7/61	1/7	6/54	1.000
Preoperative immunosuppressant use (+/−)	4/64	1/7	3/57	0.401
History of AE (+/−)	2/66	1/7	1/59	0.223
Radiologic findings				
Emphysema (+/−)	58/10	8/0	50/10	0.593
Honeycombing (+/−)	13/55	4/4	9/51	0.038
HRCT pattern (UIP/probable/indeterminate/alternative diagnosis)	13/4/45/6	4/0/3/1	9/4/42/5	0.097
GAP score	3 [3, 3]	3 [3, 3.25]	3 [3, 3]	0.434
Blood Test				
LDH (U/l)	220 [185, 241]	211 [186, 229]	220 [187, 242]	0.607
CRP (mg/dl)	0.17 [0.07, 0.35]	0.18 [0.15, 0.66]	0.17 [0.07, 0.33]	0.463
KL-6 (U/ml)	444 [328, 740]	473 [371, 653]	433 [327, 733]	0.871
HbA1c (%)	6.1 [5.6, 6.6]	6.3 [6.2, 7.5]	6.0 [5.6, 6.4]	0.030
Pulmonary function test				
VC (l)	3.11 [2.79, 3.59]	2.55 [2.29, 2.98]	3.18 [2.89, 3.62]	0.027
%VC (%)	102.9 [91.7, 116.8]	87.3 [78.3, 112.4]	103.9 [93.5, 116.9]	0.114
FVC (l)	3.10 [2.79, 3.59]	2.55 [2.16, 2.93]	3.21 [2.87, 3.61]	0.019
%FVC (%)	106.0 [90.6, 117.9]	87.3 [77.2, 106.7]	106.5 [94.1, 118.2]	0.049
$FEV_{1.0}$ (l)	2.28 [2.02, 2.60]	2.09 [1.83, 2.20]	2.32 [2.05, 2.62]	0.092
%$FEV_{1.0}$ (%)	108.7 [96.8, 126.8]	100.9 [95.0, 120.6]	110.2 [97.1, 126.3]	0.601
DLco (ml/min/mmHg)	12.1 [9.3, 15.5]	11.1 [8.96, 13.2]	12.2 [9.42, 15.5]	0.332
%DLco (%)	85.3 [72.2, 99.0]	81.4 [73.2, 88.4]	87.8 [72.3, 98.3]	0.499

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Variables	Total (n=68)	Group A (n=8)	Group N (n=60)	*P*-value
Surgical procedure (wedge resection/segmentectomy/lobectomy)	23/2/42	2/0/6	21/2/36	0.697
Surgical time (min)	172 [107, 205]	157 [111, 190]	175 [107, 211]	0.505
O_2 consumption (l)	435 [347, 677]	487 [438, 642]	420 [332, 625]	0.429
In-Out balance (l)	+1.32 [+0.86, +1.83]	+1.42 [+0.78, +1.85]	+1.32 [+0.92, +1.82]	0.992

Results are median values (interquartile ranges in parentheses).
BMI, body mass index; AE, acute exacerbation; HRCT, high resolution computed tomography; UIP, usual interstitial pneumonia; GAP score, gender, age, and physiology score; LDH, lactate dehydrogenase; CRP, C-reactive protein; HbA1c, hemoglobin A1c; VC, vital capacity; FVC, forced vital capacity; $FEV_{1.0}$, forced expiratory volume in one second; DLco, diffusing capacity of lung for carbon monoxide.

Table 2 Univariate logistic regression analysis of predictive parameters for postoperative AE

Variables	Odds ratio	95% CI	*P*-value
Age	1.015	0.912–1.131	0.782
Sex (Male)	1.571	0.160–15.465	0.698
BMI	0.963	0.802–1.157	0.690
Performance status	3.322	1.265–8.724	0.015
Charlson Comorbidity Index	2.020	0.831–4.910	0.121
Liver disease	3.000	0.491–18.300	0.234
Peripheral vascular disease	2.714	0.274–29.784	0.414
Diabetes mellitus	2.158	0.487–9.564	0.311
Preoperative steroid use	1.286	0.134–12.305	0.827
History of AE	8.429	0.473–150.212	0.147
Radiologic findings			
Honeycombing	5.667	1.195–26.874	0.029
GAP score	1.705	0.488–5.963	0.403
Blood test			
LDH	0.995	0.979–1.012	0.584
CRP	1.113	0.599–2.068	0.735
KL-6	0.999	0.997–1.001	0.607
HbA1c	2.952	1.157–7.530	0.023
Pulmonary function test			
VC	0.271	0.072–1.018	0.053
%VC	0.969	0.929–1.010	0.134
FVC	0.241	0.064–0.914	0.036
%FVC	0.963	0.923–1.006	0.088
$FEV_{1.0}$	0.243	0.046–1.291	0.097
$\%FEV_{1.0}$	0.993	0.962–1.025	0.652
DLco	0.890	0.718–1.103	0.287
%DLco	0.989	0.955–1.023	0.517
Surgical procedure (not WR)	1.615	0.299–8.719	0.577
Surgical time	0.998	0.986–1.009	0.675
O_2 consumption	1.000	0.998–1.002	0.988
In-Out balance	1.000	0.999–1.001	0.821

BMI, body mass index; AE, acute exacerbation; GAP score, gender, age, and physiology score; LDH, lactate dehydrogenase; CRP, C-reactive protein; HbA1c, hemoglobin A1c; VC, vital capacity; FVC, forced vital capacity; $FEV_{1.0}$, forced expiratory volume in one second; DLco, diffusing capacity of lung for carbon monoxide; WR, wedge resection.

associated with preoperative PS, honeycombing, HbA1c level, and FVC, but not with several comorbidities.

The present study demonstrated that comorbidities were not associated with postoperative AE. This result might be influenced by the status of the comorbidities in the individual patients. That is, because the present patients underwent thoracic surgery, attempts would have been made to control any comorbidities before surgery. Indeed, in a previous report on patients undergoing lung resection for non-small cell lung cancer, none of the examined comorbidities affected the rates of postoperative complications or survival [10]. On the other hand, Pedraza-Serrano *et al.* reported that several comorbidities, including peripheral vascular disease, cerebrovascular disease, dementia, mild liver disease, cancer, and pulmonary hypertension, were associated with in-hospital mortality in patients with ILD [11]. In addition, Ando *et al.* showed that comorbidities and CCI were prognostic factors in patients with chronic ILD without honeycombing [12]. Although the

Table 3 Receiver operating characteristic curve analysis of predictive parameters for postoperative AE

Variables	AUC	Cut-Off Level	Sensitivity	Specificity
Performance status	0.744	1	25	96.7
Honeycombing	NE	NE	50	85
HbA1c	0.739	6.1	87.5	51.7
FVC	0.758	2.92	75	71.7

AE, acute exacerbation; AUC, area under the curve; HbA1c, hemoglobin A1c; FVC, forced vital capacity; NE, not evaluated.

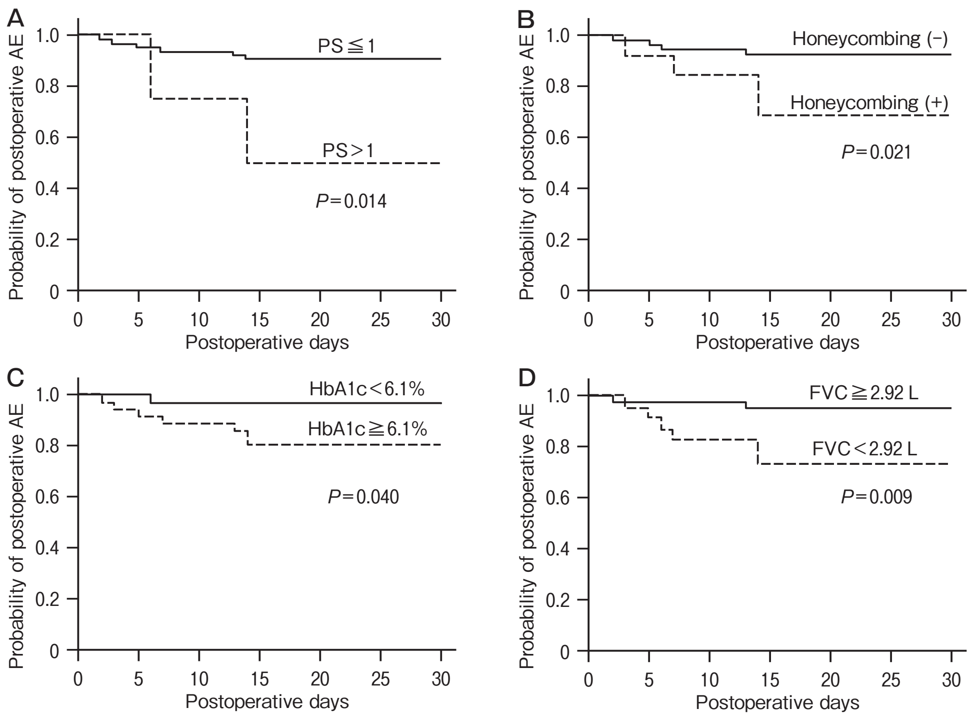

Fig. 2 Kaplan-Meier curves of probability of postoperative AE. Patients were divided into two groups according to the cutoff value of each variable [(A) PS, (B) Honeycombing, (C) HbA1c, and (D) FVC] determined by receiver operating characteristic curves. Statistical analysis was performed using the log-rank test. AE, acute exacerbation; PS, performance status; HbA1c, hemoglobin A1c; FVC, forced vital capacity.

end points and inclusion criteria in previous studies differed from those in our study, uncontrolled comorbidities may also influence postoperative AE.

The present study demonstrated that a high preoperative HbA1c level was a significant risk factor for postoperative AE. HbA1c is a common clinical test to evaluate average blood glucose levels over the past 1-2 months and is a good indicator of chronic hyperglycemia [13,14]. Previous studies reported associations between preoperative HbA1c levels and postoperative complications. Jehan *et al.* revealed that the preoperative HbA1c level independently predicts postoperative hyperglycemia in patients undergoing emergency general surgery [15]. Arya *et al.* reported that peripheral artery disease patients with high preoperative HbA1c levels have significantly high risks of amputation and major advanced limb events after revascularization [16]. It was also reported that a high preoperative HbA1c

Table 4 Clinical data of patients with postoperative AE

	Age (years)	Sex	PS	CCI	Honey-combimg	FVC(l)	HbA1c (%)	Preoperative steroid use	Surgical time (min)	Surgical procedure	Onset of AE (post-operative day)	Post-operative complication	Initial Treatment for AE	Outcome
Case 1	74	Male	1	4	(+)	2.12	7.5	(−)	195	lobectomy	14	(−)	Steroid pulse	Survived
Case 2	68	Male	1	7	(+)	2.62	7.6	(+)	205	lobectomy	3	(−)	Steroid pulse + Sivelestat	Dead
Case 3	71	Male	0	4	(+)	2.47	6.4	(−)	145	lobectomy	7	(−)	Steroid pulse	Survived
Case 4	74	Male	0	4	(−)	2.89	6.1	(−)	151	lobectomy	5	bacterial pneumonia	PSL 0.5 mg/kg/day	Survived
Case 5	74	Male	2	3	(+)	2.03	6.2	(−)	163	lobectomy	14	(−)	Steroid pulse	Survived
Case 6	78	Male	0	5	(−)	4.34	8.4	(−)	176	lobectomy	13	bacterial pneumonia	PSL 0.5 mg/kg/day	Survived
Case 7	85	Male	1	4	(−)	3.04	6.2	(−)	100	wedge resection	2	aspiration pneumonia	PSL 0.5 mg/kg/day	Survived
Case 8	84	Female	2	4	(−)	2.17	5.7	(−)	95	wedge resection	6	bacterial pneumonia	PSL 2.0 mg/kg/day	Survived

AE, acute exacerbation; PS, performance status; CCI, Charlson comorbidity index; FVC, forced vital capacity; HbA1c, hemoglobin A1c; PSL, prednisolone.

level was a risk factor for surgical site infections after replacement arthroplasty or spine surgery [17,18]. Regarding associations between HbA1c levels and postoperative AE, no reports have evaluated this phenomenon. On the other hand, it was reported that diabetes is one of the factors associated with significantly higher mortality in patients with idiopathic pulmonary fibrosis [19]. In the present study, preoperative HbA1c levels were significantly high in the postoperative AE group. Upon dividing patients into two groups based on cutoff levels of HbA1c determined by ROC curves, the rates of patients without postoperative AE differed significantly between the two groups. These results suggested that chronic hyperglycemia assessed by HbA1c may be a predictor of postoperative AE.

Unlike the preoperative Hba1c level, a history of diabetes mellitus was not significantly associated with postoperative AE. This result suggested that strictly controlling glucose levels lowers the risk of postoperative AE, even in patients with diabetes mellitus. Actually, in the present study, HbA1c levels of diabetes mellitus patients with postoperative AE [medians with interquartile ranges: 7.6% (6.7%, 8.2%)] were higher than those without postoperative AE [medians with interquartile ranges: 6.7% (6.5%, 7.0%)]. It was also reported that HbA1c levels >6% (but not 6.2%) were associated with an increase in complications within 30 days of surgery in patients undergoing emergency general surgery [15].

Several studies have shown that the HRCT pattern (honeycombing) and pulmonary function indices were predictive markers of postoperative AE. Sugiura *et al.* reported that the incidence of postoperative AE in patients with typical or possible honeycombing was significantly higher than in those without honeycombing [20]. It was also reported that a UIP pattern on chest CT was an independent predictor of postoperative AE [1,21]. Regarding pulmonary function indices, several studies showed that %VC and %DLco were significantly correlated with postoperative AE [1,21,22]. In addition, Taya *et al.* reported that %FVC was an independent risk factor for AE in patients undergoing lung cancer treatment [23]. Similar to the results of previous reports, the present study demonstrated that the presence of honeycombing and that of FVC were each significantly associated with postoperative AE.

In contrast with previous reports [3,23], this study showed that preoperative PS was a risk factor for postoperative AE. Few studies have assessed the association between preoperative PS and postoperative AE. Moreover, the previous studies enrolled only small numbers of patients [3,23]. PS is a significant prognostic marker for patients with ILD or LC [23,25]. Therefore, it may also be associated with postoperative AE. Hence, further studies are needed to evaluate this phenomenon.

Limitations. There were some limitations to this study. First, this was a retrospective, single-center study, and the number of patients was small. Second, detailed classifications of ILD were not performed. Third, perioperative blood glucose monitoring was not evaluated. Fourth, the severity of ILD was mild in most patients (the median level of %DLco was 85.3%). Such mild ILD severity may have contributed to the lower mortality of postoperative AE compared with previous studies [1]. Finally, we did not assess all the risk factors for postoperative AE that had been reported in previous studies. For example, although preoperative exertion dyspnea (Hugh-Jones classification), or the maximum standardized F-18 fluorodeoxyglucose uptake values of tumors and that of noncancerous lung areas were reported to be independent predictors of postoperative AE in patients with LC-ILD [3,26], we did not evaluate any of these variables.

In conclusion, the present results suggest that preoperative comorbidities other than ILD are not risk factors for postoperative AE in patients with LC-ILD. On the other hand, a high preoperative HbA1c level, a poor PS, a low FVC, and honeycombing may each be associated with postoperative AE of LC-ILD. A prospective, multicenter, large-scale study is required to examine the reproducibility of the present study.

References

1. Sato T, Teramukai S, Kondo H, Watanabe A, Ebina M, Kishi K, Fujii Y, Mitsudomi T, Yoshimura M, Maniwa T, Suzuki K, Kataoka K, Sugiyama Y, Kondo T and Date H; Japanese Association for Chest Surgery. Impact and predictors of acute exacerbation of interstitial lung diseases after pulmonary resection for lung cancer. J Thorac Cardiovasc Surg (2014) 147: 1604–1611.
2. Sato T, Kondo H, Watanabe A, Nakajima J, Niwa H, Horio H, Okami J, Okumura N, Sugio K, Teramukai S, Kishi K, Ebina M, Sugiyama Y, Kondo T and Date H: A simple risk scoring system for predicting acute exacerbation of interstitial pneumonia after pulmonary resection in lung cancer patients. Gen Thorac Cardiovasc Surg (2015) 63: 164–172.
3. Koizumi K, Hirata T, Hirai K, Mikami I, Okada D, Yamagishi S, Kawashima T, Nakajima Y and Shimizu K: Surgical treatment of lung cancer combined with interstitial pneumonia: the effect of surgical approach on postoperative acute exacerbation. Ann Thorac Cardiovasc Surg (2004) 10: 340–346.
4. Sakamoto S, Homma S, Mun M, Fujii T, Kurosaki A and Yoshimura K: Acute exacerbation of idiopathic interstitial pneumonia following lung surgery in 3 of 68 consecutive patients: a retrospective study. Intern Med (2011) 50: 77–85.
5. Mizuno Y, Iwata H, Shirahashi K, Takamochi K, Oh S, Suzuki K and Takemura H: The importance of intraoperative fluid balance for the prevention of postoperative acute exacerbation of idiopathic pulmonary fibrosis after pulmonary resection for primary lung cancer. Eur J Cardiothorac Surg (2012) 41: e161–165.
6. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CL, Lederer DJ, Behr J, Cottin V, Danoff SK, Morell F, Flaherty KR, Wells A, Martinez FJ, Azuma A, Bice TJ, Bouros D, Brown KK, Collad HR, Duggal A, Galvi L, Inoue Y, Jenkins RG, Johkoh T, Kazerooni EA, Kitaichi M, Knight SL, Mansour G, Nicholson AG, Pipavath SNJ, Buendia-Roldan I, Selman M, Travis WD, Walsh S and Wilson KC: Diagnosis of Idiopathic Pulmonary Fibrosis An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med (2018) 198: e44–68.
7. Collard HR, Ryerson CJ, Corte TJ, Jenkins G, Kondoh Y, Lederer DJ, Lee JS, Maher TM, Wells AU, Antoniou KM, Behr J, Brown KK, Cottin V, Flaherty KR, Fukuoka J, Hansell DM, Johkoh T, Kaminski N, Kim DS, Kolb M, Lynch DA, Myers JL, Raghu G, Richeldi L, Taniguchi H and Martinez FJ: Acute exacerbation of idiopathic pulmonary fibrosis an international working group report. Am J Respir Crit Care Med (2016) 194: 265–275.
8. Charlson ME, Pompei P, Ales KL and MacKenzie CR: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis (1987) 40: 373–383.
9. Ley B, Ryerson CJ, Vittinghoff E, Ryu JH, Tomassetti S, Lee JS, Poletti V, Buccioli M, Elicker BM, Jones KD, King TE and Collard HR: A multidimensional index and staging system for idiopathic pulmonary fibrosis. Ann Intern Med (2012) 156: 684–691.
10. Benker M, Citak N, Neuer T, Opitz I and Inci I: Impact of preoperative comorbidities on postoperative complication rate and outcome in surgically resected non-small cell lung cancer patients. Gen Thorac Cardiovasc Surg (2022) 70: 248–256.
11. Pedraza-Serrano F, Jiménez-García R, López-de-Andrés A, Hernández-Barrera V, Sánchez-Muñoz G, Puente-Maestu L and de-Miguel-Díez J: Characteristics and outcomes of patients hospitalized with interstitial lung diseases in Spain, 2014 to 2015. Medicine (Baltimore) (2019) 98: e15779.
12. Ando K, Ohkuni Y, Makino H, Kawamura Y, Motojima S and Kaneko N: Relationship between the prognosis of interstitial pneumonia and its comorbidities. Nihon Kokyuki Gakkai Zasshi (2011) 49: 800–809 (in Japanese).
13. Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH Jr, Probstfield JL, Simons-Morton DG and Friedewald WT: Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med (2008) 358: 2545–2559.

14. Saudek CD, Derr RL and Kalyani RR: Assessing glycemia in diabetes using self-monitoring blood glucose and hemoglobin A1c. JAMA (2006) 295: 1688–1697.
15. Jehan F, Khan M and Sakran JV: Perioperative glycemic control and postoperative complications in patients undergoing emergency general surgery. J Trauma Acute Care Surg (2018) 84: 112–117.
16. Arya S, Binney ZO, Khakharia A, Long CA, Brewster LP, Wilson PW, Jordan WD Jr and Duwayri Y: High hemoglobin A1c associated with increased adverse limb events in peripheral arterial disease patients undergoing revascularization. J Vasc Surg (2018) 67: 217–228.e1.
17. Hikata T, Iwanami A, Hosogane N, Watanabe K, Ishii K, Nakamura M, Toyama Y, Matsumoto M and Kamata M: High preoperative hemoglobin A1c is a risk factor for surgical site infection after posterior thoracic and lumbar spinal instrumentation surgery J Orthop Sci (2014) 19: 223–228.
18. Chrastil J, Anderson MB, Stevens V, Anand R, Peters CL and Pelt CE: Is Hemoglobin A1c or perioperative hyperglycemia predictive of periprosthetic joint infection or death following primary total joint arthroplasty? J Arthroplasty (2015) 30: 1197–1202.
19. Hyldgaard C, Hilberg O and Bendstrup E: How does comorbidity influence survival in idiopathic pulmonary fibrosis? Respir Med (2014) 108: 647–653.
20. Sugiura H, Takeda A, Hoshi T, Kawabata Y, Sayama K, Jinzaki M and Kuribayashi S: Acute exacerbation of usual interstitial pneumonia after resection of lung cancer. Ann Thorac Surg (2012) 93: 937–943.
21. Miyajima M, Watanabe A, Sato T, Teramukai S, Ebina M, Kishi K, Sugiyama Y, Kondo H, Kobayashi S, Takahashi Y, Ito H, Yamamoto R, Sawada S, Fujimori H, Okabe K, Arikura J, Shintani Y, Nakamura H, Toyooka S, Hasumi T, Watanabe T, Hata Y, Iwata H, Aoki M, Funai K, Inoue S, Kawashima O, Iida T and Date H: What factors determine the survival of patients with an acute exacerbation of interstitial lung disease after lung cancer resection? Surg Today (2018) 48: 404–415.
22. Ohsawa M, Tsutani Y, fujiwara M, Mimae T, Miyata Y and Okada M: Predicting severe postoperative complication in patients with lung cancer and interstitial pneumonia. Ann Thorac Surg (2020) 109: 1054–1060.
23. Taya T, Chiba H, Yamada G, Takahashi M, Ikeda K, Mori Y, Otsuka M and Takahashi H: Risk factors for acute exacerbation of idiopathic interstitial pneumonia in patients undergoing lung cancer treatment. Jpn J Clin Oncol (2019) 49: 1126–1133.
24. Migita K, Arai T, Jiuchi Y, Izumi Y, Iwanaga N, Kawahara C, Suematsu E, Miyamura T, Tsutani H, Hawabe Y, Matsumura R, Mori S, Ohshima S, Yoshizawa S, Suenaga Y, Ogushi F, Kawabata M, Furukawa H, Matsui T, Bito S and Tohma S: Predictors of mortality in patients with interstitial lung disease treated with corticosteroids: results from a cohort study. Medicine (Baltimore) (2014) 93: e175.
25. Paesmans M, Sculier JP, Libert P, Bureau G, Dabouis G, Thiriaux J, Michael J, Cutsem OV, Sergysels R and Mommen P: Prognostic factors for survival in advanced non-small-cell lung cancer: univariate and multivariate analyses including recursive partitioning and amalgamation algorithms in 1,052 patients. The European Lung Cancer Working Party. J Clin Oncol (1995) 13: 1221–1230.
26. Yamamichi T, Shimada Y, Masuno R, Ohira T, Abe S, Yoshimura A and Ikeda N: Association between F-18 fluorodeoxyglucose uptake of noncancerous lung area and acute exacerbation of interstitial pneumonia in patients with lung cancer after resection. J Thorac Cardiovasc Surg (2020) 159: 1111–1118.e2.