Original Article

Risks and outcome of fatal respiratory events after lung cancer surgery: cohort study in South Korea

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Background: Severe complications such as acute respiratory distress syndrome or respiratory failure can occur after lung cancer surgery. However, the prevalence and risk factors have not been well identified. The aim of this study was to investigate the prevalence of and risk factors for fatal respiratory events after lung cancer surgery in South Korea.

Methods: The National Health Insurance Service database in South Korea was used to extract data of all adult patients who were diagnosed with lung cancer and underwent lung cancer surgery from January 1, 2011, to December 31, 2018, for a population-based cohort study. Diagnosis of acute respiratory distress syndrome or respiratory failure after surgery was defined as postoperative fatal respiratory event.

Results: A total of 60,031 adult patients who received lung cancer surgery were included in the analysis. Among them, 0.5% (285/60,031) experienced fatal respiratory events after the lung cancer surgery. In multivariable logistic regression, some risk factors (older age, male sex, higher Charlson comorbidity index score, underlying severe disability, bilobectomy, pneumonectomy, redo-case, lower case volume, and open thoracotomy) for developing postoperative fatal respiratory events were identified. Moreover, the development of postoperative fatal respiratory events was associated with high in-hospital mortality, 1-year mortality, longer length of hospital stays, and higher total hospitalization costs.

Conclusions: Postoperative fatal respiratory events might worsen the clinical outcomes of lung cancer surgery. The knowledge of potential risk factors related to postoperative fatal respiratory events could enable earlier intervention to reduce the occurrence of these events and improve the postoperative clinical outcome.

Keywords: Lung neoplasms; carcinoma; non-small cell lung cancer (NSCLC); mortality; acute respiratory distress syndrome (ARDS)

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Introduction

Lung cancer is one of the major causes of mortality worldwide despite major advances in chemotherapy and targeted immunotherapy (1). The incidence of lung cancer is 11.6% of total cancer diagnoses and 18.4% of total cancer deaths (1,2). Lung resection surgery is the standard treatment for early-stage non-small cell lung cancer (NSCLC) (3). Patients with stage I, II, or IIIA NSCLC usually undergo lung resection surgery if the tumor is indicated for surgery and the patient can tolerate surgery (3,4). The clinical outcomes after lung resection surgery have improved over the past decade. However, pulmonary complications of lung cancer surgery increased from 13% to 40%, because a large proportion of patients were old, smokers, and experienced loss of large volumes of normal lung tissue after lung cancer surgery (5,6).

The prevalence of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) after lung cancer surgery have been reported as 4.2–5.3%, and 1.5–3.1%, respectively (7,8). ALI and ARDS are rare but fatal pulmonary complications necessitating admission to the intensive care unit (ICU), and associated with increased mortality (9). The risk factors for ALI and ARDS following lung resection surgery have been previously evaluated; however, the results were mixed, debatable, and from small heterogeneous groups (10-12). Kutlu *et al.* reported age >60 years, male sex, greater extent of resection, and lung cancer as factors associated with the incidence of ALI/ARDS after pulmonary resection in a single-center study (n=1,139) (10). Perioperative excess fluid administration or blood transfusion, the intraoperative ventilator setting (tidal volume, or airway pressure), and preoperative lung function were considered to be associated with ALI/ARDS in an analysis of 146–197 cases of pneumonectomy (11,12).

The prevalence of and risk factors for fatal respiratory events such as ARDS or respiratory failure after lung cancer surgery have not been reported using a national registration database with a large sample size. The National Health Insurance Service (NHIS) provides information on all patients who underwent lung cancer surgery after the diagnosis of lung cancer in South Korea. Using this database, we aimed to investigate the prevalence of and risk factors for fatal respiratory events after lung cancer surgery in South Korea. Moreover, we examined the impact of fatal respiratory events after lung cancer surgery on in-hospital mortality, 1-year mortality, total cost of hospitalization, and length of stay (LOS). We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1361/rc).

Highlight box

Key findings
- Postoperative fatal respiratory events may worsen the clinical outcomes of lung cancer surgery.

What is known and what is new?
- Severe complications such as acute respiratory distress syndrome or respiratory failure can occur after lung cancer surgery.
- Development of fatal respiratory events was related to increased hospital mortality and 1-year mortality after lung cancer surgery.

What is the implication, and what should change now?
- Earlier intervention is needed to reduce the occurrence of these events and improve the clinical outcome after lung cancer surgery.

Methods

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board (IRB) of Seoul National University Bundang Hospital (No. X-2111-721-901) and individual consent for this retrospective analysis was waived. The study protocol was approved by the ethics committee of NHIS for data sharing (approval No. NHIS-2021-1-616).

Study design, setting, and data source

As a population-based cohort study, this study followed the specific guidelines of "strengthening the reporting of observational studies in epidemiology" (13). Data were extracted from the NHIS database, which contains information regarding disease diagnoses and drug prescriptions and/or procedures since it is the sole public insurance system in South Korea. In addition, the demographic, socio-economic, and death information was included in the NHIS database. For information on disease diagnoses, the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) codes were used.

Study population

We included adult patients (≥18 years) who received lung cancer surgery after hospitalization from January 1, 2011, to December 31, 2018, with a diagnosis of lung cancer (ICD-10 code: C34). All patients with cancer had to be registered by ICD-10 codes in the NHIS database to avail of financial aid from the South Korean government. Approximately 95% of all expenses involved in the examination and treatment were covered by the South Korean government according to policy. Additionally, the prescription code for lung cancer surgery should also be registered in the NHIS database by physicians in South Korea, suggesting that there was no missing case of lung cancer surgery in this study.

Study endpoint and outcome: *postoperative fatal respiratory event*

We defined postoperative fatal respiratory events as the diagnosis of ARDS (ICD-10 code J80) or respiratory failure (ICD-10 code J96) during hospitalization because ARDS and respiratory failure can occur as severe pulmonary complications after lung cancer surgery (14,15). To account for any missed cases of fatal respiratory event, we also included cases in which the main cause of death during hospitalization after lung cancer surgery was ARDS or respiratory failure. Patients who experienced ARDS or respiratory failure postoperatively were considered the postoperative fatal respiratory event group.

Potential confounders

Age and sex were collected as the physical variables. As socio-economic status-related information, data regarding residence, employment, and household income level at the time of lung cancer surgery were collected. In terms of residence, the capital city and other metropolitan cities were considered urban areas, while the remaining areas were considered rural. Regarding employment, self-employment was not considered in this study; household income level was divided into four groups using the quartile ratio. In South Korea, the household income level must be registered in the NHIS database to determine insurance premiums for subscribers. In addition, we calculated the Charlson comorbidity index (CCI) to determine the patients' comorbid status at the time of lung cancer surgery using the ICD-10 codes of individual comorbidity (Table S1), that were registered within 1-year before the date of the lung cancer surgery. Among the individual diseases, preoperative chronic pulmonary diseases (ICD-10 codes I27.8, I27.9, J40-J47, J60- J67, J68.4, J70.1, and J70.3) were used as independent covariates. Moreover, data on the underlying disability at the time of lung cancer surgery was collected. All individuals with any form of disability had to be registered in the national registration database. These registrations enable people with disabilities to receive benefits from the social welfare system in South Korea. The severity of each disability was evaluated by a specialist doctor and graded from 1 (most severe) to 6 (mildest). Patients with grade 1, 2, or 3 were considered as the severe disability group, while those with grade 4, 5, or 6 were considered as the mild-to-moderate disability group. For surgery-related information, redo case or first case of lung cancer surgery, type of surgery, video-assisted thoracic surgery (VATS), or open thoracotomy were collected as covariates. The type of surgery was classified into five groups: wedge resection, segmentectomy, lobectomy, bilobectomy, and pneumonectomy. A patient who underwent wedge resection in addition to segmentectomy was included in the segmentectomy group. Similarly, a patient who underwent segmentectomy in addition to lobectomy was included in the lobectomy group. Since a high case volume was related to decreased mortality after lung cancer surgery (16), we calculated the annual volume of lung cancer surgery cases in each hospital in South Korea. In addition, all the patients were divided into two groups, based on the hospital where the lung cancer surgery was performed: tertiary general hospital group and general hospital group.

Statistical analyses

Numbers (percentages) for categorical variables and mean values [standard deviation (SD)] for continuous variables were used to present clinicopathological characteristics. Using receiver operating characteristic analysis, the cut-off value for the annual case volume of lung cancer surgery in South Korea was determined as 621. On the basis of this cut-off value, the patients were divided into two groups (<621 or ≥ 621). We fitted a multivariable logistic regression model for development of postoperative fatal respiratory events. All the variables were included in the multivariate model. The Hosmer-Lemeshow test was used to confirm that the goodness of the fit in the model was appropriate, and the results were presented as odds ratios (ORs) with 95% confidence intervals (CIs). Next, we constructed a multivariable logistic regression model for in-hospital mortality to examine whether the development of postoperative fatal respiratory events was associated with in-hospital mortality. We also constructed a multivariable Cox regression model for 1-year mortality to examine whether the development of postoperative fatal respiratory events was associated with 1-year mortality. The results of the Cox regression model were presented as hazard ratios (HRs) with 95% CIs. Moreover, we also constructed a multivariable generalized linear model (GLM) for LOS and total cost of hospitalization to investigate how the development of postoperative fatal respiratory events affects the LOS and total cost of hospitalization. In the GLMs, the Poisson distribution with log-link function and the gamma distribution with log-link function were calculated for LOS and total cost of hospitalization, respectively. The

Table 1 The clinicopathological characteristics of all the patients

Variables	Mean ± SD or n (%)
Age, years	65.6±9.9
Sex, male	36,778 (61.3)
Household income level	
Q1 (lowest)	12,207 (20.3)
Q2	9,149 (15.2)
Q3	13,361 (22.3)
Q4 (highest)	24,057 (40.1)
Unknown	1,257 (2.1)
Having a job at surgery	37,808 (63.0)
Residence at surgery	
Urban area	23,803 (39.7)
Rural area	36,228 (60.3)
Type of surgery	
Wedge resection	11,489 (19.1)
Segmentectomy	4,041 (6.7)
Lobectomy	40,788 (67.9)
Bilobectomy	1,957 (3.3)
Pneumonectomy	1,756 (2.9)
VATS	48,888 (81.4)
CCI at surgery	6.2±3.0
Having a disability at surgery	
Mild to moderate	5,433 (9.1)
Severe	1,784 (3.0)
Redo case	2,786 (4.6)
Annual case volume of lung cancer surgery	
<621	35,929 (59.9)
≥621	24,102 (40.1)
Type of hospital	
Tertiary general hospital	46,648 (77.7)
General hospital	13,383 (22.3)
Fatal respiratory adverse event	285 (0.5)
Postoperative ARDS	156 (0.3)
Postoperative respiratory failure	135 (0.2)
Total cost for hospitalization, USD	8,890.5±4,334.4
Length of hospital stays, day	11.6±7.9
In-hospital mortality	391 (0.7)
1-year mortality	4,744 (7.9)
Year of surgery	
2011	5,479 (9.1)
2012	6,164 (10.3)
2013	6,640 (11.1)
2014	7,050 (11.7)
2015	7,303 (12.2)
2016	8,260 (13.8)
2017	9,076 (15.1)
2018	9,959 (16.6)

Table 1 (*continued*)

Table 1 (*continued*)

SD, standard deviation; VATS, video-assisted thoracic surgery; CCI, Charlson comorbidity index; ARDS, acute respiratory distress syndrome; USD, United States Dollars.

GLM results were presented as exponentiated regression coefficients (Exp. Coef) with 95% CIs. Lastly, we performed subgroup analyses according to sex, VATS, and type of surgery using multivariable logistic regression modeling for in-hospital mortality. All the variables were included in the multivariable models for adjustment, and there was no multicollinearity between variables with variance inflation factors <2.0, in the multivariable models. R software was used for all statistical analyses (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria), and statistical significance was set at P<0.05.

Results

A total of 60,031 adult patients who underwent lung cancer surgery following a diagnosis of lung cancer between January 1, 2011, and December 31, 2018, were included in the study. The clinicopathological characteristics of all the patients are described in *Table 1*. The mean age (±SD) of the patients was 65.6 years (±9.9 years), and the proportion of male patients was 61.3% (36,778/60,031). In total, 0.5% (285/60,031) experienced fatal respiratory events after lung cancer surgery; 156 (0.3%) patients and 135 (0.2%) patients experienced postoperative ARDS and respiratory failure, respectively. In addition, 0.7%

(391/60,031) of the patients died during hospitalization, while 7.9% (4,744/60,031) died within 1-year after lung cancer surgery.

Development of postoperative respiratory event

Table 2 shows the results of the multivariable logistic regression model for fatal respiratory events after lung cancer surgery. Older age (OR: 1.07, 95% CI: 1.05, 1.09; P<0.001), male sex (OR: 3.26, 95% CI: 2.27, 4.70; P<0.001), bilobectomy (*vs.* wedge resection; OR: 1.97, 95% CI: 1.08, 3.58; P=0.026), pneumonectomy (*vs.* wedge resection; OR: 4.92, 95% CI: 3.02, 8.00; P<0.001), increased CCI point (OR: 1.05, 95% CI: 1.01, 1.09; P=0.018), underlying severe disability (OR: 1.87, 95% CI: 1.19, 2.96; P=0.007), and redo case of lung cancer surgery (OR: 1.81, 95% CI: 1.13, 2.92; P=0.014) were significantly associated with a higher prevalence of postoperative fatal respiratory event. Moreover, a higher annual case volume [≥621 (*vs.* <621), OR: 0.44, 95% CI: 0.29, 0.62; P<0.001] and VATS (*vs.* open thoracotomy; OR: 0.72, 95% CI: 0.55, 0.96; P=0.023) were associated with a lower prevalence of postoperative fatal respiratory events.

Mortality, LOS, and total cost for hospitalization

The analyses of the in-hospital mortality, 1-year mortality, LOS, and total cost of hospitalization are presented in *Table 3*. In the multivariable logistic regression, the postoperative fatal respiratory event group showed a 41.21-fold higher in-hospital mortality than did the other patients (OR: 41.21, 95% CI: 30.24, 56.16; P<0.001). All ORs with 95% CIs of the other covariates are presented in Table S2. In the multivariable Cox regression, the postoperative fatal respiratory event group showed a 9.87-fold higher 1-year mortality than did the other patients (HR: 9.87, 95% CI: 8.45, 11.48; P<0.001). The survival plot derived from the multivariable Cox regression model for 1-year mortality showed a similar trend (*Figure 1*). In the multivariable GLM, the postoperative fatal respiratory event group showed a 1.65-fold longer LOS (Exp. Coef: 1.65, 95% CI: 1.62, 1.69; P<0.001) and a 2.34-fold higher cost for hospitalization (Exp. Coef: 2.34, 95% CI: 2.26, 2.43; P<0.001) than did the other patients. *Table 4* shows the results of the subgroup analyses for in-hospital mortality according to sex, VATS, and type of surgery. The postoperative fatal respiratory event group showed a higher in-hospital mortality than the other patients, in all the subgroups.

Discussion

In this nationwide cohort study, we showed that fatal respiratory events (ARDS or respiratory failure) occurred in 0.5% of patients who underwent lung cancer surgery in South Korea. Factors such as older age, male sex, higher CCI point, underlying severe disability, bilobectomy, pneumonectomy, and redo-case of lung cancer surgery were risk factors for postoperative fatal respiratory events. On the other hand, a higher case volume and VATS were associated with a lower prevalence of fatal postoperative respiratory events. Additionally, the development of postoperative fatal respiratory events was related to increased in-hospital mortality and 1-year mortality, longer LOS, and higher total hospitalization cost.

Patient factors for ALI/ARDS following lung cancer surgery have been evaluated in several studies (9,10). Postoperative ALI after lobectomies for NSCLC was associated with underlying heart and lung disease in a previous study that analyzed 297 patients with lung cancer who underwent lobectomies (9). Another study on lung resection surgery for not only lung cancer but also benign lung diseases found that age >60 years, male sex, and lung cancer were related to ALI/ARDS after pulmonary resection (10). Although the subjects of the study were different from that of our study, the results of our study were generally similar to theirs.

The significant surgical factors for postoperative fatal respiratory events were extent of surgery (bilobectomy of the lung and pneumonectomy), open thoracotomy (*vs.* VATS), and redo case of surgery (*vs.* first case). Pneumonectomy or extended lung surgery has been shown to be associated with postoperative lung injury in a few studies (8,17). One observational study (n=879) reported that pneumonectomy was associated with ALI after lung resection (8). Another observational study by Ruffini *et al.* showed that ALI/ARDS was associated with a high mortality, and the highest mortality rates were observed following right pneumonectomy and extended surgery (17). Patients with lung cancer might lose large amounts of normal lung tissue after lung cancer surgery, especially patients with poor preoperative lung function; this is related to a higher mortality after extended lung cancer surgery (4,12). As for the surgical technique, VATS was associated with reduced postoperative complications, even after adjusting for sex, age, forced expiratory volume in one second, lung cancer stage, year of surgery, and CCI (18,19). Postoperative vital capacity following VATS was significantly more improved

Table 2 Multivariable logistic regression for postoperative fatal respiratory event after lung cancer surgery

Variables	OR (95% CI)	P value
Age	1.07 (1.05, 1.09)	<0.001
Sex, male (*vs.* female)	3.26 (2.27, 4.70)	<0.001
Household income level		
Q1 (lowest)	1.00	
Q2	0.79 (0.54, 1.18)	0.251
Q3	0.85 (0.61, 1.20)	0.362
Q4 (highest)	0.78 (0.57, 1.06)	0.117
Unknown	0.73 (0.29, 1.81)	0.491
Having a job at surgery	0.99 (0.78, 1.27)	0.958
Residence at surgery		
Urban area	1.00	
Rural area	1.03 (0.81, 1.31)	0.820
Type of surgery		
Wedge resection	1.00	
Segmentectomy	1.53 (0.88, 2.67)	0.129
Lobectomy	1.34 (0.94, 1.91)	0.107
Bilobectomy	1.97 (1.08, 3.58)	0.026
Pneumonectomy	4.92 (3.02, 8.00)	<0.001
VATS (*vs.* open thoracotomy)	0.72 (0.55, 0.96)	0.023
CCI at surgery, point	1.05 (1.01, 1.09)	0.018
Preoperative chronic pulmonary disease	1.41 (0.96, 2.07)	0.082
Having a disability at surgery		
Mild to moderate (*vs.* no disability)	1.25 (0.90, 1.74)	0.192
Severe (*vs.* no disability)	1.87 (1.19, 2.96)	0.007
Redo case (*vs.* first case)	1.81 (1.13, 2.92)	0.014
Annual case volume of lung cancer surgery		
<621	1.00	
≥621	0.44 (0.29, 0.62)	<0.001
Type of hospital		
Tertiary general hospital	1.00	
General hospital	0.84 (0.64, 1.11)	0.227
Year of surgery		
2011	1.00	
2012	1.22 (0.76, 1.98)	0.409
2013	0.72 (0.42, 1.23)	0.228
2014	0.81 (0.48, 1.36)	0.419
2015	0.96 (0.58, 1.54)	0.832
2016	0.77 (0.46, 1.28)	0.316
2017	0.95 (0.58, 1.54)	0.832
2018	0.69 (0.41, 1.14)	0.148

Hosmer-Lemeshow test: Chi-square, 9.4, df=8, P=0.310. OR, odds ratio; CI, confidence interval; VATS, video-assisted thoracic surgery; CCI, Charlson comorbidity index.

Table 3 In-hospital mortality, 1-year mortality, LOS, and total cost for hospitalization according to fatal respiratory event after lung cancer surgery

Variables	Event (%) or mean ± SD	OR, HR, Exp. Coef (95% CI)	P value
In-hospital mortality (model 1)			
Other patients	307/59,746 (0.5%)	1.00	
Postoperative fatal respiratory event group	84/285 (29.5%)	41.21 (30.24, 56.16)	<0.001
1-year mortality (model 2)			
Other patients	4,231/59,746 (7.1%)	1.00	
Postoperative fatal respiratory event group	180/285 (63.2%)	9.87 (8.45, 11.48)	<0.001
LOS (model 3)			
Other patients	11.6±7.8 days	1.00	
Postoperative fatal respiratory event group	24.4±14.7 days	1.65 (1.62, 1.69)	<0.001
Total cost for hospitalization (model 4)			
Other patients	8,826.3±4,086.2 USD	1.00	
Postoperative fatal respiratory event group	22,349.2±16,610.4 USD	2.34 (2.26, 2.43)	<0.001

LOS, length of hospital stay; SD, standard deviation; OR, odds ratio; HR, hazard ratio; Exp. Coef, exponentiated regression coefficients; CI, confidence interval; USD, United States Dollars.

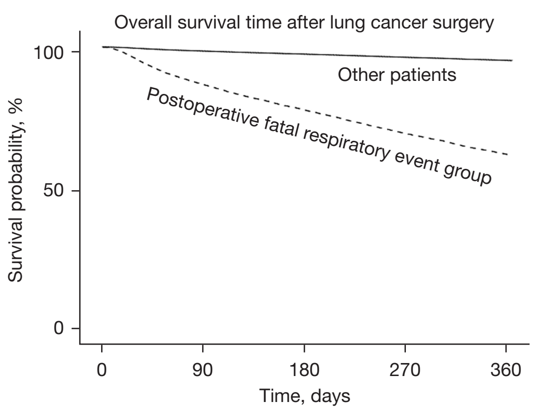

Figure 1 Survival plot derived from the multivariable Cox regression model for 1-year mortality (postoperative fatal respiratory event group *vs.* other patients).

than that after open thoracotomy for lung cancer (18). Moreover, compared to open thoracotomy for lung cancer, VATS was associated with a shorter LOS in the hospital and a reduced need for chemotherapy following surgery (18). These findings support our findings that VATS is associated with a lower prevalence of postoperative fatal respiratory events. However, this should be carefully interpretated because cases where lung cancer surgeries were performed via open thoracotomy may have been more complicated than those where lung cancer surgeries were performed via VATS. This could have resulted in selection bias that may have influenced the results. Additionally, a redo case of lung cancer surgery was expected to be associated with an increased prevalence of postoperative fatal respiratory events because of more surgical complications, greater blood loss, and longer LOS than those observed with the first lung cancer surgery (20).

In terms of hospital factors, we found that a higher case volume of lung cancer surgery was associated with a lower prevalence of postoperative fatal respiratory events. Previous studies have evaluated whether hospital case volume influences the clinical outcome of lung cancer or lung cancer surgery (16,21). A higher case volume center or teaching facility status was associated with improvements in both short-term and long-term mortality in patients who underwent lung cancer surgery (21). Similarly, we showed that an annual case volume of lung cancer surgery of ≥621 (*vs.* <621) and tertiary general hospitals (*vs.* general hospitals) were associated with a lower in-hospital mortality, as shown in Table S2. This result may be related to the higher prevalence of postoperative fatal respiratory events in the low case volume center, as shown in *Table 2*. However, a previous study reported that the impact of hospital case volume on clinical outcomes was not fixed and might be improved by education, systematic, and

Table 4 Subgroup analyses for in-hospital mortality according to sex, VATS, and type of surgery

Variables	Event (%)	OR (95% CI)	P value
Male sex			
Other patients	276/36,527 (0.8)	1.00	
Postoperative fatal respiratory event group	77/251 (30.7)	37.93 (27.46, 52.39)	<0.001
Female sex			
Other patients	31/23,219 (0.1)	1.00	
Postoperative fatal respiratory event group	7/34 (20.6)	120.30 (40.23, 359.78)	<0.001
VATS			
Other patients	177/48,701 (0.4)	1.00	
Postoperative fatal respiratory event group	50/187 (26.7)	48.78 (33.02, 72.07)	<0.001
Open thoracotomy			
Other patients	130/11,045 (1.2)	1.00	
Postoperative fatal respiratory event group	34/98 (34.7)	29.62 (17.74, 49.48)	<0.001
Wedge resection			
Other patients	52/11,449 (0.5)	1.00	
Postoperative fatal respiratory event group	11/40 (27.5)	46.95 (20.59, 107.05)	<0.001
Segmentectomy			
Other patients	16/4,022 (0.4)	1.00	
Postoperative fatal respiratory event group	3/19 (15.8)	50.26 (6.33, 399.22)	<0.001
Lobectomy			
Other patients	171/40,614 (0.4)	1.00	
Postoperative fatal respiratory event group	41/174 (23.6)	41.69 (27.56, 63.09)	<0.001
Bilobectomy			
Other patients	30/1,941 (1.5)	1.00	
Postoperative fatal respiratory event group	8/16 (50.0)	41.91 (10.65, 164.92)	<0.001
Pneumonectomy			
Other patients	38/1,720 (2.2)	1.00	
Postoperative fatal respiratory event group	21/36 (58.3)	55.60 (22.53, 137.2)	<0.001

VATS, video-assisted thoracic surgery; OR, odds ratio; CI, confidence interval.

faculty improvement (22). In a previous study conducted in Taiwan, hospital case volume alone was not a significant predictor of in-hospital mortality following lung cancer surgery after adjusting for patient, surgeon, and hospital characteristics (23). In this study, a higher case volume hospital was associated with a lower prevalence of both postoperative fatal respiratory events and in-hospital mortality. For postoperative patient management, it is more likely that high case volume hospitals with a large number of specialized medical staff and better 24-hour care enable the prevention of fatal respiratory events through faster and adequate diagnosis and intervention (22,24).

Wang *et al.* reported that pulmonary complications after lung resection were associated with prolonged LOS and increased hospitalization costs (25). A previous study by Brunelli *et al.* reported that postoperative complications after lung resection were associated with higher postoperative costs during hospitalization and prolonged LOS (26). Furthermore, the increasing postoperative cost is correlated with the severity of postoperative complications after lung resection (26). As fatal respiratory events such as ARDS or respiratory failure are among the most severe complications (10), the development of postoperative fatal respiratory events might have led to increased costs of hospitalization and prolonged LOS in patients who underwent lung cancer surgery in this study.

This study has some limitations. First, data on perioperative variables such as preoperative lung function, anesthetic duration and technique, ventilator setting state, duration of one lung ventilation, and laboratory results could not be evaluated as risk factors for postoperative fatal respiratory events because NHIS database did not include the required information. Second, the smoking history, which could influence the occurrence of postoperative pulmonary complications, was not included as a covariate because of the lack of information in the NHIS database. Third, we obtained the information about the patients' comorbidities from the ICD-10 codes registered in the NHIS database; however, these may differ from the actual comorbidities in the patients because of missing registration. Fourth, residual or unmeasured confounders might have affected the results. Fifth, we did not consider postoperative complications other than fatal respiratory events, such as surgical site infection, pulmonary edema, and urinary tract infection, which might be related to the incidence of postoperative fatal respiratory events. Finally, we could not assess the number of thoracic surgeons, thoracic anesthesiologists, or intensivists that were involved in the study. Therefore, further research including the factors excluded from the present study is needed to confirm our findings.

Conclusions

In conclusion, postoperative fatal respiratory events such as ARDS or respiratory failure occurred in 0.5% of patients after lung cancer surgery in South Korea. Factors such as older age, male sex, higher CCI point, underlying severe disability, bilobectomy, pneumonectomy, redo case, lower case volume, and open thoracotomy were potential risk factors for the development of postoperative fatal respiratory events. Additionally, the development of postoperative fatal respiratory events was associated with increased in-hospital mortality and 1-year mortality, longer LOS, and higher total hospitalization costs. The knowledge of factors associated with postoperative fatal respiratory events could allow for earlier intervention to potentially reduce fatal respiratory events after lung cancer surgery.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1361/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1361/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1361/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board (IRB) of Seoul National University Bundang Hospital (No. X-2111-721-901) and individual consent for this retrospective analysis was waived.

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA

Cancer J Clin 2018;68:394-424.
2. Didkowska J, Wojciechowska U, Mańczuk M, et al. Lung cancer epidemiology: contemporary and future challenges worldwide. Ann Transl Med 2016;4:150.
3. Uramoto H, Tanaka F. Recurrence after surgery in patients with NSCLC. Transl Lung Cancer Res 2014;3:242-9.
4. Myrdal G, Gustafsson G, Lambe M, et al. Outcome after lung cancer surgery. Factors predicting early mortality and major morbidity. Eur J Cardiothorac Surg 2001;20:694-9.
5. Busch E, Verazin G, Antkowiak JG, et al. Pulmonary complications in patients undergoing thoracotomy for lung carcinoma. Chest 1994;105:760-6.
6. Lugg ST, Agostini PJ, Tikka T, et al. Long-term impact of developing a postoperative pulmonary complication after lung surgery. Thorax 2016;71:171-6.
7. Alam N, Park BJ, Wilton A, et al. Incidence and risk factors for lung injury after lung cancer resection. Ann Thorac Surg 2007;84:1085-91; discussion 1091.
8. Licker M, de Perrot M, Spiliopoulos A, et al. Risk factors for acute lung injury after thoracic surgery for lung cancer. Anesth Analg 2003;97:1558-65.
9. Kim HJ, Cha SI, Kim CH, et al. Risk factors of postoperative acute lung injury following lobectomy for nonsmall cell lung cancer. Medicine (Baltimore) 2019;98:e15078.
10. Kutlu CA, Williams EA, Evans TW, et al. Acute lung injury and acute respiratory distress syndrome after pulmonary resection. Ann Thorac Surg 2000;69:376-80.
11. van der Werff YD, van der Houwen HK, Heijmans PJ, et al. Postpneumonectomy pulmonary edema. A retrospective analysis of incidence and possible risk factors. Chest 1997;111:1278-84.
12. Parquin F, Marchal M, Mehiri S, et al. Post-pneumonectomy pulmonary edema: analysis and risk factors. Eur J Cardiothorac Surg 1996;10:929-32; discussion 933.
13. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Int J Surg 2014;12:1500-24.
14. Nakahara K, Ohno K, Hashimoto J, et al. Prediction of postoperative respiratory failure in patients undergoing lung resection for lung cancer. Ann Thorac Surg 1988;46:549-52.
15. Grichnik KP, D'Amico TA. Acute lung injury and acute respiratory distress syndrome after pulmonary resection. Semin Cardiothorac Vasc Anesth 2004;8:317-34.
16. Lüchtenborg M, Riaz SP, Coupland VH, et al. High procedure volume is strongly associated with improved survival after lung cancer surgery. J Clin Oncol 2013;31:3141-6.
17. Ruffini E, Parola A, Papalia E, et al. Frequency and mortality of acute lung injury and acute respiratory distress syndrome after pulmonary resection for bronchogenic carcinoma. Eur J Cardiothorac Surg 2001;20:30-6, discussion 36-7.
18. Cheng D, Downey RJ, Kernstine K, et al. Video-assisted thoracic surgery in lung cancer resection: a meta-analysis and systematic review of controlled trials. Innovations (Phila) 2007;2:261-92.
19. Laursen LØ, Petersen RH, Hansen HJ, et al. Video-assisted thoracoscopic surgery lobectomy for lung cancer is associated with a lower 30-day morbidity compared with lobectomy by thoracotomy. Eur J Cardiothorac Surg 2016;49:870-5.
20. Fabian T, Van Backer JT, Ata A. Perioperative Outcomes of Thoracoscopic Reoperations for Clinical Recurrence of Pulmonary Malignancy. Semin Thorac Cardiovasc Surg 2021;33:230-7.
21. Cheung MC, Hamilton K, Sherman R, et al. Impact of teaching facility status and high-volume centers on outcomes for lung cancer resection: an examination of 13,469 surgical patients. Ann Surg Oncol 2009;16:3-13.
22. von Itzstein MS, Lu R, Kernstine KH, et al. Closing the gap: Contribution of surgical best practices to outcome differences between high- and low-volume centers for lung cancer resection. Cancer Med 2020;9:4137-47.
23. Lien YC, Huang MT, Lin HC. Association between surgeon and hospital volume and in-hospital fatalities after lung cancer resections: the experience of an Asian country. Ann Thorac Surg 2007;83:1837-43.
24. Wang S, Lai S, von Itzstein MS, et al. Type and case volume of health care facility influences survival and surgery selection in cases with early-stage non-small cell lung cancer. Cancer 2019;125:4252-9.
25. Wang J, Olak J, Ultmann RE, et al. Assessment of pulmonary complications after lung resection. Ann Thorac Surg 1999;67:1444-7.
26. Brunelli A, Drosos P, Dinesh P, et al. The Severity of Complications Is Associated With Postoperative Costs After Lung Resection. Ann Thorac Surg 2017;103:1641-6.

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Supplementary

Table S1 The ICD-10 codes

Myocardial infarction: I21.x, I22.x, I25.2
Congestive heart failure: I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5 - I42.9, I43.x, I50.x, P29.0
Peripheral vascular disease: I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Cerebrovascular disease: G45.x, G46.x, H34.0, I60.x - I69.x
Dementia: F00.x - F03.x, F05.1, G30.x, G31.1
Chronic pulmonary disease: I27.8, I27.9, J40.x–J47.x, J60.x–J67.x, J68.4, J70.1, J70.3
Rheumatic disease: M05.x, M06.x, M31.5, M32.x–M34.x, M35.1, M35.3, M36.0
Peptic ulcer disease: K25.x - K28.x
Mild liver disease: B18.x, K70.0–K70.3, K70.9, K71.3–K71.5, K71.7, K73.x, K74.x, K76.0, K76.2–K76.4, K76.8, K76.9, Z94.4
Diabetes without chronic complication: E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9
Diabetes with chronic complication: E10.2–E10.5, E10.7, E11.2–E11.5, E11.7, E12.2–E12.5, E12.7, E13.2–E13.5, E13.7, E14.2–E14.5, E14.7
Hemiplegia or paraplegia: G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0 - G83.4, G83.9
Renal disease: I12.0, I13.1, N03.2–N03.7, N05.2–N05.7, N18.x, N19.x, N25.0, Z49.0–Z49.2, Z94.0, Z99.2
Any malignancy, including lymphoma and leukaemia, except malignant neoplasm of skin: C00.x–C26.x, C30.x–C34.x, C37.x–C41.x, C43.x, C45.x–C58.x, C60.x–C76.x, C81.x–C85.x, C88.x, C90.x–C97.x
Moderate or severe liver disease: I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7
Metastatic solid tumour: C77.x–C80.x
AIDS/HIV: B20.x–B22.x, B24.x
Alcoholic liver disease: K70
Toxic liver disease: K71
Hepatic failure: K72
Chronic hepatitis: K73
Liver cirrhosis: K74
Other inflammatory liver diseases (K75)
Other liver diseases (K76)

ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th revision.

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Table S2 Other covariates in model 1

Variables	OR (95% CI)	P value
Age, year	1.08 (1.07, 1.10)	<0.001
Sex, male (*vs.* female)	3.25 (2.30, 4.59)	<0.001
Household income level		
Q1 (lowest)	1.00	
Q2	0.93 (0.66, 1.31)	0.673
Q3	0.92 (0.68, 1.25)	0.592
Q4 (highest)	0.76 (0.57, 1.00)	0.053
Unknown	0.67 (0.29, 1.57)	0.357
Having a job at surgery	1.02 (0.82, 1.27)	0.863
Residence at surgery		
Urban area	1.00	
Rural area	0.87 (0.70, 1.08)	0.212
Type of surgery		
Wedge resection	1.00	
Segmentectomy	0.93 (0.54, 1.60)	0.789
Lobectomy	0.93 (0.69, 1.25)	0.627
Bilobectomy	2.46 (1.58, 3.84)	<0.001
Pneumonectomy	3.55 (2.35, 5.38)	<0.001
VATS (*vs.* open thoracotomy)	0.63 (0.50, 0.80)	<0.001
CCI at surgery, point	1.09 (1.06, 1.13)	<0.001
Preoperative chronic pulmonary disease	1.16 (0.82, 1.64)	0.393
Having a disability at surgery		
Mild to moderate (*vs.* no disability)	0.93 (0.68, 1.28)	0.662
Severe (*vs.* no disability)	1.04 (0.64, 1.687)	0.881
Redo case (*vs.* first case)	1.34 (0.82, 2.18)	0.247
Annual case volume of lung cancer surgery		
<621	1.00	
≥621	0.48 (0.35, 0.66)	<0.001
Type of hospital		
Tertiary general hospital	0.66 (0.52, 0.83)	<0.001
General hospital	1.00	
Year of surgery		
2011	1.00	
2012	0.64 (0.44, 0.95)	0.025
2013	0.61 (0.41, 0.91)	0.015
2014	0.37 (0.23, 0.57)	<0.001
2015	0.49 (0.33, 0.74)	0.001
2016	0.50 (0.34, 0.75)	0.001
2017	0.39 (0.26, 0.59)	<0.001
2018	0.31 (0.20, 0.48)	<0.001

Hosmer-Lemeshow test: Chi-square, 9.4, df=8, P=0.310. OR, odds ratio; CI, confidence interval; VATS, video-assisted thoracic surgery; CCI, Charlson comorbidity index.

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