Original Article

Risk Factors of Severe Postoperative Complication in Lung Cancer Patients with Diabetes Mellitus

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Purpose: Clinically, postoperative complications are occasionally observed in lung cancer patients with diabetes mellitus (DM). The increased risk of postoperative complications in DM patients has been reported in other fields. This study aims to identify risk factors for severe postoperative complications in lung cancer patients with DM.

Methods: Of 2756 consecutive patients who underwent complete resection for lung cancer between 2008 and 2018 in our hospital, 475 patients (20%) were complicated by DM. Clinical factors and diabetic factors (HbA1c, preoperative fasting blood glucose [FBG], postoperative mean FBG on 1, 3 postoperative days [PODs], and use of insulin) were evaluated by univariable and multivariable analyses to identify independent risk factors of severe complication.

Results: The 349 (73%) patients were male. Their median age was 71 years. Severe perioperative complications occurred in 128 (27%) patients. In the multivariable analysis, male (p <0.01), age (≥75 years) (p = 0.04), preoperative FBG (≥140 mg/dL) (p = 0.03), and increased mean FBG on 1, 3 PODs (≥180 mg/dL) (p <0.01) were significantly associated with severe perioperative complications.

Conclusion: Increased FBG on 1, 3 PODs (≥180 mg/dL) was an independent risk factor for severe perioperative complications in lung cancer with DM. Postoperative hyperglycemia may be correlated to severe perioperative complications.

Keywords: lung cancer, lung severe perioperative complications, diabetes mellitus, mean fasting blood glucose on postoperative days 1, 3

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Abbreviations

DM = diabetes mellitus
FBG = fasting blood glucose
POD = postoperative day
PS = performance status
BMI = body mass index
COPD = chronic obstructive pulmonary disease
IP = interstitial pneumonia
NSCLC = non-small-cell lung cancer

Introduction

Lung cancer is the leading cause of the most common malignant tumors that threaten human health due to its high morbidity and mortality. Non-small-cell

lung cancer (NSCLC) accounts for more than 85% of all lung cancers.[1,2] For early-stage NSCLC, surgical resection will be the most favorable option, and locally advanced NSCLC will be appropriately selected.[3] Diabetes mellitus (DM) is also a common disease with a rapidly increasing prevalence worldwide.[4] Some studies have shown that DM increases the risk of cancer, and the prevalence of DM is reported to range from 1% to 42% (median prevalence: 10%) in cancer patients.[5–7]

Clinically, we occasionally see pulmonary complications such as postoperative wound infection, pneumonia, and pyothorax in patients with DM-associated lung cancer. In addition, postoperative complications are particularly common in patients with poorly controlled blood glucose levels.

In several types of cancer, DM is associated with postoperative complications and survival.[8,9] Also, the guideline of "The Society of Thoracic Surgeons" states the importance of perioperative glycemic control (<180 mg/dL) in cardiovascular surgery.[10] However, the influence of postoperative complications after lung cancer is complicated,[11,12] and there are no reports on perioperative target blood glucose levels or risk factors of postoperative complications in patients with DM-associated lung cancer. Therefore, this study aims to identify risk factors for severe postoperative complications in lung cancer patients with DM.

Materials and Methods

Patient recruitment and data collection

The complete resection of NSCLC was performed on 2756 consecutive patients at National Cancer Center Hospital East between January 2008 and December 2018. Complete resection was defined as cancer-free surgical margins both macroscopically and histologically. This study excluded 2281 patients based on the following criteria: (a) patients for whom sublobar resection was performed (n = 336), (b) patients with missing data (n = 86), and (c) patients with nondiabetic patients (n = 1895). There were 117 duplicate patients. The remaining 475 patients (20%) with DM were enrolled in the present study (**Fig. 1**), among 330 patients (70%) had a history of type 1 or 2 DM or use of antidiabetic medication, and 145 patients (30%) were diagnosed incidentally during a preoperative medical examination (preoperatively elevated fasting glucose ≥126 mg/dL or casual glucose ≥200 mg/dL, and HbA1c ≥6.5% (National Glycohemoglobin Standardization Program) despite an unknown history of DM). This retrospective study was approved by the National Cancer Ethical Review Board.

In most patients, the preoperative HbA1c level for NSCLC was measured within the month before surgery. We have categorized the DM group in either of the following five patients of conditions which we have shown in **Fig. 2**. We have collected the information on the highest fasting blood glucose (FBG) level at two different periods: perioperatively (including intraoperative period and first 24 hours postoperatively) and between 48 and 72 hours postoperatively.[13] Abstractors identify the highest FBG within the immediate perioperative period, and between 48 and 72 hours postoperatively, from both finger checks and laboratory tests. Dietary, continuous oral hypoglycemic, and sliding-scale insulin therapies are the perioperative treatments of the DM group. Patients are considered to have received insulin if they are given insulin at any time point during the postoperative period.

By laboratory, radiologic, and physiological examinations, comorbidities and postoperative complications were diagnosed and recorded during daily clinical practice. The questionnaires regarding comorbidity comprised 23 items: sex, age, active smoking history within 1 month before surgery, obesity (body mass index ≥25 kg/m^2), chronic obstructive pulmonary disease (forced expiratory volume in 1 second ≤70%), interstitial pneumonia (apparent interstitial shadow detected by chest CT), hypertension, hyperlipidemia, ischemic heart disease (positive stress test), cerebrovascular or neurologic diseases, renal dysfunction (serum creatinine ≥2.0 mg/dL), bronchoplasty, combined resection of the other organs, bronchial stump coverage, operative time (≥180 min), Interoperative bleeding (≥100 mL), pathological stage (≥III), perioperative complications (Clavien–Dindo Grade ≥3), DM (HbA1c ≥7.0%), preoperative FBG (≥140 mg/dL), mean FBG on 1, 3 postoperative day (POD) (≥180 mg/dL), diabetes status (dietary, continuous oral hypoglycemic, and sliding-scale insulin therapies). Each cutoff value was separated in this study based on the guidelines of the Diabetes Association of Japan,[14] and also the guideline of "The Society of Thoracic Surgeons" states the importance of perioperative glycemic control (<180 mg/dL) in cardiovascular surgery.[10]

The postoperative complications were defined according to the Clavien–Dindo classification system.[15] To plan safer surgical interventions and improve patient selection and care, predictive factors of postoperative complications are useful.[16] Grade III complications included

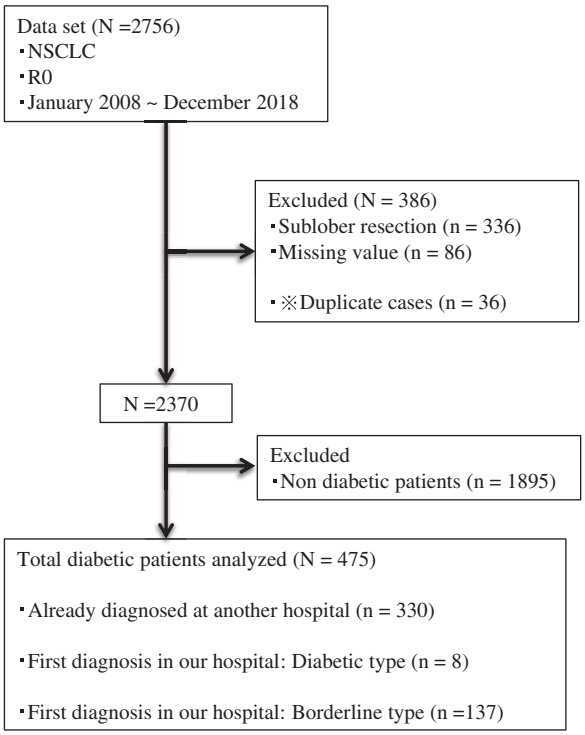

Fig. 1 The scheme of this study. NSCLC: non-small-cell lung cancer.

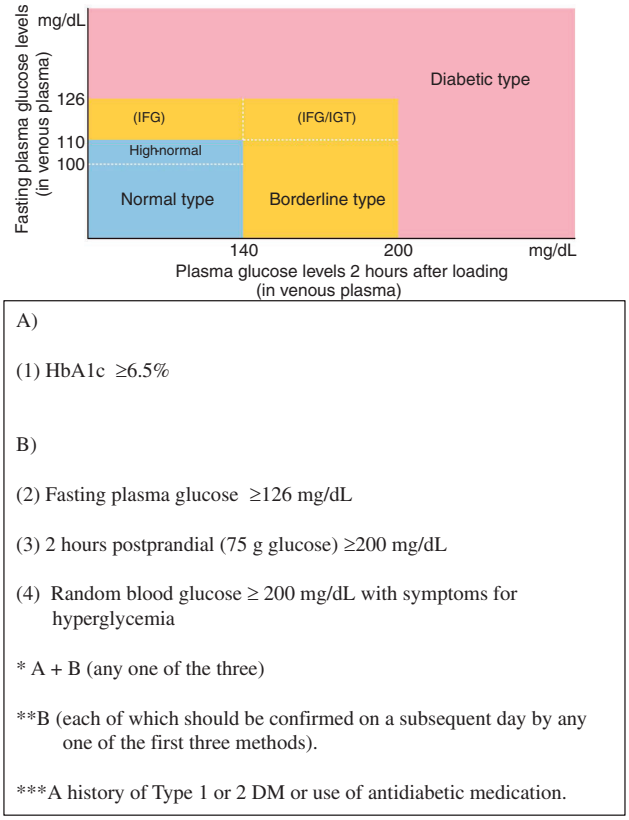

Fig. 2 Diagnostic criteria for diabetes mellitus recommended by the American Diabetes Association. DM: diabetes mellitus

major complications requiring surgical, endoscopic, or radiological intervention; grade IV complications included life-threatening complications requiring intermediate care/intensive care unit management; and grade V complications included death of the patient. Considering that higher grade complications are associated with a greater burden to patients,[15,17] higher than grade III were evaluated in this study. The postoperative complications were as follows: pulmonary complications (prolonged air leakage [5 days or longer], pneumonia [presenting abnormal shadow by chest radiograph], thoracic empyema, atelectasis/sputum requiring bronchoscopic intervention, which was normally indicated for hypoxemic patients with clinically and/or radiologically relevant findings, bronchopleural fistula, pleural effusion), cardiovascular complications (cardiac failure, arrhythmia), cerebral complications (cerebral infarction), and other related to operative procedure (wound infection, chylothorax, postoperative hemorrhage [500 mL/h or more], recurrent nerve palsy, wound pain, and delirium).

Statistical analysis

For patient characteristics, frequency and proportion were presented in categorical variables, and median and range were presented in continuous variables. Univariate and multivariate analyses were performed using logistic regression analysis to estimate odds ratios and 95% confidence intervals (CIs) to identify clinical factors associated with postoperative complications. All reported p values were determined using two-sided analyses, and statistical significance was set at $p < 0.05$. All statistical analyses were performed by EZR software (R version 4.2.2; Jichi Medical University, Saitama Medical Center. Saitama, Japan).[18]

Results

Patient characteristics

Table 1 shows the clinicopathological characteristics of 475 diabetes patients. The 349 (73%) patients were male. The median age of them was 71 years. Only four patients were performed by thoracoscopic approach, others were open thoracotomy. Severe perioperative complications occurred in 128 (27%) patients. Preoperative HbA1c (≥7%) was 141(30%) patients. Preoperative FBG (≥140 mg/dL) was 190 (40%) patients. Increased mean FBG on 1, 3 POD (≥180 mg/dL) was 101 (21%)

patients. Details of the diabetes status, dietary therapy (±no known DM) were 145 (31%), oral medications were 184 (39%), and the insulin (±oral medications) were 102 (21%) patients.

Details of severe perioperative complications

Table 2 shows the severe perioperative complications classified according to Clavien–Dindo (Grade ≥3). Pulmonary complications were the most common postoperative complications. There were 51 patients with pulmonary air leak, 24 patients with pneumonia, 20 patients with thoracic empyema, 10 patients with atelectasis, 9 patients with bronchopleural fistula, and 3 patients with cerebral infarction. There was some overlapping. On the others related to operative procedures, there were nine patients with wound infection.

Univariable and multivariable analyses of predictive risk factors of severe postoperative complications in diabetic patients

Table 3 shows the univariable and multivariable analyses of predictive risk factors of postoperative complications (Clavien–Dindo Grade ≥3) in diabetic patients with NSCLC. In the univariable analysis, male (hazard ratio [HR], 2.38 [95% CI, 1.40–4.03]; p <0.01), smoker ([HR], 4.03 [95% CI, 0.98–2.27]; p <0.01), interoperative bleeding (≥100 mL) ([HR], 1.71 [95% CI, 1.06–3.75]; p = 0.02), and increased mean FBG on 1, 3 PODs (≥180 mg/dL) ([HR], 4.76 [95% CI, 2.93–7.73]; p <0.01) were risk factors of severe perioperative complications. In the multivariable analysis, male ([HR], 2.07 [95% CI, 1.27–3.36]; p <0.01), age (≥75years) ([HR], 1.41 [95% CI, 1.02–1.96]; p = 0.04), preoperative FBG (≥140 mg/dL) ([HR], 1.71 [95% CI, 1.05–2.78]; p = 0.03), and increased mean FBG on 1, 3 POD (≥180 mg/dL) was significantly associated with severe perioperative complications ([HR], 5.44 [95% CI, 3.20–9.25]; p <0.01).

Discussion

The target values for perioperative blood glucose control given in the Japanese and U.S. diabetes guidelines are based on previous reports in the fields of cardiovascular surgery and gastrointestinal surgery.[14,19]

In the field of cardiovascular surgery, the target value for perioperative glycemic control is reported to be less than 180 mg/dL,[10] and poor preoperative glycemic control has been reported to cause increased mortality and postoperative complications such as sternal bone marrow and mediastinitis.[20,21]

DM and perioperative hyperglycemia have been reported to be risk factors for postoperative complications in the field of gastrointestinal oncology and all noncancer surgical patients.[22] In addition, a 2009 NEJM reported that strict (80–110 mg/dL) glycemic control reduced postoperative complications and mortality but increased mortality due to severe hypoglycemia.[23]

On the other hand, in the field of thoracic surgery, there is a paucity of literature reporting an association between complications after lung resection and DM.[24,25] There are no reports on perioperative target blood glucose levels or predictors of postoperative complications in lung cancer patients with DM.

We identified predictive factors for postoperative complications in lung cancer patients with DM. Multivariable analysis, including surgical factors, revealed that preoperative insulin use and high preoperative HbA1c were not risk factors for postoperative complications, but preoperative fasting hyperglycemia and postoperative hyperglycemia were risk factors for serious postoperative complications. Thus, our results imply that perioperative glycemic control in diabetic patients with lung cancer may prevent postoperative complications.

The same results were reported that high preoperative HbA1c levels (>6.5) were associated with poor OS in elderly patients undergoing complete resection of NSCLC but not with risk factors for postoperative complications.[26]

What makes it different from other studies is its novelty because although it has been reported that diabetic patients with poor glycemic control are a risk factor for postoperative complications of lung surgery, there are no reports on the study of postoperative complications in lung cancer patients with DM.

As in the field of cardiovascular surgery, the results suggest that a target blood glucose control level of less than 180 mg/dL during the perioperative period (average blood glucose level during the first and third postoperative sick days) may prevent postoperative complications.[20]

Of all patients, 475 (20%) had DM. Furthermore, 145 (30%) of these patients were incidentally diagnosed with DM preoperatively (8 with DM and 137 with borderline DM). These results suggest that one in five postoperative lung cancer patients has concomitant DM, which is about the same proportion (16%–20%) compared to several other reports.[27,28]

Table 1 Overall characteristics of diabetes patients (n = 475)

Variables	Number (%)
Sex	
Male	349 (73)
Female	126 (27)
Age (years) median (range)	71 (43–88)
Smoking status	
Never	90 (19)
Smoker	385 (81)
Performance status	
0	418 (88)
≥1	57 (12)
BMI	
<25	305 (64)
≥25	170 (36)
COPD	
Yes	109 (23)
No	366 (77)
IP	
Yes	27 (4)
No	448 (96)
Hypertension	
Yes	177 (37)
No	298 (63)
Hyperlipidemia	
Yes	157 (33)
No	318 (67)
Ischemic heart disease	
Yes	31 (7)
No	444 (93)
Cerebrovascular disease	
Yes	26 (5)
No	449 (95)
Chronic renal failure	
Yes	16 (3)
No	459 (97)
Bronchoplasty	
Yes	22 (5)
No	453 (95)
Combined resection of the other organs	
Yes	35 (7)
No	440 (93)
Bronchial stump coverage	
Yes	156 (33)
No	319 (67)
Operative time (min)	
≥180	115 (24)
<180	360 (76)
Interoperative bleeding (mL)	
≥100	77 (16)
<100	398 (84)
Pathological stage	
I, II	419 (88)
III	56 (12)
Perioperative complications (Clavien–Dindo)	
Grade 1, 2	347 (73)
Grade ≥3	128 (27)
Preoperative HbA1c (%)	
≥7	141 (30)
<7	334 (70)
Preoperative FBG (mg/dL)	
≥140	190 (40)
<140	285 (60)
Mean FBG on 1, 3 POD (mg/dL)	
≥180	101 (21)
<180	374 (79)
Diabetes status	
No therapy	44 (9)
Dietary Therapy (±no known diabetes mellitus)	145 (31)
Oral medications	184 (39)
Insulin (±oral medications)	102 (21)

BMI: body mass index; COPD: chronic obstructive pulmonary disease; IP: interstitial pneumonia; FBG: fasting blood glucose; POD: postoperative day

In addition, many patients were incidentally diagnosed with DM; in fact, 35% of all patients were not measured for HbA1c before exclusion, so there may be more DM patients than we expected. However, after reviewing all the excluded patients, we included patients with DM who had hyperglycemia twice at different times, even though their HbA1c was not measured. There is no report on the approximate percentage of patients with DM who are incidentally noted preoperatively, but there are reports that it is a risk factor for postoperative complications.[29] In fact, we believe there is a need to examine whether diabetic patients who are incidentally noted at our institution are risk factors for postoperative complications.

Several literature reports that DM patients with poor glycemic control are prone to pulmonary complications, even in the absence of pulmonary resection. The pathophysiology is that hyperglycemia leads to impaired immune function and microvascular damage by macrophages and neutrophils, and long-term systemic changes affect lung pulmonary function. In addition, hyperglycemia causes prolonged hypercatabolism, which is an inflammatory response, resulting in impaired collagen tissue formation and prolonged wound healing. It has also been reported that they are more susceptible to respiratory infections caused by atypical microorganisms. Therefore, it has been reported that the lungs are more susceptible to severe pneumonia, pulmonary fistula, pyothorax, and airway obstruction due to mucus than normal lungs.

Table 2 Severe Perioperative complications classified according to Clavien–Dindo (Grade ≥3)

Variables	No. of patients	
	Any grade	Grade ≥3
All	179	128
Pulmonary		
Air leak	63 (35)	51 (40)
Pneumonia	31 (17)	24 (19)
Thoracic empyema	22 (12)	20 (16)
Atelectasis	12 (7)	10 (8)
Bronchopleural fistula	9 (5)	9 (7)
Pleural effusion	5 (3)	0 (0)
Cardiovascular		
Cardiac failure	6 (3)	4 (3)
Arrhythmia	8 (4)	0 (0)
Cerebral		
Cerebral infarction	3 (2)	3 (2)
Others related to the operative procedure		
Wound infection	9 (4)	5 (4)
Chylothorax	5 (3)	0 (0)
Hemorrhage	6 (3)	4 (3)
Recurrent nerve palsy	7 (4)	0 (0)
Wound pain	1 (0.5)	0 (0)
Delirium	5 (3)	0 (0)

In the present study, air leak was the most common cause, followed by pneumonia, pyothorax, atelectasis/impaired sputum evacuation, and wound infection.[30]

Three patients had cerebral infarction after lobectomy which is thought to be related to left upper lobectomy, and thus, surgical procedure is more responsible for cerebral infarction after lung resection than other kinds of medical comorbidity. However, in our study, three cases of cerebral infarction consisted of two left lower lobectomies and one right upper lobectomy, so it was not possible to determine whether thrombus at the resection margin after lobectomy was directly involved.

This study had several limitations and biases. First, the study was a single-center, retrospective analysis and may not be reproducible because no center reported the same results. Furthermore, even if the blood glucose levels are listed as fasting before and after surgery, the patients may have eaten and drank small amounts of food and drink. Second, 35% of the patients had not had their HbA1c measured before exclusion from the initial sample. This means that there may be more diabetic patients than there should be since there is a certain percentage of borderline DM patients like this one. The most important limitation is that there is no clear definition of the best way to measure blood glucose in the perioperative period. However, some reports use the highest blood glucose level by 2POD postoperatively and the average blood glucose level up to 1 week postoperatively as the index, which is controversial.

Prospective studies are necessary to confirm whether perioperative hyperglycemia is related to postoperative complications in lung cancer surgery patients with DM and to identify more precise timing of perioperative interventions because some patients have different DM severities, different treatment modalities, and different backgrounds. There is a need to define perioperative target blood glucose levels in lung cancer patients with DM in the field of respiratory surgery.

The HbA1c and blood glucose levels should be measured in all patients with lung cancer, at least in the present study as well. Since many diabetic patients were incidentally detected before lung cancer surgery. Furthermore, it is desirable to perform surgery with blood glucose levels controlled below 140 mg/dL immediately prior to surgery. Even in diabetic patients who are not poorly controlled to begin with, if postoperative hyperglycemia is observed, insulin should be used to control blood glucose levels below 180 mg/dL.

We also believe that prospective studies are needed to determine whether postoperative hyperglycemia is indeed associated with postoperative complications in lung cancer patients without DM. In fact, perioperative hyperglycemia has been reported to be a risk factor for postoperative complications in patients without DM in other cancer fields as well.[13] We also reported that postoperative hyperglycemia was an independent high-risk factor for postoperative complications in non-DM lung cancer patients, although this was a retrospective study. Further investigation of perioperative glycemic control is needed.

Conclusion

Male, age 75 years or older, preoperative FBG (≥140 mg/dL), and increased mean FBG on 1, 3 PODs (>180 mg/dL) were predictive factors for postoperative complications. To prevent postoperative complications of lung cancer in DM patients, further measures for perioperative glycemic control should be considered.

Table 3 Univariable and multivariable analyses of predictive risk factors of postoperative complications (Clavien–Dindo Grade ≥3) in diabetic patients with NSCLC

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
Sex						
Female						
Male	2.38	1.40–4.03	<0.01	2.07	1.27–3.36	<0.01
Age						
<75						
≥75	1.49	0.98–2.27	0.06	1.41	1.02–1.96	0.04
Smoking history						
Never						
Ever smoker	4.03	1.96–8.29	<0.01	1.29	0.74–2.25	0.36
PS						
<1						
≥1	1.20	0.67–2.13	0.53	1.49	0.96–1.94	0.08
BMI						
<25						
≥25	0.90	0.57–1.41	0.67	1.15	0.71–1.87	0.56
COPD						
Negative						
Positive	1.04	0.64–1.68	0.87	1.37	0.96–1.94	0.08
IP						
Negative						
Positive	0.76	0.30–1.94	0.57	0.92	0.45–1.88	0.81
Hypertension						
Negative						
Positive	0.80	0.53–1.23	0.32	0.81	0.58–1.13	0.21
Hyperlipidemia						
Negative	0.63	0.23–1.71	0.37	0.52	0.23–1.15	0.11
Positive						
Ischemic heart disease						
Negative						
Positive	1.12	0.50–2.50	0.78	1.17	0.64–2.14	0.62
Cerebrovascular disease						
Negative						
Positive	3.70	0.82–16.8	0.09	1.09	0.56–2.12	0.79
Chronic renal failure						
Negative						
Positive	1.66	0.59–4.66	0.34	0.96	0.35–2.63	0.95
Bronchoplasty						
Negative						
Positive	1.92	0.70–4.99	0.15	2.41	0.76–7.71	0.14
Combined resection of the other organs						
Negative						
Positive	1.88	0.85–4.02	0.11	2.16	0.91–5.11	0.08
Bronchial stump coverage						
Negative						
Positive	1.18	0.40–3.13	0.81	0.32	0.09–1.07	0.06
Operative time (min)						
<180						
≥180	1.25	0.79–1.94	0.32	0.78	0.43–1.44	0.43

(Continued)

Table 3 (Continued)

Interoperative bleeding (mL)						
<100						
≥100	1.71	1.06–3.75	0.02	1.25	0.67–2.32	0.49
Pathological stage						
I, II						
III	1.46	0.83–2.53	0.16	1.30	0.68–2.49	0.43
Preoperative HbA1c (%)						
<7						
≥7	1.35	0.88–2.08	0.18	0.84	0.46–1.53	0.57
Preoperative FBG (mg/dL)						
<140						
≥140	1.29	0.86–1.95	0.22	1.71	1.05–2.78	0.03
FBG on 1, 3 POD (mg/dL)						
<180						
≥180	4.76	2.93–7.73	<0.01	5.44	3.20–9.25	<0.01
Diabetes status						
No insulin						
Insulin	1.79	1.12–2.82	0.02	1.16	0.61–2.21	0.64

PS: performance status; BMI: body mass index; COPD: chronic obstructive pulmonary disease; IP: interstitial pneumonia; FBG: fasting blood glucose; POD: postoperative day

Declarations

Ethics approval and consent to participate

The medical record of each patient was reviewed retrospectively under a waiver of authorization approved by the Institutional Review Board (2017-418) of the National Cancer Center East, Chiba, Japan.

Consent for publication

Not applicable.

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Data availability

Not applicable.

Author contributions

Yutaro Koike and Keiju Aokage designed this study, analyzed the data, prepared the figures, and wrote the original draft. All authors reviewed the article.

Disclosure statement

The authors have no conflicts of interest to declare.

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