

# Effects of degree of pulmonary fissure completeness on major in-hospital outcomes after video-assisted thoracoscopic lung cancer lobectomy: a retrospective-cohort study

Shuangjiang Li<sup>1,\*</sup>  
 Zhiqiang Wang<sup>2,\*</sup>  
 Kun Zhou<sup>1,\*</sup>  
 Yan Wang<sup>1</sup>  
 Yanming Wu<sup>1</sup>  
 Pengfei Li<sup>1</sup>  
 Guowei Che<sup>1</sup>

<sup>1</sup>Department of Thoracic Surgery, West China Hospital, Sichuan University, Chengdu,

<sup>2</sup>Department of Thoracic Surgery, Chongqing University Cancer Hospital, Chongqing Cancer Institute, Chongqing Cancer Hospital, Chongqing University, Chongqing China

\*These authors contributed equally to this work

**Background:** To evaluate the clinical significance of degree of pulmonary fissure completeness (PFC) on major in-hospital outcomes following video-assisted thoracoscopic (VATS) lobectomy for non-small-cell lung cancer (NSCLC).

**Materials and methods:** We carried out a single-center retrospective analysis on the prospectively maintained database at our unit between August 2014 and October 2015. Patients were divided into two groups based on their fissure sum average (FSA). Patients with FSA >1 (1 < FSA ≤3) were considered to have incomplete pulmonary fissures (group A), while patients with FSA of 0–1 were considered to have complete pulmonary fissures (group B). Demographic differences in perioperative characteristics and surgical outcomes between these two groups were initially assessed. Then, a multivariate logistic-regression analysis was further conducted to identify the independent predictors for major in-hospital outcomes.

**Results:** A total of 563 patients undergoing VATS lobectomy for NSCLC were enrolled. There were 190 patients in group A and 373 patients in group B. The overall morbidity and mortality rates of our cohort were 30.6% and 0.5%, respectively. Group A patients had a significantly higher overall morbidity rate than group B patients (42.1% vs 24.7%,  $P < 0.001$ ). Both minor morbidity (40.5% vs 22%,  $P < 0.001$ ) and major morbidity (11.1% vs 5.6%,  $P = 0.021$ ) rates in group A patients were also significantly higher than group B patients. No significant difference was observed in mortality rate between these two groups (1.1% vs 0.3%,  $P = 0.26$ ). The incomplete degree of PFC was significantly correlated with length of stay and chest-tube duration (log-rank  $P < 0.001$ ) after surgery. Finally, the incomplete degree of PFC was found to be predictive of overall morbidity (OR 2.08,  $P < 0.001$ ), minor morbidity (OR 2.39,  $P < 0.001$ ), and major morbidity (OR 2.06,  $P = 0.031$ ) by multivariate logistic-regression analyses.

**Conclusion:** Degree of PFC is an excellent categorical predictor for both major and minor morbidity after VATS lobectomy for NSCLC.

**Keywords:** pulmonary fissure completeness, video-assisted thoracoscopic surgery, lobectomy, non-small-cell lung cancer, morbidity, mortality

## Introduction Rationale

Lung cancer is currently the worldwide leading cause of cancer-related deaths and remains the most prevalent cancer in both developed and developing countries. Non-small-cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases, with a poor 5-year survival rate <20%.<sup>1</sup> Nowadays, radical surgery is regarded

Correspondence: Guowei Che  
 Department of Thoracic Surgery,  
 West China Hospital, Sichuan University,  
 37 Guoxue Alley, Chengdu, Sichuan  
 610041, China  
 Tel +86 189 8060 1890  
 Fax +86 28 8542 2494  
 Email guowei\_che@foxmail.com

not only as the optimal therapeutic option for early-stage NSCLC but also as a key component of multidisciplinary treatments for advanced-stage NSCLC.<sup>2,3</sup> Lobectomy is a standardized surgical procedure in treating operable NSCLC, because of its safety, capacity of en bloc resection, and ability to preserve pulmonary function.<sup>4</sup> Approximately 70% of lung cancer patients reported in many previous large-scale trials are treated with lobectomy.<sup>5,6</sup>

Since the 1990s, video-assisted thoracoscopic surgery (VATS) has emerged as a minimally invasive technique to gain access to the chest cavity, instead of dissecting the intercostal muscles and cutting off the ribs in traditional posterolateral thoracotomy.<sup>7</sup> VATS techniques have been dramatically developed and widely utilized in modern surgery for operable NSCLC, offering many more advantages to surgical patients than traditional thoracotomy, especially for pain and stress control, better cosmetic wounds, and preservation of pulmonary function.<sup>7,8</sup> However, despite advances in surgical techniques and perioperative care, the morbidity rate remains as high as 24.9%–36.3%.<sup>7–9</sup>

A number of coexisting invasive clinicopathological variables may increase both morbidity and mortality rates and then cause adverse effects on the lung cancer prognosis. Several major comorbidities that frequently accompany NSCLC, such as COPD, diabetes mellitus (DM), and tuberculosis, and procedural stress responses, such as those related to neoadjuvant (induction) therapy, surgical approaches, and extent of surgery, have significantly unfavorable influences on surgical outcomes.<sup>2,5,10–13</sup> All of these factors have been extensively explored in previous studies.

The degree of pulmonary fissure completeness (PFC) is an important issue that thoracic surgeons always deal with when performing VATS lobectomy. Current evidence indicates that incomplete interlobar fissures can increase the surgical difficulty and the probability of prolonged air leak (PAL).<sup>14</sup> However, the effects of PFC degree on other major in-hospital outcomes have never been discussed in the literature. A recent cohort study from Lee et al<sup>15</sup> confirmed the prognostic value of PFC in patients with stage I adenocarcinoma, but rarely mentioned its impact on in-hospital morbidity or mortality.

## Objectives

In the present study, we quantified degrees of PFC with a modified scoring system during the intraoperative period.

The primary purpose of this study was to evaluate the predictive roles of PFC for in-hospital morbidity and mortality following VATS lobectomy for operable NSCLC. Our secondary goal was to explore the effects of different degrees of PFC on length of hospital stay in patients undergoing VATS lobectomy.

## Materials and methods

### Ethics approval and consent to participate

This study was approved by the regional ethics committee of Sichuan University West China Hospital (2016-255), and all relevant procedures were in compliance with the Helsinki Declaration. Written informed consent forms, including the use of participant medical characteristics and files for research in this manuscript, were signed by all enrolled patients.

### Study design

This was a single-center retrospective-cohort study conducted on data from a prospectively maintained database of medical records at our unit. It was written in compliance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.<sup>16</sup>

## Patient selection

### Settings

We retrospectively analyzed clinical data of consecutive patients undergoing VATS lobectomy for operable NSCLC in our institution between August 2014 and October 2015. Their medical records were carefully reviewed, and all available data for perioperative characteristics and surgical outcomes were extracted for further analyses.

### Inclusion and exclusion criteria

Target diseases were operable primary NSCLCs. Only standardized single-lobectomy operated on by a completely VATS procedure could be included. Pneumonectomy, bilobectomy, extended lobectomy, sleeve lobectomy, segmentectomy, or wedge resections by either thoracotomy or VATS procedure were considered. In addition, we further excluded data of patients who underwent conversion to thoracotomy during VATS lobectomy, because of the well-defined effects of unexpected conversion on morbidity risks,<sup>9</sup> in order to eliminate the confounding influence that might complicate the actual roles of PFC. Patients who received neoadjuvant therapy before surgery were excluded from our study, in order to avoid the confounding-bias

risks caused by negative effects of neoadjuvant therapy on major in-hospital outcomes.<sup>13</sup> Patients had to have finished the entire clinical pathway according to our institutional policies during their hospitalization. Patients with loss of accurate records on estimated variables or outcomes were not considered.

### Follow-up

The end points of our study belong to major in-hospital outcomes. Therefore, a follow-up would be provided on each patient until 30 days after surgery or death in the hospital.

## Outcome data, measures, and definitions

We recorded and defined the following outcome data in the present study.

### Preoperative variables

Patient baseline characteristics included age, gender, body-mass index, and smoking history (formal/current/never-smoker). Preoperative underlying comorbidities included COPD, tuberculosis, asthma, preoperative respiratory infection (PRI), hypertension, DM, coronary heart disease, previous malignancy, severe liver diseases, renal insufficiency, and steroid use. We defined PRI as the presence of one or more of the following infectious diseases: obstructive pneumonia, aspiration pneumonia, lung abscess, bronchiectasis, and respiratory bacterial/fungal infections. Severe liver diseases involved hepatitis B, hepatitis C, hepatocirrhosis, severe fatty liver and hepatic parasitic infections.<sup>4,7,9</sup>

### Intraoperative variables

Intraoperative variables estimated in the comparative analyses included tumor location, degree of pleural adhesion (none/light/moderate/severe), severity of pleural invasion (none/visceral/parietal), degree of PFC, and duration of surgery.<sup>4,7,9</sup>

### Assessment of pulmonary fissure completeness

Two board-certified surgeons with 8-year clinical experience quantified degrees of PFC independently during the intraoperative period using the fissure-development score system reported by Lee et al<sup>15</sup> in their cohort study. In cases of intraoperative mapping where the two surgeons disagreed, a consensus assessment would be determined by a third surgeon with 15-year experience.

For thoracic surgeons, it is widely accepted that the integrity of interlobar fissure in its depth is more clinically meaningful and worthy of evaluation than in its length when dissecting the pulmonary artery at the base of the oblique fissure. As such, in a this study, the fissure-development score was based on a modified assessment model based on the original classification for stratification of PFC:<sup>17</sup>

- grade 0 – fully complete fissure with well-separated lobes;
- grade 1 – complete visceral cleft with more than 70% completeness of the interlobar fissure within the lung parenchyma;
- grade 2 – partly evident visceral cleft with 30%–70% completeness of the interlobar fissure within the lung parenchyma;
- grade 3 – no evident fissural line with absent 30% completeness of the interlobar fissure within the lung parenchyma.

As an important anatomical factor, PFs can be classified as upper major fissures (right/left), lower major fissures (right/left), and minor fissures (right). At least two of these interlobar fissures would be divided when performing VATS lobectomy. Therefore, the fissure sum average (FSA), an average of the fissure-development score of two dissected fissures, was utilized for further grouping and comparison.<sup>4</sup>

### Pathological variables

The following pathological parameters were estimated, including differentiation degree (low/moderate/high), tumor invasion (T status), lymph node-metastasis (N status), and tumour, node, and metastasis (TNM) stage, which were defined according to *Union for International Cancer Control TNM Classification* (seventh edition).<sup>4,7,9</sup>

### Postoperative outcomes

#### Primary outcomes of interest

Overall morbidity was defined by the presence of one or more postoperative complications according to the Clavien–Dindo classification system.<sup>18</sup> A range of postoperative complications were assigned to five morbidity grades in compliance with this classification system, as reported in our previous studies.<sup>19–21</sup> Then, we defined minor morbidity as the presence of any Clavien–Dindo grade I–II complication, including pneumonia, atelectasis, hemoptysis, atrial arrhythmia, sinus irregularity, wound infection, delirium, gastrointestinal discomforts, urinary retention, PAL, subcutaneous emphysema, pneumothorax, and pleural effusion, all of which were cured by conservative treatment.

Clavien–Dindo grade III–IV complications, including severe atelectasis needing bronchoscopic aspiration, acute respiratory distress syndrome, chylothorax, pulmonary embolism, hemothorax, bronchial fistula, ventricular arrhythmia, PAL, subcutaneous emphysema, pneumothorax, and pleural effusion needing chest-tube replacement, thoracentesis, or reoperation, were categorized as major morbidities for further analysis. Furthermore, we defined in-hospital mortality as any death within 30 days after surgery or during the entire perioperative period, which was also regarded as a Clavien–Dindo grade V complication. All of these complications following VATS lobectomy were judged in compliance with US Society of Thoracic Surgeons and European Society of Thoracic Surgeons joint definitions.<sup>22</sup>

### Secondary outcomes of interest

Length of stay was calculated from the operation day to the discharge day. Duration of chest-tube drainage refers to days of pleural drainage.

### Grouping criteria

With reference to the cutoff proposed by Lee et al,<sup>15</sup> patients were divided into two groups based on their FSA. Patients with an FSA >1 ( $1 < \text{FSA} \leq 3$ ) were classified as group A, indicating that they had incomplete PFs. On the contrary, patients with an FSA of 0–1 were classified as group B, suggesting that they had good completeness of PFs. This cutoff of FSA >1 would be included in the multivariate logistic-regression model to stratify patients at high surgical risk.

### Surgical procedure and perioperative care

VATS lobectomy with systematic mediastinal lymph-node dissection was performed via three-portal access using a single-direction thoracoscopic technique previously described by Liu et al:<sup>23,24</sup> a modified “hilum-first-fissure last” technique that avoids early dissections through the fissural parenchyma. Staple-line buttressing was then implemented on the bronchial stumps of all enrolled patients.

Surgical patients were managed in compliance with our standardized clinical pathway, including comprehensive routine assessments, antibiotic prophylaxis, and pulmonary rehabilitation physiotherapy.<sup>25</sup> All these patients received intravenous patient-controlled analgesia for postoperative pain control. A chest tube was placed on the suction device (–20 cm H<sub>2</sub>O) at the end of the operation and then either alternated or removed according to our institutional policies. A chest radiograph was done to stratify levels of lung recruitment on

postlobectomy day 1. Chest-tube removal was allowed with pleural drainage <200 mL in 24 hours and air leak (AL) cessation detected in the chest-drainage system. Analgesic management was stopped after removing the chest tube.<sup>4,7,9</sup>

### Statistical analysis

Continuous data are presented as the means with SDs and medians with IQRs, while categorical data are presented as patient numbers and percentages. In the univariate analysis, we used Pearson’s  $\chi^2$  or Fisher’s exact test to compare categorical variables and Student’s *t*-test to compare mean values of continuous variables.

Then, a multivariate logistic-regression analysis was performed to identify independent risk factors for major in-hospital morbidities. Dichotomous data with univariate  $P < 0.05$  were put into the logistic-regression model, utilizing the Hosmer–Lemeshow test for precision and the *C*-statistic for calibration. Finally, ORs with 95% CIs were derived from multivariate logistic-regression analysis. Statistical significance was set at  $P < 0.05$ . All statistical analyses were accomplished with SPSS 22.0 software (IBM Corporation, Armonk, NY, USA).

## Results

### Basic characteristics and outcomes

#### Patient characteristics

There were 563 patients meeting the eligibility criteria who underwent VATS lobectomy for primary NSCLC during the study period included in the present study. Patient baseline characteristics and surgical outcomes are outlined in Table 1. Our cohort consisted of 359 male (63.8%) and 204 female patients (36.2%), with a mean age of  $62.2 \pm 8.3$  years (median 62 years, IQR 57–69 years). Mean body-mass index was  $23.4 \pm 2.9$  kg/m<sup>2</sup> (median 23.3 kg/m<sup>2</sup>, IQR 21.3–25.4 kg/m<sup>2</sup>). A total of 316 were active smokers (56.1%), and 403 patients (71.6%) suffered from one or more underlying comorbidities, as shown in Table 1. There were 237 patients that received adjuvant chemotherapy followed by VATS lobectomy (42.1%).

Tumors located in the right upper lobe ( $n=185$ ) accounted for the largest proportion of the entire cohort – 32.9%. The mean operation time of the cohort was  $129.3 \pm 42.4$  (median 120, IQR 110–140) minutes. The majority of patients were diagnosed with stage I–II NSCLC ( $n=493$ , 87.5%). Lung adenocarcinoma accounted for 70.2% ( $n=395$ ) of all enrolled cases, followed by squamous-cell carcinoma in 150 patients (26.6%), large-cell carcinoma in eleven (2%), and other subtypes of NSCLC in seven (1.2%). In addition, lymph-node metastasis was confirmed by pathological criteria after surgery in 150 patients (26.6%) (Table 1).

**Table 1** Patient characteristics and outcomes

	<b>Total, N=563</b>	<b>Group A (1 &lt; FSA ≤3), n=190</b>	<b>Group B (FSA 0–1), n=373</b>	<b>P-value</b>
<b>Baseline information</b>				
Age (years)				
Mean ± SD	62.2±8.3	63.5±8.3	61.5±8.3	<0.001
Median (IQR)	62 (57–69)	63 (58–71)	62 (56–67)	
Gender (male)	359 (63.8)	129 (67.9)	230 (61.7)	0.15
Body-mass index (kg/m <sup>2</sup> )				
Mean ± SD	23.4±2.9	23.2±2.8	23.5±3	0.42
Median (range)	23.3 (21.3–25.4)	22.9 (21–25.6)	23.5 (21.3–25.4)	
Smoking history	316 (56.1)	118 (62.1)	198 (53.1)	0.041
COPD	138 (24.5)	48 (25.3)	90 (24.1)	0.77
Asthma	10 (1.8)	3 (1.6)	7 (1.9)	0.8
Tuberculosis	38 (6.7)	20 (10.5)	18 (4.8)	0.011
Preoperative respiratory infection	62 (11)	23 (12.1)	39 (10.5)	0.55
Hypertension	188 (33.4)	70 (36.8)	118 (31.6)	0.22
Diabetes mellitus	56 (9.9)	29 (15.3)	27 (7.2)	0.003
Coronary heart disease	65 (11.5)	29 (15.3)	36 (9.7)	0.052
Renal insufficiency	43 (7.6)	18 (9.5)	25 (6.7)	0.24
Severe liver disease	55 (9.8)	17 (8.9)	38 (10.2)	0.64
Previous malignancy	25 (4.4)	14 (7.4)	11 (2.9)	0.016
Steroid use	24 (4.3)	6 (3.2)	18 (4.8)	0.35
Adjuvant chemotherapy	237 (42.1)	82 (43.2)	155 (41.6)	0.72
<b>Intraoperative parameters</b>				
Tumor location				
Right upper lobe	185 (32.9)	77 (40.5)	108 (29)	0.002
Left upper lobe	120 (21.3)	32 (16.8)	88 (23.6)	
Right lower lobe	121 (21.5)	27 (14.2)	94 (25.2)	
Left lower lobe	79 (14)	32 (16.8)	47 (12.6)	
Right middle lobe	58 (10.3)	22 (11.6)	36 (9.7)	
Degree of pleural invasion				
None	263 (46.7)	92 (48.4)	171 (45.8)	0.53
Visceral	248 (44)	84 (44.2)	164 (44)	
Parietal	52 (9.2)	14 (7.4)	38 (10.2)	
Severity of pleural adhesion				
None	214 (38)	49 (25.8)	165 (44.2)	<0.001
Light	182 (32.3)	55 (28.9)	127 (34)	
Moderate	107 (19)	47 (24.7)	60 (16.1)	
Severe/atresia	60 (10.7)	39 (20.5)	21 (5.6)	
Operation time (minutes)				
Mean ± SD	129.3±42.4	140.7±47.3	122.9±38.1	<0.001
Median (IQR)	120 (110–140)	130 (120–150)	120 (100–130)	
<b>Pathological parameters</b>				
Histology				
Adenocarcinoma	395 (70.2)	134 (70.5)	261 (70)	0.41
Squamous-cell carcinoma	150 (26.6)	53 (27.9)	97 (26)	
Large-cell carcinoma	11 (2)	2 (1.1)	9 (2.4)	
Other subtypes of NSCLC	7 (1.2)	1 (0.5)	6 (1.6)	
Differentiation degree				
Low	128 (22.7)	56 (29.5)	72 (19.3)	0.006
Moderate/high	435 (77.3)	134 (70.5)	301 (80.7)	
Tumor invasion (T stage)				
T1–T2	537 (95.4)	181 (95.3)	356 (95.4)	0.92
T3	26 (4.6)	9 (4.7)	17 (4.6)	
Lymph-node metastasis (N stage)				
N1–N2	150 (26.6)	54 (28.4)	96 (25.7)	0.5
N0	413 (73.4)	136 (71.6)	277 (74.3)	

(Continued)



**Table 1** (Continued)

	Total, N=563	Group A (1 < FSA ≤3), n=190	Group B (FSA 0–1), n=373	P-value
TNM stage				
I	355 (63)	122 (64.2)	233 (62.5)	0.36
II	138 (24.5)	49 (25.8)	89 (23.9)	
IIIA	70 (12.4)	19 (10)	51 (13.7)	
Major in-hospital outcomes				
Overall morbidity (any complication)	172 (30.6)	80 (42.1)	92 (24.7)	<0.001
Minor morbidity (Clavien–Dindo grade I–II)	159 (28.2)	77 (40.5)	82 (22)	<0.001
Major morbidity (Clavien–Dindo grade III–IV)	42 (7.5)	21 (11.1)	21 (5.6)	0.021
In-hospital mortality (Clavien–Dindo grade V)	3 (0.5)	2 (1.1)	1 (0.3)	0.26

**Note:** Data presented as n (%) unless otherwise stated.

**Abbreviations:** FSA, fissure-sum average; IQR, interquartile range; NSCLC, non-small-cell lung cancer; TNM, tumour, node, and metastasis.

### Degree of pulmonary fissure completeness

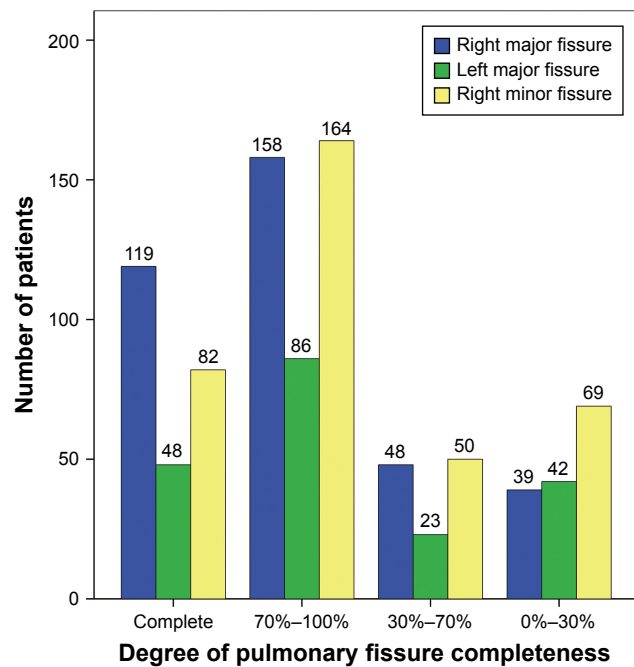
The degree of PFC estimated by fissure-development score in all enrolled patients is shown in Figure 1. There were 262 patients with an FSA of 0 (46.5%), 111 patients with FSA 0–1 (19.7%), 102 patients with 1 < FSA ≤2 (18.1%), and 88 patients with 2 < FSA ≤3 (15.6%), respectively (Figure 2). Therefore, a total of 190 patients were included in group A (33.7%), and the remaining 373 patients with FSA 0–1 were included in group B (66.3%).

When compared with group B patients, group A patients had significantly higher mean age ( $P < 0.001$ ) and duration of surgery ( $P < 0.001$ ), and higher rates of smoking history ( $P = 0.041$ ), tuberculosis ( $P = 0.011$ ), DM ( $P = 0.003$ ), malignancy history ( $P = 0.016$ ), right upper lobe-located lesion ( $P = 0.002$ ), dense pleural adhesion ( $P < 0.001$ ), and lowly

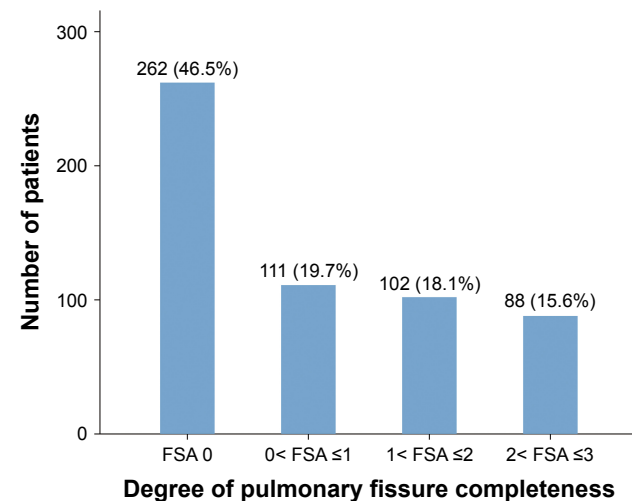
differentiated tumors ( $P = 0.006$ ). No difference was found in the other clinicopathological variables between these two groups (Table 1).

### Postoperative outcomes

A total of 298 postoperative complications developed in 172 patients, with an overall morbidity rate of 30.6%. Minor and major morbidity rates were 28.2% (n=159) and 7.5% (n=42), respectively. There were three deaths during the in-hospital period, with a mortality rate of 0.5%, as shown in Table 1. Incidence of individual complications is presented in Table 2. The five most frequent complications were PAL (n=72, 12.8%), pneumonia (n=69, 12.3%), atelectasis (n=37, 6.6%), subcutaneous emphysema (n=32, 5.7%), and pneumothorax (n=23, 4.1%). With regard to secondary outcomes, the mean duration of chest-tube drainage and length of stay of the entire cohort were 4.4±3 (median 3, IQR 2–6) and 6.9±3.5 (median 6, IQR 4–8) days, respectively.



**Figure 1** Degrees of major and minor pulmonary fissure completeness.



**Figure 2** Proportions of four different degrees of pulmonary fissure completeness. **Abbreviation:** FSA, fissure-sum average.

**Table 2** Individual postoperative complications

	Total, N=563	Group A (1 < FSA ≤3), n=190	Group B (FSA 0–1), n=373	P-value
Prolonged air leak (>5 days)	72 (12.8)	42 (22.1)	30 (8)	<0.001
Pneumonia	69 (12.3)	33 (17.4)	36 (9.7)	0.008
Atelectasis	37 (6.6)	20 (10.5)	17 (4.6)	0.007
Subcutaneous emphysema	32 (5.7)	17 (8.9)	15 (4)	0.017
Pneumothorax	23 (4.1)	13 (6.8)	10 (2.7)	0.018
Pleural effusion	7 (1.2)	5 (2.6)	2 (0.5)	0.047
ARDS	5 (0.9)	2 (1.1)	3 (0.8)	1
Chylothorax	10 (1.8)	2 (1.1)	8 (2.1)	0.56
Pulmonary embolism	5 (0.9)	3 (1.6)	2 (0.5)	0.34
Hemoptysis	7 (1.2)	5 (2.6)	2 (0.5)	0.086
Hemothorax	2 (0.4)	1 (0.5)	1 (0.3)	1
Bronchoesophageal fistula	1 (0.2)	0	1 (0.3)	1
Wound infection	4 (0.7)	0	4 (1.1)	0.31
Atrial arrhythmia	7 (1.2)	5 (2.6)	2 (0.5)	0.047
Ventricular arrhythmia	2 (0.4)	2 (1.1)	0	0.11
Sinus irregularity	5 (0.9)	2 (1.1)	3 (0.8)	0.77
Delirium	4 (0.7)	1 (0.5)	3 (0.8)	1
Gastrointestinal discomforts	3 (0.5)	2 (1.1)	1 (0.3)	0.26
Urinary retention	3 (0.5)	0	3 (0.8)	0.55

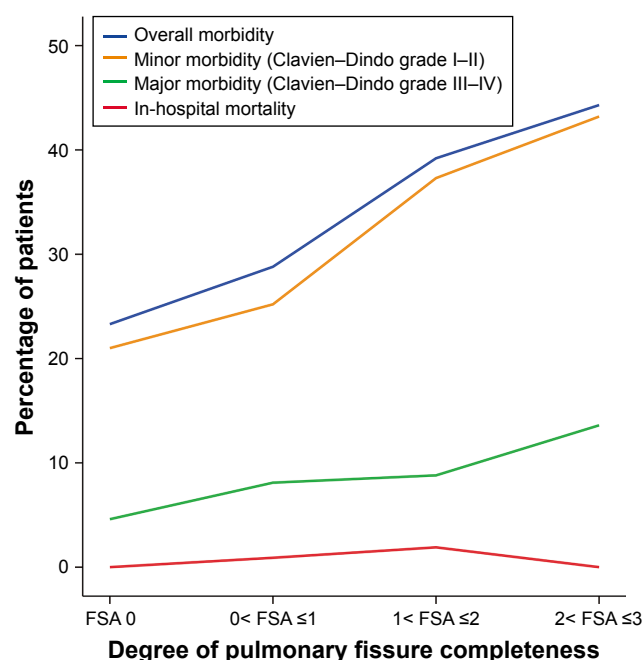
**Note:** Data presented as n (%).

**Abbreviations:** ARDS, acute respiratory distress syndrome; FSA, fissure-sum average.

## Effect of degree of PFC on postoperative complications

### Overall morbidity and mortality

Percentages of both overall morbidity and in-hospital mortality distributed over four different degrees of PFC are shown in Figure 3. The overall morbidity rate showed a steady tendency to increase with increasing FSA score, as shown



**Figure 3** Tendency of major in-hospital outcomes with increasing FSA.

**Abbreviation:** FSA, fissure-sum average.

in Figure 3. There were 80 patients in the group A that developed postoperative complications, while 92 patients in group B had postoperative complications. The overall morbidity rate in group A patients was significantly higher than in group B patients (42.1% vs 24.7%,  $P < 0.001$ ; Table 1). With regard to in-hospital mortality, two of three deaths belonged to group A, and the remaining one was from group B. No significant difference was found in mortality rate between these two groups (1.1% vs 0.3%,  $P = 0.26$ ; Table 1).

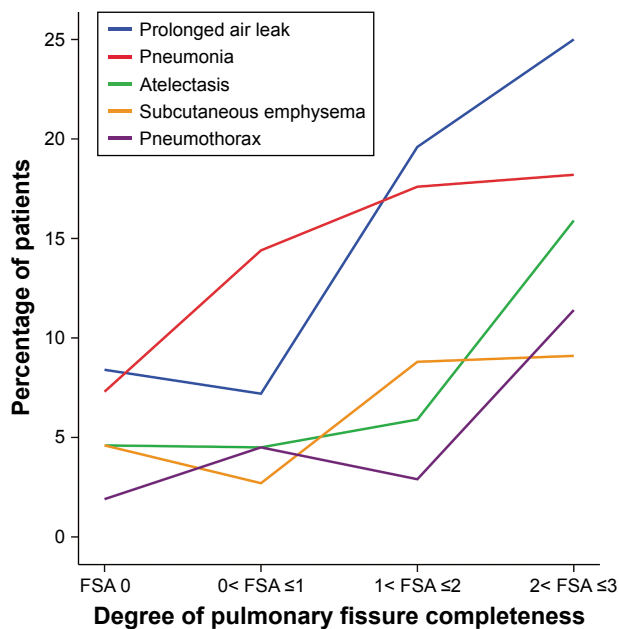
### Minor and major morbidity

Both minor and major morbidity rates were found to have a steady tendency to increase with increasing FSA score, as shown in Figure 3. Compared to group B patients, group A patients had both significantly higher rates of minor morbidity (40.5% vs 22%,  $P < 0.001$ ; Table 1) and major morbidity (11.1 vs 5.6%,  $P = 0.021$ ; Table 1).

### Individual complications

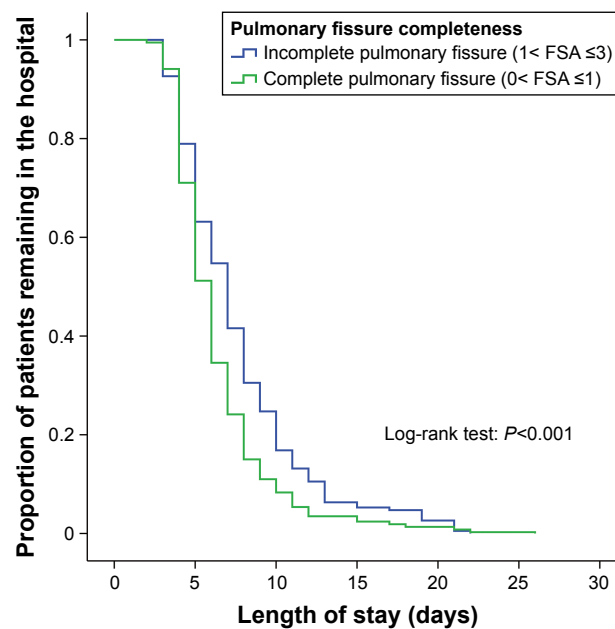
Figure 4 shows the five most frequent individual complications distributed over four different degrees of PFC. We found that only the incidence of pneumonia showed a steady tendency to increase with increasing FSA score. The incidence of PAL, atelectasis, subcutaneous emphysema, and pneumothorax all showed little fluctuation until reaching their peaks in the patients with  $2 < FSA \leq 3$ .

Incidence of individual complications between group A and group B is shown in Table 2. Incidence of five most



**Figure 4** Tendency of the five most frequent individual complications with increasing FSA.

**Abbreviation:** FSA, fissure-sum average.



**Figure 5** Kaplan–Meier curve for length of stay between patients with incomplete pulmonary fissures and complete pulmonary fissures.

**Abbreviation:** FSA, fissure-sum average.

frequent complications in group A patients, including PAL (22.1% vs 8%,  $P < 0.001$ ), pneumonia (17.4% vs 9.7%,  $P = 0.008$ ), atelectasis (10.5% vs 4.6%,  $P = 0.007$ ), subcutaneous emphysema (8.9% vs 4%,  $P = 0.017$ ), and pneumothorax (6.8% vs 2.7%,  $P = 0.018$ ) was significantly higher than group B patients. In addition, group A patients also had significantly higher incidence of pleural effusion (2.6% vs 0.5%,  $P = 0.047$ ) and atrial arrhythmia (2.6 vs 0.5%,  $P = 0.047$ ) than group B patients. No significant difference was found in other complications between these two groups.

### Effect of degree of PFC on length of hospital stay

#### Length of stay

A Kaplan–Meier curve revealing the length of stay between group A and group B patients is shown in Figure 5. The mean length of stay in group A (mean 7.7 days; 95% CI 7.1–8.2 days) was significantly longer than that group B (mean 6.4 days, 95% CI 6.1–6.7 days; log-rank  $P < 0.001$ ), indicating that incomplete degree of PFC was significantly associated with prolonged length of stay.

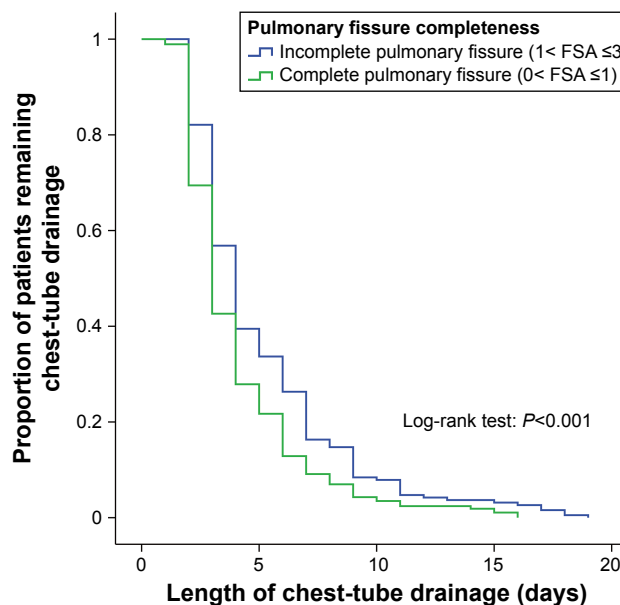
#### Duration of chest-tube drainage

Figure 6 shows the days of pleural drainage in groups A and B. Chest-tube duration in group A (mean 5.1 days, 95% CI 4.6–5.6 days) was significantly longer than group B (mean 4.1 days, 95% CI 3.8–4.4 days; log-rank  $P < 0.001$ ), revealing

a significant relationship between incomplete PF and days of pleural drainage after surgery.

### Univariate analyses on risk factors for postoperative morbidity

Relationships among perioperative patient characteristics and development of postoperative complications are shown in Table 3.



**Figure 6** Kaplan–Meier curve for duration of chest-tube drainage between patients with incomplete pulmonary fissures and complete pulmonary fissures.

**Abbreviation:** FSA, fissure-sum average.



**Table 3** Association between patient baseline characteristics and development of postoperative complications

	Without morbidity, n=391	Overall morbidity, n=172	Minor morbidity, n=159	Major morbidity, n=42	P-value
Age (years)					
Mean $\pm$ SD	61.2 $\pm$ 8.5	64.5 $\pm$ 7.5	64.6 $\pm$ 7.5	65 $\pm$ 6.9	<0.001
Median (IQR)	62 (55–68)	63 (60–71)	63 (60–71)	64 (60–72)	
Gender (male)	235 (60.1)	124 (72.1)	116 (73)	33 (78.6)	0.006
Body-mass index (kg/m <sup>2</sup> )					
Mean $\pm$ SD	23.5 $\pm$ 2.9	23.3 $\pm$ 2.9	23.4 $\pm$ 2.9	23.6 $\pm$ 2.8	0.42
Median (IQR)	23.3 (21.5–25.5)	22.8 (21.1–25.3)	23.4 (21.3–25.4)	22.1 (20.6–25.1)	
Smoking history	209 (53.5)	107 (62.2)	103 (64.8)	28 (66.7)	0.054
COPD	79 (20.2)	59 (34.3)	56 (35.2)	15 (35.7)	<0.001
Asthma	4 (1.1)	6 (3.5)	6 (3.8)	1 (2.4)	0.09
Tuberculosis	27 (6.9)	11 (6.4)	9 (5.7)	2 (4.8)	0.82
Preoperative respiratory infection	30 (7.7)	32 (18.6)	32 (20.1)	13 (31)	<0.001
Hypertension	119 (30.4)	69 (40.1)	66 (41.5)	13 (31)	0.025
Diabetes mellitus	34 (8.7)	22 (12.8)	22 (13.8)	0	0.14
Coronary heart disease	36 (9.2)	29 (16.9)	27 (17)	7 (16.7)	0.009
Renal insufficiency	30 (7.7)	13 (7.6)	12 (7.5)	4 (9.5)	0.96
Severe liver diseases	42 (10.7)	13 (7.6)	11 (6.9)	5 (11.9)	0.24
Previous malignancy	19 (4.9)	6 (3.5)	5 (3.1)	3 (7.1)	0.47
Steroid use	15 (3.8)	9 (5.2)	9 (5.7)	5 (11.9)	0.45
Adjuvant chemotherapy	167 (42.7)	70 (40.7)	67 (42.1)	13 (31)	0.66
Tumor location					
Right upper lobe	130 (33.2)	55 (32)	51 (32.1)	12 (28.6)	0.48
Left upper lobe	84 (21.5)	36 (20.9)	34 (21.4)	11 (26.2)	
Right lower lobe	81 (20.7)	40 (23.3)	36 (22.6)	11 (26.2)	
Left lower lobe	60 (15.3)	19 (11)	19 (11.9)	3 (7.1)	
Right middle lobe	36 (9.2)	22 (12.8)	19 (11.9)	5 (11.9)	
Degree of pleural invasion					
None	182 (46.5)	81 (47.1)	78 (49.1)	20 (47.6)	0.96
Visceral	172 (44)	76 (44.2)	66 (41.5)	21 (50)	
Parietal	37 (9.5)	15 (8.7)	15 (9.4)	1 (2.4)	
Severity of pleural adhesion					
None	149 (38.1)	65 (37.8)	59 (37.1)	12 (28.6)	0.38
Light	131 (33.5)	51 (29.7)	45 (28.3)	13 (31)	
Moderate	75 (19.2)	32 (18.6)	32 (20.1)	8 (19)	
Severe/atresia	36 (9.2)	24 (14)	23 (14.5)	9 (21.4)	
Degree of pulmonary fissure completeness					
Incomplete fissures (1 < FSA $\leq$ 3)	110 (28.1)	80 (46.5)	77 (48.4)	21 (50)	<0.001
Complete fissures (FSA 0–1)	281 (71.9)	92 (53.5)	82 (51.6)	21 (50)	
Operation time (minutes)					
Mean $\pm$ SD	120.5 $\pm$ 32.7	147.9 $\pm$ 53.4	146.9 $\pm$ 52.1	160.7 $\pm$ 66.8	<0.001
Median (IQR)	120 (100–130)	129 (120–160)	130 (120–150)	129 (120–210)	
Histology					
Adenocarcinoma	279 (71.4)	116 (67.4)	107 (67.3)	28 (66.7)	0.1
Squamous-cell carcinoma	96 (24.6)	54 (31.4)	50 (31.4)	14 (33.3)	
Large-cell carcinoma	9 (2.3)	2 (1.2)	2 (1.3)	0	
Other subtypes of NSCLC	7 (1.8)	0	0	0	
Differentiation degree					
Low	86 (22)	42 (24.4)	40 (25.2)	9 (21.4)	0.53
Moderate/high	305 (78)	130 (75.6)	119 (74.8)	33 (78.6)	
Tumor invasion (T stage)					
T1–T2	374 (95.7)	163 (94.8)	150 (94.4)	39 (92.9)	0.65
T3	17 (4.3)	9 (4.7)	9 (5.6)	3 (7.1)	
Lymph-node metastasis (N stage)					
N1–N2	105 (26.9)	45 (26.2)	45 (28.3)	5 (11.9)	0.86
N0	286 (73.1)	127 (73.8)	114 (71.7)	37 (88.1)	
TNM stage					
I	246 (62.9)	109 (63.4)	98 (61.6)	31 (73.8)	0.25
II	90 (23)	48 (27.9)	46 (28.9)	9 (21.4)	
IIIA	55 (14.1)	15 (8.7)	15 (9.4)	2 (4.8)	

**Note:** Data presented as n (%) unless otherwise stated.

**Abbreviations:** FSA, fissure-sum average; IQR, interquartile range; NSCLC, non-small-cell lung cancer; TNM, tumour, node, and metastasis.

### Overall morbidity

Compared to patients without any complications, patients with any complications had significantly higher mean age ( $P<0.001$ ), longer duration of surgery ( $P<0.001$ ), and higher rates of male gender ( $P=0.006$ ), COPD ( $P<0.001$ ), PRI ( $P<0.001$ ), hypertension ( $P=0.025$ ), coronary heart disease ( $P=0.009$ ), and incomplete PF (FSA  $>1$ ,  $P<0.001$ ).

### Minor morbidity

Patients who developed any minor morbidity were found to have significantly higher mean age ( $P<0.001$ ), longer duration of surgery ( $P<0.001$ ), and higher rates of male gender ( $P=0.004$ ), smoking history ( $P=0.009$ ), COPD ( $P<0.001$ ), PRI ( $P<0.001$ ), hypertension ( $P=0.010$ ), coronary heart disease ( $P=0.011$ ), and incomplete PF (FSA  $>1$ ,  $P<0.001$ ) than those with no minor morbidity.

### Major morbidity

Finally, when compared to patients with no major morbidity, patients who developed any major morbidity had significantly higher mean age ( $P=0.022$ ), longer duration of surgery ( $P=0.006$ ), and higher rates of male gender ( $P=0.038$ ),

PRI ( $P<0.001$ ), steroid use ( $P=0.031$ ), and incomplete PF (FSA  $>1$ ,  $P=0.021$ ), but significantly lower rates of DM ( $P=0.025$ ) and lymph-node metastasis ( $P=0.025$ ).

## Multivariate analysis on risk factors for postoperative morbidity

### Overall morbidity

A multivariate logistic-regression model including all eight significant clinical parameters was established, as shown in Table 4. The *C*-statistic for our logistic-regression model was 0.72, with a 95% CI of 0.67–0.77 ( $P<0.001$ ), as shown in Figure 7. Finally, we identified the PRI (OR 2.36, 95% CI 1.3–4.31;  $P=0.005$ ), COPD (OR 1.83, 95% CI 1.17–2.87;  $P=0.009$ ), incomplete PF (FSA  $>1$ , OR 2.08, 95% CI 1.38–3.14;  $P<0.001$ ), and operation time  $>120$  minutes (OR 2.37, 95% CI 1.55–3.65;  $P<0.001$ ) as independent risk factors for overall morbidity after adjusting the confounding influence by the multivariate logistic-regression analysis.

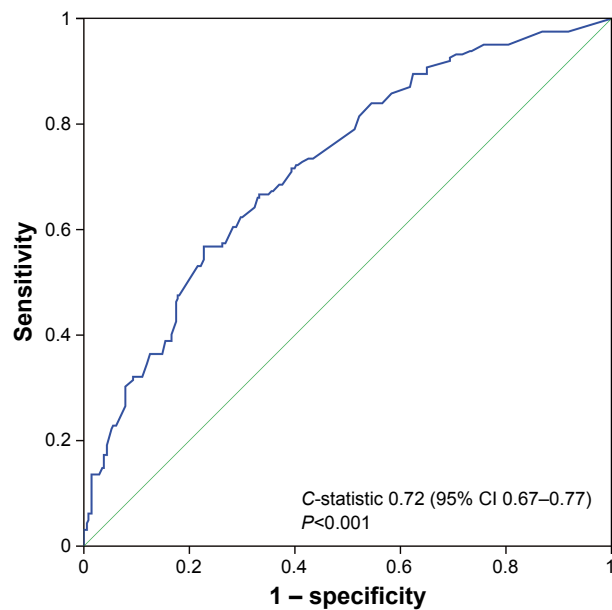
### Minor morbidity

There were nine significant contributing factors derived from the univariate analysis, as shown in Table 4. The multivariate

**Table 4** Multivariate analysis of risk factors for postoperative complications

Estimated factors	OR	95% CI	P-value
<b>Overall morbidity</b>			
Age ( $>65$ vs $\leq 65$ years)	1.24	0.8–1.93	0.34
Gender (male vs female)	1.39	0.9–2.17	0.14
COPD	1.83	1.17–2.87	0.009
Hypertension	1.34	0.87–2.08	0.19
Coronary heart disease	1.49	0.8–2.76	0.21
Preoperative respiratory infection	2.36	1.3–4.31	0.005
Pulmonary fissure completeness (1 < FSA $\leq 3$ vs FSA 0–1)	2.08	1.38–3.14	$<0.001$
Duration of surgery ( $>120$ vs $\leq 120$ minutes)	2.37	1.55–3.65	$<0.001$
<b>Minor morbidity (Clavien–Dindo grade I–II complications)</b>			
Age ( $>65$ vs $\leq 65$ years)	1.22	0.77–1.91	0.4
Sex (male vs female)	1.85	0.91–3.74	0.088
Smoking history	1.33	0.68–2.6	0.41
COPD	1.95	1.22–3.11	0.005
Hypertension	1.52	0.97–2.39	0.068
Coronary heart disease	1.39	0.73–2.62	0.31
Preoperative respiratory infection	2.86	1.56–5.23	0.001
Pulmonary fissure completeness (1 < FSA $\leq 3$ vs FSA 0–1)	2.39	1.57–3.65	$<0.001$
Duration of surgery ( $>120$ vs $\leq 120$ minutes)	2.11	1.36–3.28	0.001
<b>Major morbidity (Clavien–Dindo grade III–IV complications)</b>			
Age ( $>65$ vs $\leq 65$ years)	1.16	0.6–2.25	0.67
Sex (male vs female)	1.98	0.91–4.33	0.084
Preoperative respiratory infection	3.37	1.51–7.54	0.003
Pulmonary fissure completeness (1 < FSA $\leq 3$ vs FSA 0–1)	2.06	1.07–3.95	0.031
Duration of surgery ( $>120$ vs $\leq 120$ minutes)	2.95	1.3–6.72	0.01
Steroid use	1.91	0.58–6.32	0.29

**Abbreviation:** FSA, fissure-sum average.



**Figure 7** Receiver-operating-characteristic analysis on discriminative power of multivariate logistic-regression model for predicting overall morbidity.

**Note:** C-statistic presented as area under curve.

logistic-regression model involving these nine clinico-pathological variables, with a *C*-statistic of 0.74 (95% CI 0.69–0.79;  $P < 0.001$ ), demonstrated that COPD (OR 1.95, 95% CI 1.22–3.11;  $P = 0.005$ ), PRI (OR 2.86, 95% CI 1.56–5.23;  $P = 0.001$ ), incomplete PF (FSA  $> 1$ , OR 2.39, 95% CI 1.57–3.65;  $P < 0.001$ ), and operation time  $> 120$  minutes (OR 2.11, 95% CI 1.36–3.28;  $P = 0.001$ ) were independently predictive of the occurrence of minor morbidity.

### Major morbidity

Table 4 shows six high-risk contributing factors derived from the univariate analysis. According to the multivariate logistic-regression model involving these six clinicopathological parameters, which got a *C*-statistic of 0.69 (95% CI 0.6–0.77,  $P < 0.001$ ), history of PRI (OR 3.37, 95% CI 1.51–7.54;  $P = 0.003$ ), incomplete PF (FSA  $> 1$ , OR 2.06, 95% CI 1.07–3.95;  $P = 0.031$ ), and operation time  $> 120$  minutes (OR 2.95, 95% CI 1.3–6.72;  $P = 0.01$ ) were finally found to be independent risk factors for major morbidity.

## Discussion

### Key results

The main findings of the present study were that patients with incomplete PFs had significantly higher overall morbidity rate, minor morbidity rate, and major morbidity rate than patients with well-developed PFs. Incomplete degree of PFC was significantly associated with higher incidence of PAL, pneumonia, atelectasis, subcutaneous emphysema,

pneumothorax, pleural effusion, and atrial arrhythmia. Patients with incomplete PFs were also found to have significantly prolonged length of stay and pleural drainage than patients with well-developed PFs. The multivariate logistic-regression analysis demonstrated that incomplete degree of PFC was a strongly independent risk factor for overall morbidity, minor morbidity, and major morbidity.

### Interpretations

Nowadays, the identification and measurement of PFC can be achieved by several perioperative methods. Imaging techniques, especially high-resolution computerized tomography (CT) and multidetector CT, with their 3-D reconstructions, have mostly been used to assess the integrity of interlobar fissures preoperatively, although these computerized methods still need to be validated, especially in patients with heterogeneously diseased lungs.<sup>26,27</sup> By visual inspection of thin-section CT images, an interlobar fissure can be seen as a thin line that separates neighboring lobes, while the line is generally disconnected by vessels or lung parenchyma in cases of incompleteness. Perioperative mapping is performed only on patients with serious pulmonary diseases, although this method depends on the surgeon's area of interest and expertise.<sup>26</sup> An autopsy can also help to distinguish adjacent lobes, but with the obvious drawback that it can only be performed on eviscerated lungs postoperatively.

Prior studies have demonstrated that incomplete degree of PFC was a major risk factor for PAL, but showed no evidence of other major in-hospital outcomes.<sup>14,28,29</sup> The earliest study<sup>30</sup> indicated that incomplete PFs had no impact on 5-year survival of resected NSCLC. However, no detail about in-hospital outcome was presented in that study. In another cohort of 297 stage I adenocarcinoma patients, Lee et al<sup>15</sup> evaluated the prognostic roles of degree of PFC, and concluded that incomplete PFs had adverse effects on 5-year survival, but showed no significant impact on either in-hospital morbidity or mortality. Effects of PFC on any individual complication were not further reported.

In our series, we quantified degree of PFC by using the fissure-development score that was reported by Lee et al,<sup>15</sup> and recorded details in the intraoperative period. The FSA of two dissected fissures during VATS lobectomy was calculated and then utilized to establish our grouping criterion. As Lee et al<sup>15</sup> previously described, FSA  $> 1$  was chosen as the cutoff to indicate the incomplete degree of PFC. After that, we found a significantly higher incidence of PAL in patients with incomplete PFs, which was similar to results in the literature.<sup>25</sup> In addition, we further identified that patients

with incomplete interlobar fissures had significantly higher incidence of pneumonia, atelectasis, subcutaneous emphysema, pneumothorax, pleural effusion, and atrial arrhythmia than patients with complete interlobar fissures. However, no significant difference was found in in-hospital mortality between patients with incomplete PFs and complete PFs. We speculated that the possible reason may have been the limited sample availability for in-hospital deaths ( $n=3$ ) in our cohort, resulting in attenuated analytical power when evaluating the effects of degree of PFC on in-hospital mortality.

We further utilized the Clavien–Dindo classification system to categorize all postoperative complications into minor and major morbidity. Incomplete degree of PFC was found to be significantly associated with risks of minor and major morbidity. Kaplan–Meier analysis further showed that both length of stay and chest-tube drainage in patients with incomplete PFs were significantly longer than in patients with complete PFs. That may be because of their higher probability of postoperative morbidity, which needs much more time to be treated in hospital. Finally, after minimizing bias risks from other confounding factors by multivariate logistic-regression analysis, incomplete degree of PFC was considered a strongly independent risk factor for overall morbidity, minor morbidity, and major morbidity after VATS lobectomy. We speculate the following three reasons might be considered when trying to explain this phenomenon.

First, when performing VATS lobectomy, division of lung parenchyma overlying the artery within the fused interlobar fissures could easily produce an AL, because this procedure is usually finished by using electrocautery or blunt/sharp dissection.<sup>31,32</sup> If alveolar ALs persist without timely and effective control, a devastating PAL, sometimes with induced pneumothorax, can seriously impair lung recruitment, resulting in the development of pulmonary edema, pneumonia, and pleural effusion. Therefore, patients with poorly developed PFs are more likely to have a much higher overall morbidity rate.

Second, another important disease that may predispose to the occurrence of postoperative complications is respiratory inflammation. On the one hand, both history of COPD and PRI were found to be predictive of overall morbidity in our multivariate logistic-regression models. The proportion of fused PFs was generally higher in both patients with COPD and those with PRI, which may be attributable to the excessive exudation induced by chronic inflammatory responses. The reduced area of gas exchange and inadequate distance from the alveolar surface to the capillary endothelium in

such patients with less discrete interlobar fissures can lead to a large decline in cardiopulmonary functional reserve and increase morbidity risks.<sup>4</sup>

On the other hand, the presence of pleural adhesions, which can increase the risks of PAL and pleural morbidity following elective pulmonary resections,<sup>33</sup> was found in 29.7% of all our enrolled cases. History of COPD and PRI was more frequent in the patients with pleural adhesions, revealing a close relationship between severity of pleural adhesions and inflammatory responses of the chest. More importantly, patients with less discrete PFs were found to have a significantly higher probability of dense pleural adhesions. That might be because the inflammatory process rarely spared the visceral pleura over the internal chest wall or within the interlobar fissures. Therefore, such patients with incomplete PFs were more likely to suffer from pleural and procedural morbidities.

Finally, since PF acts as an interface between neighboring lobes, we hypothesize that the poor integrity of PFs may hinder potential interlobar collateral ventilation, which helps to maintain a certain degree of pulmonary function within obstructive areas.<sup>34</sup> Although there is no conclusive evidence supporting this assumption, a large decline in pulmonary functional reserve in patients with poorly developed PFs has the ability to increase the risk of morbidity.

## Generalizability

In clinical practice, comprehensive risk assessment can affect surgeons' decisions on surgical procedures. According to our study results, it may be more efficient to integrate the degree of PFC into an assessment model to stratify the surgical risk of lung cancer patients, in order to decide the best therapeutic strategy. In addition, for young surgeons, it may help to select participants in their early learning curve or a teaching program of VATS techniques, in order to avoid a high morbidity rate and train themselves more effectively.

## Limitations

Several limitations must be taken into account regarding the interpretations. First, the present study was subject to the inherent limitations of any single-center retrospective-cohort study. Potential selection bias might still complicate our findings, although a multivariate logistic-regression analysis involved as many clinicopathological variables as possible to attempt to minimize the bias risks from potential confounding factors. Second, the sample in our single-center study was relatively small, which may limit the analytical power. Third, there has been no standardized assessment tool

on the degree of PFC until now. The fissure-development score and corresponding cutoff proposed by Lee et al<sup>15</sup> were consulted and modified in our cohort study, but essentially this subjective intraoperative mapping may be limited by the surgeon's area of interest and expertise. Fourth, morbidity rate can also depend on surgeon experience. However, it may be difficult to conduct a quantitative analysis on this artificial factor appropriately. This is another important limitation that cannot be ignored. Fifth, according to our primary objectives, only VATS lobectomy was analyzed, so our findings may not be generalized to sublobar resections. Finally, complete details of laboratory indices were not available in all enrolled patients, so their relevant clinical significance was not analyzed.

## Conclusion

The present study demonstrates that degree of PFC is an excellent categorical predictor of overall morbidity, minor morbidity, and major morbidity in patients undergoing VATS lobectomy for NSCLC. Incomplete degree of PFC is also significantly associated with prolonged duration of chest-tube drainage and length of stay following VATS lobectomy. Our results suggest that degree of PFC should be considered when informing surgical patients about the morbidity risks and selecting suitable cases in a surgeon's early learning curve of VATS techniques. Large-scale cohort studies are needed further to confirm and modify our findings in the future.

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## Disclosure

The authors report no conflicts of interest in this work.

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