# Preoperative Assessment of Risk Factors as a Predictor of 30-Day Mortality and Morbidity after Lung Resection for Lung Cancer

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= 국문 초록 =

폐암 환자에서 폐절제술 후의 유병율과 30일-사망률을 예견할 수 있는 위험 요인의 술 전 평가

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목 적: 본 연구는 폐암 환자에서 폐절제술 후 부정맥을 포함한 심장 합병증과 폐합병증 및 30일-사망률의 임상적 의미와 빈도를 평가하고 동반된 위험 요인을 분석하는 것을 목적으로 한다. 분석에서 얻어지는 결과로 실제적인 수술 지침을 제공하고 개발할 수 있다.

방 법: 7년간 일차적 폐암으로 폐절제술을 시행받은 모든 환자를 후향적으로 조사하였다. 술전 평가항목으로는 흡연의 기왕력, 만성 폐쇄성 폐질환의 과거력, 심질환의 과거력과 연령, 채질량지수, 폐기능검사 결과, 미국마취과학회 신체등급, 수술방법, 수술시간, 병리학적 단계, 술 후 발생한 폐합병증 및 심장 합병증의 기록을 확인하였다.

**결 과**: 467명의 환자 중에서 51명의 환자에서(11.3%) 술 후 폐합병증이 발생하였고 97명은(21.0%) 술 후 심장 합병증이 발생하였으며, 13명의 환자가(2.9%) 수술 후 30일 내에 사망하였다. 술 후 폐 합병 중의 위험 요인으로는 수술방법과 폐기능 검사상 예상 술 후 이산화탄소 확산증이 있고(p<0.05) 술 후 심장 합병증의 위험 요인에서는 연령, 심질환의 과거력(p<0.001)과 수술 방법(p<0.05)이 포함된다. 30일-사망률의 위험요인에는 폐질환의 과거력과 수술 방법 및 수술시간(p<0.05)이 있다.

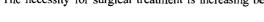
**결 론**: 본 연구의 결과에서 술 후 폐합병증의 유무에 술 전 폐기능검사 결과와 미국마취과학회 신체등 급이 관련성이 있음을 확인하지는 못하였다. 그러나 수술방법이 술 후 폐합병증과 심장 합병증, 30일-사 망률 모두에 중요한 요인이 되며 폐질환과 심장 질환의 과거력, 수술방법을 결정하는 것도 술 후 합병증 및 사망률을 줄이는 방법이 될 것이다.

**중심 단어**: 폐암·폐절제술·술 후 합병증·사망률.

## Introduction

The necessity for surgical treatment is increasing be-

cause complete surgical removal of a tumor offers the best chance for a cure in patients with non-small cell lung cancer (NSCLC). A lobectomy remains the standard the-





rapeutic option in most patients with early stage NSCLC. Although the operative mortality and morbidity following lobectomy or pneumonectomy has decreased over the past decade, both factors still contribute significantly to the cost of treating such patients. Careful selection of the operative modalities is therefore required to reduce the overall mortality and morbidity. 1) Patients undergoing thoracotomy associated with lung resection are thought to be at high risk for the development of postoperative pulmonary complications (PPCs)2) and postoperative cardiac complications (PCCs) during the perioperative period, and these complications may lead to serious morbidity<sup>3)</sup>. Although current operative and anesthetic techniques have resulted in significantly improved outcome, 4) mortality and morbidity after lung resection for carcinoma are still high: 4% to 6% and 20% to 40%, respectively<sup>4)5)</sup>, and higher in the elderly and other high-risk patients<sup>5)6)</sup>. Clinical studies have identified numerous patient- or procedure-related risk factors for mortality and PPCs following pulmonary resection, using various research designs and definitions. In most but not all studies, the most frequent risk factors were as follows: age<sup>7)8)</sup>, altered preoperative pulmonary function test (PFT)<sup>2)</sup>, cardiovascular comorbidity<sup>7)</sup>, type of surgery<sup>9)</sup>, ASA score<sup>15)</sup>, time of operation<sup>15)</sup>, peripheral vascular disease or insulin-dependent diabetes mellitus history<sup>10)</sup>, and smoking status<sup>2)12)</sup>.

The objectives of the present study were as follows:

1) to examine the incidence and clinical implications of
30 day mortality, PPCs, and PCCs after thoracic surgery
in a tertiary-care center; and 2) to identify the preoperative or intraoperative factors, especially ASA score, that
may predispose to the development of 30 day mortality,
PPCs, and PCCs in this subset of patients.

# Methods

We retrospectively reviewed the cases of all patients who underwent lung surgery, including wedge resection, segmental resection, lobectomy, bilobectomy and pneumonectomy for lung cancer. Four hundred sixty-seven patients underwent thoracotomy for primary lung cancer. Charts of these patients were reviewed after the study protocol was approved by the Human Research Ethic

Committee of University hospital.

Preoperative evaluation included a complete history (age, sex, weight, height, body mass index, duration of admission, smoking history, medical disease history), complete blood cell count, biochemical profile, arterial blood gas level and pulmonary function tests. ASA classification and stage of cancer were also evaluated. Unfortunately, not all the patients had been explored with a lung perfusion scan or any other lateralizing test. Therefore, the predicted postoperative FEV1 (ppoFEV1) was estimated by the formula published by Juhl and Frost<sup>13)</sup>. ppoFEV1=preoperative FEV1  $\times$  (1-[S  $\times$  5.26]/100), where S is the number of bronchopulmonary segments removed. A right pneumonectomy was considered to cause a 55% decrement in preoperative FEV1, and a left pneumonectomy to cause 45% decrement. In patients undergoing wedge resections, each wedge resection was assumed to account for one bronchopulmonary segment. The right and left lower lobes were considered to have five bronchopulmonary segments, the right middle lobe to have two bronchopulmonary segments, the right upper lobe to have three bronchopulmonary segments, and the left upper lobe to have four bronchopulmonary segments. The postoperative values obtained by this method of calculation have a good agreement with postoperative values calculated from preoperative regional lung function tests using <sup>133</sup>Xe. Predicted postoperative DL<sub>CO</sub> (ppoDL<sub>CO</sub>) was estimated by the same formula.

Intraoperatively, type and duration of operation were evaluated. Postoperative complications, both pulmonary and nonpulmonary, were ascertained by detailed chart review according to the operational definitions reported below. It is acknowledged that retrospective identification of PPCs depends on the detail and completeness of the medical record. To minimize this factor, the analysis was limited to postoperative complications thought to be clinically significant and thus unlikely to be omitted from the medical record. All complications divided into four categories, surgical complications, cardiac complications, pulmonary complications and other complications. Surgical complications are air leak more than 7 days, pneumothorax, hemothorax (postoperative bleeding), bronchopleural fistular, empyema, subcutaneous emphysema and pleural effusion. Cardiac complications include symp-



Table 1. Baseline characteristics of 467 patients undergoing lung resection

Characteristic	No. of patients	
Sex(n=467)		
Male	283	60.6
Female	184	39.4
Age(n=467)		
Mean±SD(year)	65.0±11.0	
Range(year)	22-88	
Smoking history (n=463)		
Past or present	413	89.2
Still smoking	153	33.0
Never smoked	50	10.8
Associated medical illness (n=330)		
Cardiac disease	98	29.7
Chronic obstructive pulmonary disease	140	42.4
Hypertension	126	38.2
Diabetes	31	9.4
Peripheral vascular disease	38	11.5
Preoperative treatment(n=299)		
None	240	79.7
Chemotherapy	14	4.7
Radiotherapy	10	3.3
Both	35	11.7
ASA classification (n=323)		
1	2	0.6
2	95	29.4
3	213	65.9
4	13	4.0
Type of operation(n=467)		
Wedge resection	52	11.1
Segmental resection	12	2.6
Lobectomy	305	65.3
Bilobectomy	20	4.3
Pneumonectomy	78	16.7
Site(n=461)	, 3	10
Right	256	55.5
Left	204	44.3
Tumor staging (n=441)	204	-1-1.0
	252	57.1
1	66	15.0
IIIA	59	13.4
IIIB	38	8.6
IV	26	5.9
iv Histology of tumor(n=458)	20	J.7
Ristology of turnor (n=456)  Squamous cell cancer	166	36.2
Adeno cancer	178	38.9



Table 1. Continued

Characteristic	No. of patients	%
Bronchioloalveolar cancer	35	7.6
Large cell cancer	27	5.9
Others	52	11.4
Postoperative treatment (n=285)		
None	214	75.1
Chemotherapy	7	2.5
Radiotherapy	53	18.6
Both	11	3.8

Table 2. Complication after lung surgery

Variables	Lesser surgery than lobectomy (64/467)	Lobectomy (325/467)	Pneumonectomy (78/467)
Surgical Complications (98/431, 22.7%)			
Pneumothorax(14.6%)	14 / 59	48 / 295	1 / 77
Air leak >7days (3.5%)	0 / 59	15 / 295	0 / 77
Pleural effusion (2.1%)	0 / 59	8 / 295	1 / 77
Subcutaneous emphysema (1,2%)	0 / 59	3 / 295	2 / 77
Hemothorax (postop. Bleeding) (0.7%)	0 / 59	1 / 295	2 / 77
Broncho-pleural Fistular (0.5%)	0 / 59	1 / 295	1 / 77
Empyema (0.2%)	0 / 59	1 / 295	0 / 77
Respiratory complications (51/450, 11.3%)			
Pneumonia (8.4%)	1 / 62	23 / 316	14 / 72
Atelectasis (1.8%)	0 / 62	8 / 316	0 / 72
Pul. Edema (0.4%)	0 / 62	1/316	1 / 72
Reintubation (0.2%)	0 / 62	1/316	0 / 72
Pul. Embolism (0.2%)	0 / 62	0/316	1 / 72
Resp. Insufficiency (0.2%)	0 / 62	1/316	0 / 72
Mechanical ventilation >24hrs(0%)	0 / 62	0/316	0 / 72
Cardiac complications (97/462, 21.0%)			
Arrhythmia(19.5%)	4 / 67	67 / 319	19 / 76
Cardiac failure (0.5%)	0 / 67	2/319	0 / 76
Myocardial infarction (1.0%)	0 / 67	3 / 319	2/76
Other complications (71/452, 15.7%)			
Renal complication (8.8%)	5 / 64	28 / 311	7 / 77
Vocal cord palsy (2.4%)	2 / 64	7 / 311	2 / 77
Brain complication (1.8%)	0 / 64	3 / 311	5 / 77
Sepsis (1.1%)	0 / 64	3 / 311	2 / 77
Venous thrombosis (0.9%)	0 / 64	1/311	3 / 77
GI complication (0.7%)	1 / 64	2/311	0 / 77

tomatic arrhythmia needed treatments, myocardial infarction (elevated CPK or EKG alteration) and cardiac failure. Pulmonary complications include atelectasis diagnosed by chest x-ray, pneumonia with sputum test, mechanical ventilation more than 24 hours, reintubation, pulmonary embolism, ARDS and pulmonary edema. And other complications are brain complications, renal complication, gastrointestinal complications, thyroid compli-



cations, venous thrombosis, vocal cord palsy and sepsis.

Statistical analysis were performed using Wilcoxon (rank sum) comparisons in categoric data and two-tailed t-test in the analysis of continuous data. The data reported as the mean+SD. p<0.05 is statistically significant.

# Results

Four hundred sixty-seven patients (mean age  $65\pm11$  years; 283 men and 184 women) underwent pulmonary resections (Table 1). Of the 464 patients we could get the smoking history, patients who had never smoked were only 50(10.8%) and the patients who had still smoking were 153(33.0%). Chronic obstructive pulmonary disease was the major associated medical illness (42.4%). Lobectomy including bilobectomy, the most common operation was performed in 325 cases (69.6%), while 78 patients (16.7%) underwent pneumonectomy, and 64 patients (13.7%) underwent wedge and segmental resections. Staging was as follows: stage I(57.1%), stage III (15.0%), stage IIIa (13.4%), stage IIIb (8.6%), stage

IV (5.9%). Two main types of tumor are squamous cell carcinoma (36.2%) and adeno carcinoma (38.9%). 97 patients (30%) were classified as ASA 1 or 2 and 226 patients (70%) as ASA 3 or 4 by the anesthesiologist.

Overall surgical complication rate was 22.7%, respiratory complication rate was 11.3%, cardiac complication rate was 21.0%, and the other complication rate was 15.7% (Table 2). Of the surgical complication, pneumothorax was the most common complication (14.6%). Pneumonia was the most common complication of the respiratory complications (8.4%). And arrhythmia was the most common complication of the cardiac complications (19.5%).

Operation procedure was a risk factor for postoperative pulmonary complication (Table 3, p=0.0042). And ppo-DLCO % was statistically different between patients group with postoperative pulmonary complication and patients group without postoperative pulmonary complication (Table 4). Age (p=0.001), cardiac disease history (p<0.001) and operation procedure (p=0.003) were statistically different between patients group with postope-

Table 3. Characteristic of patients with and without pulmonary complications

Variables	Patients with pulmonary complications	Patients without pulmonary complications	p value
Total Rate	51 / 450(11.3%)	399 / 450	
Sex(M:F)	35 : 16	235:164	NS
Age(years)	$62.3 \pm 11.8$	$65.1 \pm 10.8$	NS
Weight(kg)	$80.1 \pm 19.2$	77.5±17.6	NS
BMI	27.7± 5.5	26.6± 5.3	NS
Smoking history	20 / 51	133 / 399	NS
Pulmonary disease history			NS
Yes	14 / 130	126 / 130	
No	16 / 190	174 / 190	
ASA class			NS
1 or 2	7 / 94	87 / 94	
3 or 4	21 / 212	191 / 212	
Operation procedure			0.0042
Wedge or segmental resection	1 / 62	61 / 62	
Lobectomy	33 / 315	282 / 315	
Pneumonectomy	16 / 72	56 / 72	
Duration of procedure (minutes)	$232.2 \pm 70.0$	$202.6 \pm 80.5$	NS
Tumor stage			NS
I, II	34 / 308	274 / 308	
Illa	7 / 55	48 / 55	
IIIb, IV	6 / 63	57 / 63	



Table 4. Preoperative pulmonary function tests in 384 patients

Parameters	Patients with pulmonary complications	Patients without pulmonary complications	p value
FEV1 (L)	2.11± 0.77	2.03± 0.77	NS
FEV1%	76.4 ±21.4	75.9 ±23.7	NS
ppoFEV1%	51.2 ±18.7	57.3 ± 19.3	NS
FVC	3.55± 1.07	3.26 ± 0.95	NS
DLCO%	76.7 ±25.2	79.5 ± 24.5	NS
ppoDLCO%	52.9 ±23.3	60.4 ± 20.4	0.0415
PaO <sub>2</sub> at FiO <sub>2</sub> 0.21mmHg	75.9 ± 9.7	$76.2 \pm 10.3$	NS
A-a DO <sub>2</sub>	18.8 ±10.0	17.8 ± 9.5	NS
VO <sub>2</sub> max	17.1 ± 2.9	17.0 ± 4.6	NS

Table 5. Characteristic of patients with and without cardiac complications

Variables	Patients with cardiac complications	Patients without cardiac complications	p value
Total rate	97 / 462±21.0%)	373 / 462	
Sex(M:F)	59 : 38	223 :150	NS
Age(years)	68.2±10.0	63.4±11.1	0.0001
Weight(kg)	$75.8 \pm 16.8$	77.8±18.0	NS
BMI	26.2± 5.6	26.7± 5.4	NS
Cardiac disease history			<0.0001
Yes	37 / 96	59 / 96	
No	33 / 235	202 / 235	
ASA Class			NS
1 or 2	22 / 97	75 / 97	
3 or 4	49 / 224	175 / 224	
Operation procedure			0.0030
Wedge or segmental resection	4 / 67	63 / 67	
Lobectomy	72 / 319	247 / 319	
Pneumonectomy	21 / 76	55 / 76	
Duration of procedure (minutes)	$222.8 \pm 84.4$	$201.8 \pm 79.4$	NS
Tumor stage			NS
l, II	61 / 316	255 / 316	
Illa	16 / 56	40 / 56	
IIIb, IV	14 / 69	55 / 69	

rative cardiac complication and patients group without postoperative cardiac complication (Table 5).

Overall 30-day mortality in our study group was 2.9% (13/467). Pulmonary disease history, operation procedure and the duration of operation were risk factors of 30-day mortality (Table 6). Sex, age, smoking history, medical disease history except pulmonary disease, ASA classification and tumor staging were not significant for 30-day mortality in our group.

# Discussion

Patients undergoing thoracotomy associated with lung resection are thought to be at high risk for the development of PPCs up to 49%<sup>2)</sup> during the perioperative period, and these complications may lead to serious morbidity.<sup>3)</sup> Although current operative and anesthetic techniques have resulted in significantly improved outcome,<sup>4)</sup> mor-



Table 6. Characteristic of patients with and without 30-day mortality

Variables	Patients with 30-day mortality	Patients without 30-day mortality	p value
Total rate	13 / 467 (2.9%)		
Sex(M:F)	10:3	273 : 181	NS
Age (yrs)	66.4± 6.4	64.7±11.0	NS
ВМІ	<b>24.2</b> ± <b>4.1</b>	26.6± 5.4	NS
Smoking history	4 / 157 (2.5%)	153 / 157	NS
Pulmonary disease history	9 / 140 (6.4%)	131 / 140	0.0074
Cardiac disease history	2 / 98 (2.1%)	96 / 98	NS
Diabetes mellitus	0 / 31 (0%)	31 / 31	NS
Hypertension	5 / 126 (4.0%)	121 / 126	NS
Peripheral vascular disease	2 / 38 (5.3%)	36 / 38	NS
ASA Class			NS
1 or 2	2 / 96 (2.1%)	94 / 96	
3 or 4	8 / 226 (3.5%)	218 / 226	
Operation procedure			0.0056
Wedge or Segmental Resection	2 / 64(3.1%)	62 / 64	
Lobectomy	4 / 325(1.2%)	321 / 325	
Pneumonectomy	7 / 78 (9.0%)	71 / <i>7</i> 8	
Duration of procedure(min)	303.3±91.9	204.1 ± 77.9	0.0002
Tumor stage			NS
1, 11	9 / 317 (2.8%)	308 / 317	
illa	2 / 59 (3.4%)	57 / 59	
IIIb, IV	1 / 64(1.6%)	63 / 64	

tality and morbidity after lung resection for carcinoma are still high: 4% to 6% and 20% to 40%, respectively<sup>4)5)</sup>, and higher in the elderly and other high-risk patients<sup>5)6)</sup>. Clinical studies have identified numerous patient- or procedure-related risk factors for mortality and PPCs following pulmonary resection, using various research designs and definitions.

Investigators have attempted to predicted outcome using spirometry, blood gas analysis, carbon monoxide diffusion capacity, and split lung function testing. Individual parameters have shown some promise at predicting pulmonary complications including death. Pierce and colleagues<sup>14)</sup> investigated to demonstrate the usefulness of a composite index, the predicted postoperative product (PPP), or the algebraic product of the predicted postoperative forced expiratory volume in 1 second (ppoFEV1) percentage and the predicted postoperative carbon monoxide diffusion capacity (ppoDLco) percentage, incorporated values for ventilation, gas exchange,

lung perfusion. And Melendez and Barrera<sup>15)</sup> developed a new index, based on the methodology of Pierce and colleagues<sup>14)</sup>, that provided not only a measure of mortality but also one of severe respiratory complication. They constructed the predictive respiratory complication quotient (PRQ) to predict the probability of pulmonary morbidity and mortality in thoracic surgery.

# 1. 30 day mortality-comparison with previous studies

30-day mortality were recorded between 3% and 7.5% after lung resection for lung cancer<sup>10)16</sup>, especially higher after pneumonectomy 3.2–10.5%<sup>8)17</sup>. The current available literature suggests that acceptable 30-day mortality rates after pneumonectomy range between 7 and 11%<sup>18</sup>). In our study 30-day mortality is lower (2.9%) than any other reports previously reported because less extensive surgery than lobectomy, including segmental resection and wedge resection were included in our study. There



are well-known factors affecting 30-day mortality including PPP<sup>14</sup>, ppoFEV1<sup>19</sup>, sex<sup>17</sup>, type of operation and age<sup>8</sup>. Knott-Craig et al<sup>16</sup> lessened the mortality rate by 1.6% with preoperative use of digitalis, subcutaneous heparin and venoocclusive stocking, aggressive perioperative pulmonary toilet and recommended video-directed limited resection as a lung surgery. Pulmonary disease history, operation procedure and the duration of operation were risk factors of 30-day mortality in our study.

#### 2. Morbidity

There are various reports about postoperative morbidity for the lung cancer patients between 10 and  $60\%^{911112116117}$ . Old  $age^{20}$  and type of operation  $age^{12116}$  are reported as a major factor, and very high morbidity (78.5%) was shown in older patients over 70 undergoing pneumonectomy  $age^{21}$ . Other risk factors are ppoFEV1 and MVO<sub>2</sub>. Patients with a ppoFEV1 of <0.8 to 1.0 L are classically considered to be at high risk for postoperative complications. And postoperative complications are more likely to develop in patients with peripheral vascular disease or insulin-dependent diabetes mellitus or both  $age^{11}$ .

Atrial fibrillation is a frequent complication of the postoperative course in patients undergoing thoracic operation for lung cancer. The cause remains unclear and is almost certainly multifactorial. Hypoxia, hypovolemia, sepsis, electrolyte imbalances, augmented vagal activity, and increased cardiac load after the reduction of the pulmonary vascular bed are all well-known predisposing factors that can increase atrial vulnerability to supraventricular arrythmias after thoracic operations<sup>22)</sup>. The reason why postoperative atrial fibrillation is of importance lies, not only in the immediate hemodynamic consequences in often critically ill patients, but also in the longer term potential for atrial thrombosis and systemic embolization. But early atrial fibrillation occurrence after operation for lung cancer did not show any negative impact on short- and long-term mortality or on occurrence rate in one report<sup>23)</sup>. Overall rate of supraventricular arrhythmia including atrial fibrillation were reported between  $8.4-12\%^{12)23}$ , increased to 24-34%after pneumonectomy and increased as the patients' age was increased. So persistent arrhythmia was reported up to 47.6% in the patients aged over 70 after pneumonectomy<sup>21)</sup>. Other factors affecting the incidence of postoperative arrhythmia were SaO<sub>2</sub>, PaO<sub>2</sub>, PaCO<sub>2</sub>, MVO<sub>2</sub><sup>14)</sup>. In our study, cardiac disease history and operation procedure were major factors affecting the incidence of postoperative cardiac complications.

Pulmonary complications after lung resection can have serious consequences because the remaining lung tissue is severely compromised during the immediate postoperative period. Many reports suggested 22.5-39% of postoperative pulmonary complication after lung resection with lung cancer 1)24). And the most frequent cause of an extended length of hospital stay in patients undergoing radical upper lobectomy is prolonged air leak (15.2%). In our study, relatively low postoperative pulmonary complication rate (11.3%) was reported because we did not include many other surgical complications like air leak over 7-days, pneumothorax, and so on that many authors mentioned as pulmonary complications to this category. Although the preoperative prediction of pulmonary complications after lung major surgery has been reported in various papers, it still remains unclear. ppoFEV1% was reported as the most or only significant independent predictor of PPCs12). Some authors suggested that ASA score over 3, operation time over 80 minutes and postoperative mechanical ventilation support needed over 48 hours were independent factors associated with PPCs and preoperative pulmonary function test do not appear to contribute to the identification of high-risk patients<sup>10</sup>. There is a report that serum LDH levels of >230 U/l, residual volume/total lung capacity >30%, and PaO<sub>2</sub>< 10.6 kPa may be associated with pulmonary complications in patients undergoing a lobectomy for NSCLC<sup>3</sup>). And postoperative pulmonary complication is associated with MVO2 and multifactorial CPRI (cardiopulmonary risk index) by Ebstein et al<sup>25)</sup> and Pierce et al<sup>14)</sup> reported BMI as a risk factor. Melendez et al<sup>15)</sup> reported that postoperative pulmonary complication increased in case PRQ<2200 and ppoDLCO % is a most important factor. As above mentioned, there are many other reports about the factors associated with postoperative pulmonary complication because characteristics of subjects were different according to study design, sample size were various, retro- or prospective study, and preoperative and postoperative treatment. And we can't conclude the exact factor



affecting postoperative pulmonary complication. But we can suggest that cardiovascular comorbidity and type of surgery are major factors for postoperative cardiopulmonary complication for lung cancer patients undergoning lung resection procedure. Pulmonary disease history, operation procedure and the duration of operation were risk factors of 30-day mortality. Sex, age, smoking history, medical disease history except pulmonary disease, ASA classification and tumor staging were not significant for 30-day mortality and postoperative cardiopulmonary complications in our group.

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