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Postoperative Pulmonary Complications after Surgery in Patients with Interstitial Lung Disease

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Key Words

Interstitial lung disease · Postoperative complication · Idiopathic pulmonary fibrosis · Anesthesia · Surgery · Acute exacerbation

Abstract

Background: Patients with interstitial lung disease (ILD) have a high incidence of postoperative pulmonary complications (PPCs) after lung resection, but there is little data about these complications in ILD after other types of surgery. ***Objectives:*** The aim of this study was to examine the characteristics and predictors of PPCs after major surgery in patients with ILD. ***Methods:*** We included 336 patients with ILD who underwent major surgery between January 2005 and December 2010 at two tertiary hospitals in Korea. All types of surgery that had been performed under general anesthesia were included. Demographic characteristics, preoperative lung function, and operative conditions including anesthesia time and estimated blood loss were compared between patients with and without PPCs. ***Results:*** PPCs occurred in 37 patients (11%). Thirteen patients developed pneumonia, the most common PPC, and 11 had acute exacerbation of ILD. In multivariable analysis, BMI <23 (OR = 2.488, 95% CI: 1.084–5.710, p = 0.031), emergency surgery (OR = 23.992, 95% CI: 2.629–218.949, p = 0.005), lung surgery (OR = 5.090, 95% CI: 1.391–18.628, p = 0.014), and longer anesthesia time (OR = 1.595, 95% CI: 1.143–2.227, p = 0.006) were statistically significant risk factors. ***Conclusions:*** The incidence of PPCs detected over all surgeries was not as high as that reported for lung surgery alone in ILD patients. Lower BMI, emergency surgery, lung surgery, and longer anesthesia time were risk factors. Operative conditions as well as lung function should be considered in preoperative planning and management for ILD patients undergoing major surgery.

Introduction

Postoperative pulmonary complications (PPCs) are frequent and an important cause of perioperative morbidity and mortality. They contribute to the risk of surgery and anesthesia, and are associated with increased length of hospital stay. A rate of PPCs of 6.8% was reported in a systematic review across all types of surgery [1].

Chronic obstructive pulmonary disease, along with other chronic lung diseases, is a major risk factor for PPCs [2–4]. The incidence of PPCs in patients with chronic ob-

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structive pulmonary disease has been reported at 6–26% [5–7]. On the other hand, the incidence, morbidity, mortality, and risk factors for PPCs after surgery in patients with interstitial lung diseases (ILDs) have not been well described.

The most common ILD is idiopathic pulmonary fibrosis (IPF). Patients with IPF have shown markedly higher rates of postoperative pulmonary morbidity (26%) and mortality (8%) after surgical resection for lung cancer as compared to those without IPF [8, 9]. Several studies have shown that other types of ILD also influence PPCs and mortality after lung surgery [10], and the patients with ILD had a higher incidence of these complications compared to those without ILD after lung resection. Among all types of PPCs, acute respiratory distress syndrome was reported at a significantly higher percentage in ILD patients versus those without ILD (13.5 vs. 2.3%), and mortality was also higher in the patients with ILD (8.1 vs. 1.4%) [11]. However, there is little published data focusing on the incidence and characteristics of PPCs after surgery other than lung surgery in patients with ILD.

The aim of this study was to examine the characteristics and predictors of PPCs after major surgery in patients with ILD.

Materials and Methods

Patients with ILD who underwent surgery under general anesthesia at two tertiary hospitals, Seoul National University Hospital and Seoul National University Bundang Hospital, between January 2005 and December 2010 were retrospectively reviewed. Using the patients' operation code (general anesthesia) and ILD diagnostic code, we selected 566 ILD patients who had undergone any kind of surgery under general anesthesia. After review of medical records, we excluded 230 patients who did not have real ILD at the time of surgery or had been intubated before the surgery. Finally, 336 patients were included in the analysis.

The surgeries included all types of surgery that had been performed under general anesthesia: head and neck, thoracic, abdominal, pelvic surgeries, etc. The ILDs included IPF, nonspecific interstitial pneumonia (NSIP), cryptogenic organizing pneumonia, connective tissue disease-related ILD (CTD-ILD), respiratory bronchiolitis-ILD, and other unclassified interstitial fibrosis.

IPF was diagnosed by lung biopsy (in 98 patients) or clinically (in 92 patients). All NSIPs and cryptogenic organizing pneumonias were confirmed by surgical lung biopsies. Patients who did not meet any of the ILD subtype criteria after surgical lung biopsies were classified as 'unclassified interstitial fibrosis'. Patients with interstitial fibrosis, as revealed by CT imaging, but who did not undergo surgical lung biopsy were classified as 'others'. In patients diagnosed clinically, a multidisciplinary discussion was carried out between two pulmonologists and two radiologists according to the guideline [12].

Data collected included demographic characteristics, preoperative lung function, operative conditions such as anesthesia time and estimated blood loss (EBL), type of PPC, and follow-up data including mortality. We defined EBL as 'the blood collected in suction bottles during the operation period'.

PPCs were defined as any of the following: (1) pneumonia, diagnosed by new radiologic infiltrates with clinical findings such as fever, purulent sputum, and laboratory abnormalities suggestive of infection; (2) acute exacerbation (AE) of underlying ILD, defined as an increase of bilateral lung infiltrates if infection and cardiac problem had been excluded; (3) prolonged air leakage via chest tube (≥7 days) after thoracotomy, and (4) others, which were hemothorax, pulmonary infarction, and spontaneous pneumothorax. We also reviewed in-hospital mortality after surgery.

Statistical analyses were done with SPSS 17.0 (Chicago, Ill., USA). Variables were compared between patients with and without PPC with Student's t test or a Mann-Whitney U test for continuous variables and a χ^2 test or Fisher's exact test for categorical variables in univariable analyses. Multivariable logistic regression analysis was performed to evaluate predictors of PPCs. A p value <0.05 was regarded as statistically significant.

This study was approved by the Seoul National University Hospital and Seoul National University Bundang Hospital Institutional Review Boards for Clinical Research (IRB No.: B-1105/128-401) and the informed consent requirement was waived due to the retrospective study design.

Results

Baseline Characteristics of Study Patients

The records of a total of 336 patients with ILD who underwent surgery under general anesthesia were reviewed. The median age was 64 years. The most common ILD was IPF (56.5%). Rates of NSIP and CTD-ILD were 15.5 and 14.5%, respectively (table 1).

Comparison between Patients with and without PPCs

PPCs were reported in 37 patients (11%). Comparison of baseline characteristics of patients with and without these complications is shown in table 1. Underlying comorbidities such as hypertension and diabetes mellitus were similar in both groups. The PPC group tended to have more male patients (70.3 vs. 55.2%), more patients with a history of smoking (62.2 vs. 46%), and more patients with a BMI <23 (62.2 vs. 44.8%) compared to the group without PPCs. There were more patients with concurrent malignant diseases (40.5 vs. 22.7%) and lung cancer in the PPC group (18.9 vs. 5.7%). The patients with PPCs tended to have lower preoperative forced expiratory volume in 1 s % predicted (FEV_1%), and forced vital capacity % predicted (FVC%), while the FEV_1/FVC ratio and diffusing capacity for carbon monoxide % predicted (DLCO%) were similar in both groups.

Table 1. Baseline characteristics of the study patients

	Total (n = 336)	PPC group (n = 37)	No-PPC group (n = 299)	p
Median age (range), years	64 (27–93)	65 (37–85)	64 (27–93)	0.954
Males	191 (56.8)	26 (70.3)	165 (55.2)	0.056
BMI <23	157 (46.7)	23 (62.2)	134 (44.8)	0.013
History of smoking	161 (47.9)	23 (62.2)	138 (46)	0.063
Current malignant disease	83 (24.7)	15 (40.5)	68 (22.7)	0.017
Lung cancer		7 (18.9)	17 (5.7)	0.003
Other malignancies		8 (21.6)	51 (17.1)	0.491
Hypertension	100 (29.8)	8 (21.6)	93 (31.3)	0.240
Diabetes mellitus	53 (15.8)	9 (24.3)	44 (14.7)	0.128
Immunosuppressive agent	41 (12.2)	7 (18.9)	34 (11.4)	0.187
Respiratory symptom				
Cough	150 (44.6)	21 (56.8)	129 (43)	0.112
Sputum	89 (26.5)	17 (45.9)	72 (24)	0.004
Dyspnea	161 (47.9)	25 (67.6)	136 (45.3)	0.011
Type of ILD				
IPF	190 (56.5)	21 (56.8)	169 (56.5)	0.978
NSIP	52 (15.5)	3 (8.1)	49 (16.4)	0.189
COP	23 (6.8)	4 (10.8)	19 (6.4)	0.300
CTD-ILD	53 (14.5)	7 (18.9)	46 (15.4)	0.578
RB-ILD	2 (0.6)	0 (0)	2 (0.7)	>0.999
Unclassified interstitial fibrosis	9 (2.7)	2 (5.4)	7 (2.3)	0.260
Others[a]	8 (2.4)	1 (2.7)	7 (2.3)	>0.999
Pulmonary function test				
FEV% predicted[b]	86.1±22.1	79.5±19.7	86.9±22.2	0.061
FVC% predicted[b]	77.6±18.7	72.2±15.7	78.0±19.4	0.073
FEV_1/FVC[b]	79.5±8.4	79.3±9.9	79.6±8.2	0.895
DLCO% predicted[c]	67.3±21.5	63.13±22.8	67.9±21.3	0.241
Arterial blood gas analysis[d]				
Median PaO_2 (IQR), mm Hg	86.5 (76.4–104.5)	82.25 (71.8–93.5)	86.7 (76.9–105.2)	0.132
Median $PaCO_2$ (IQR), mm Hg	39.6 (36.4–42.7)	38.9 (34.6–38.9)	39.7 (36.5–42.8)	0.521

Data are presented as n (%) or means ± SD unless otherwise indicated. COP = Cryptogenic organizing pneumonia; RB = respiratory bronchiolitis; PaO_2 = arterial partial pressure of oxygen; $PaCO_2$ = arterial partial pressure of carbon dioxide; IQR = interquartile range. [a] Patients with interstitial fibrosis, as revealed by CT imaging, but did not undergo surgical lung biopsy. [b] Missing: 13. [c] Missing: 70. [d] Missing: 43.

Symptoms on admission for surgery were different between the groups. More respiratory symptoms such as sputum and dyspnea were described in the patients who developed PPCs than in those who did not (45.9 vs. 24%, p = 0.004, and 67.6 vs. 45.3%, p = 0.011, respectively). Among several procedure-related variables, greater EBL (p = 0.020) and longer anesthesia time (p = 0.056) were noted in the patients with PPCs (table 2).

There were more patients who underwent thoracotomy in the PPC group, and more patients with lung surgery in the PPC group (p = 0.004 and p = 0.07, respectively). There were no patients who underwent head and neck surgery in the PPC group, and 24 (8%) in the no-PPC group (p = 0.091). We also found more patients with emergency operation in the PPC group (8.1 vs. 1.7%, p = 0.047; table 2).

Incidence and Characteristics of PPCs

Table 3 shows the incidence and types of PPCs. These complications were defined as severe if the patient developed respiratory failure requiring mechanical ventilation, or if the patient died, regardless of application of mechanical ventilation. PPCs were reported in a total of 37 (11.0%) patients. Pneumonia, in 13 patients, was the most common, and 30.8% of the cases were severe. There were 11 cases of AE of underlying ILD after surgery, and 81.8% of these cases were considered severe. There were several cases with subsegmental atelectasis; however, no case with clinically significant atelectasis (lobar or whole lung atelectasis evidenced on a chest radiograph or requiring bronchoscopic toileting) was observed. In addition, we did not encounter any case of pulmonary embo-

Table 2. Perioperative variables between patients with or without PPCs

	Total (n = 336)	PPC group (n = 37)	No-PPC group (n = 299)	p
Anesthesia time, h	1.83 (1.4–3.2)	2.1 (1.5–4.3)	1.8 (1.4–3.1)	0.056
EBL, ml	20 (0–100)	100 (0–300)	10 (0–100)	0.020
Surgery site				
Head and neck	24 (7.1)	0 (0)	24 (8.0)	0.091
Thoracic (lung)	209 (62.2)	28 (75.7)	181 (60.3)	0.07
Thoracic (extrapulmonary)	12 (3.6)	2 (5.4)	10 (3.3)	0.629
Abdominal-pelvis	69 (20.5)	6 (16.2)	63 (21.0)	0.491
Spine	13 (3.9)	0 (0)	13 (4.3)	0.375
Extremities	9 (2.7)	1 (2.7)	8 (2.7)	>0.999
Surgical modality of thoracic surgery				
Open thoracotomy	26 (7.7)	8 (21.6)	18 (6.0)	0.004
VATS	193 (57.4)	22 (59.5)	171 (57.0)	0.775
Mediastinoscopy	2 (0.5)	0 (0)	2 (0.7)	>0.999
Transfusion during surgery	25 (7.4)	4 (10.8)	21 (7)	0.500
Emergent surgery	8 (2.4)	3 (8.1)	5 (1.7)	0.047

Data are presented as n (%) or median (interquartile range).

Table 3. Types of PPCs

PPC	Severe[a]	Not severe	n (%)[b]
Pneumonia	4	9	13 (3.9)
Exacerbation of underlying ILD[c]	9	2	11 (3.3)
Prolonged air leakage via chest tube	0	10	10 (3.0)
Others[d]	0	3	3 (0.9)
Total	13	24	37 (11.0)

[a] Needed mechanical ventilation or dead. [b] Percentage of the total patients (total = 336). [c] Defined as increase of bilateral lung infiltrates if infection and cardiac problem had been excluded. [d] Hemothorax, pulmonary infarction, pneumothorax after coronary artery bypass surgery.

Table 4. Mortality and cause of death

Cause of death	n (%)[a]
Pulmonary complication	
Pneumonia	3 (0.9)
Aggravation of underlying ILD	6 (1.8)
Nonpulmonary complication	
Myocardial infarction	1 (0.3)
Total	10 (3.0)

[a] Percentage of the total patients (total = 336).

lism, which is not an unusual finding because the incidence of postoperative pulmonary embolism in Asian countries is far lower than in Western countries [13].

The overall postoperative mortality was approximately 3% (10/336), and most of the deaths was associated with pulmonary complications (9/10; 3 patients with pneumonia and 6 with aggravation of the underlying ILD). The remaining patient died from myocardial infarction after a surgery (table 4). Clinical characteristics of the 10 patients who died are shown in table 5. Three of the 10 fatal complications developed after nonpulmonary surgery. There was 1 patient with IPF and prostate cancer who died of aggravation of the underlying ILD after prostatectomy who had normal preoperative FVC% and no preoperative respiratory symptoms.

Risk Factors for PPCs

Risk factors were analyzed (table 6) and BMI <23 (OR = 2.488, 95% CI: 1.084–5.710, p = 0.031), emergency surgery (OR = 23.992, 95% CI: 2.629–218.3949, p = 0.005), lung surgery (OR = 5.090, 95% CI: 1.391–18.628, p = 0.014), and longer anesthesia time (OR = 1.595, 95% CI: 1.143–2.227, p = 0.006) were statistically significant risk factors for PPCs in multivariable analysis.

Subgroup Analysis

Of the 336 patients, 179 underwent diagnostic video-assisted thoracoscopic surgery (VATS) or mediastinoscopy. To evaluate the outcome of other types of major therapeutic surgery in patients with ILD, we did a sub-

Table 5. Description of patients who died after surgery

Sex/ age	Smoking	Type of ILD	Underlying disease	FVC pred%	DLCO pred%	Reason for surgery	Time of death, postop. days	Surgery	Emergency surgery	Cause of death
M/69	current	IPF	HTN	90	74	prostate cancer	39	robot-assisted laparoscopic radical prostatectomy	no	AE of ILD
F/66	former	CTD-ILD	rheumatoid arthritis	NA	NA	hemo-peritoneum	7	small-to-small intestinal anastomosis, incidental appendectomy	yes	AE of ILD
M/71	former	IPF	current lung cancer	72	35	gastric perforation	22	primary repair and omental patch apply for gastric perforation	yes	pneumonia
M/74	former	IPF	s/p CABG, HTN	56	50	ILD	7	wedge resection of RUL via VATS	no	STEMI
M/66	former	IPF	HTN, DM	78	60	lung cancer	48	LUL lobectomy, chest wall resection and reconstruction	no	pneumonia
F/66	never	NSIP		53	46	ILD	18	wedge resection of RLL via VATS	no	AE of ILD
M/74	current	IPF	s/p LLL lobectomy d/t lung cancer, HTN, DM	97	77	lung cancer	37	RUL lobectomy via VATS	no	AE of ILD
M/52	former	NSIP		53	63	ILD	26	wedge resection of RLL via VATS	no	AE of ILD
M/42	never	NSIP		56	56	ILD	54	wedge resection of LLL via VATS	no	AE of ILD
M/70	never	IPF	DM	85	66	lung cancer	15	LLL lobectomy with mediastinal LN dissection	no	pneumonia

HTN = Hypertension; AE = acute exacerbation; NA = not applicable; s/p = status post; CABG = coronary artery bypass graft; DM = diabetes mellitus; STEMI = ST-elevation myocardial infarction; RUL = right upper lobe; LLL = left lower lobe; LUL = left upper lobe; LN = lymph node.

Table 6. Independent risk factors for PPCs in patients with ILD

Variables	OR	95% CI	p
Age	1.011	0.973–1.051	0.580
Male	1.826	0.547–6.092	0.327
BMI <23	2.488	1.084–5.710	0.031
History of smoking	1.694	0.554–5.178	0.355
Dyspnea	1.115	0.448–2.766	0.815
Sputum	2.139	0.916–4.996	0.079
FEV_1%	0.996	0.955–1.040	0.868
FVC%	0.978	0.930–1.028	0.376
Emergency surgery	23.992	2.629–218.949	0.005
Lung surgery	5.090	1.391–18.628	0.014
Anesthesia time, h	1.595	1.143–2.227	0.006
EBL, ml	0.999	0.998–1.001	0.366

group analysis that excluded the patients who underwent diagnostic VATS lung biopsy and mediastinoscopy. A total of 157 patents were included in the subgroup analysis and PPCs were reported in 18 (11.5%). Comparison of baseline characteristics and perioperative variables for patients with and without PPCs is shown in online supplementary tables 1 and 2 (for all online suppl. material, see www.karger.com/doi/10.1159/000357046). Risk factors for PPCs in these patients were analyzed by multivariable analysis (online suppl. table 3). Higher DLCO% (OR = 0.946, 95% CI: 0.900–0.994, p = 0.027) seemed to reduce the risk for PPCs while longer anesthesia time (OR = 1.965, 95% CI: 1.182–3.266, p = 0.009) and lung surgeries (OR = 5.786, 95% CI: 1.129–29.644, p = 0.035) were identified as risk factors.

Discussion

The association between ILD and PPCs after pulmonary resection is well known, and the influence of ILD on postoperative complications, morbidity, and survival in lung cancer patients is well documented [8, 10, 14, 15]. Preexisting comorbidities and decreased preoperative DLCO have also recently been suggested as risk factors for the development of acute pulmonary complications after pulmonary resection in patients with lung cancer and ILD [16]. However, there is as yet no consensus guideline for perioperative management in patients with ILD, and there is little published data focusing on the incidence and characteristics of PPCs after surgery other than lung surgery in patients with ILD.

In our study, PPCs were reported across all types of surgery in 37 out of 336 patients (11%) with ILDs, and the overall postoperative mortality rate was approximately 3% (10/336) in patients with ILD. Nine patients died due to postoperative pneumonia or aggravation of the underlying ILD. A recent study in a population-based surgical cohort showed a 5% incidence of PPCs [17], and the incidence of PPCs in ILD patients was higher than in the general population.

Previous studies have reported that the incidence of PPCs was 42–53% after lung resection surgery in ILD patients [10, 16]. In the present study, the incidence of PPCs reported over all surgery, including lung surgery, was not as high as that reported for lung surgery alone in ILD patients.

We found that lower BMI (<23), emergency surgery, lung surgery, and longer anesthesia time were independent risk factors for PPCs in ILD patients, and our results suggest that operation-related factors had greater influence on the development of PPCs than patient-related factors such as lung function or preoperative respiratory symptoms. Our results also differed from the other studies that included only lung resection surgeries and reported lower preoperative FVC% and DLCO% in association with PPCs [11, 16]. Moreover, the results differed from those in chronic obstructive pulmonary disease patients that showed increased incidence of PPCs according to underlying pulmonary function [18–20].

To highlight the outcomes of major therapeutic surgery, we conducted a subgroup analysis including ILD patients who had therapeutic surgeries and excluded those who underwent diagnostic VATS or mediastinoscopy. In the subgroup analysis, the independent risk factors for PPCs were lower DLCO, lung surgery, and longer anesthesia time, and were not much different from the entire patient group.

Previous studies have reported that typical honeycombing or IPF itself was a potential risk factor for AE after pulmonary resection for lung cancer [21, 22]. Therefore, we expected a higher incidence of PPCs in patients with IPF compared to those with other type of ILD. However, this was not the case. Our study showed that the incidence of PPCs was similar in patients with IPF or with other types of ILD (11.1 and 11.2%, respectively). The prognostic value of different types of ILD after pulmonary or nonpulmonary surgery remains unknown. The prognosis of IPF/usual interstitial pneumonia is generally the worst among the ILDs, with a median survival of only 3–5 years from the diagnosis [23, 24]. We did not find any significant difference in the incidence of PPCs according to the type of ILD.

Surgical intervention of any form has been thought to be an inciting factor. However, there are few published data for AE of IPF or other ILDs following nonpulmonary surgery. One recent study reported 3 cases of AE in IPF in patients who underwent nonpulmonary surgery [25], and in our study 2 patients experienced AE of ILD after nonpulmonary surgery: 1 after prostatectomy and 1 after intestinal surgery. Although most of the PPCs occurred after lung surgery, there were fatal AEs of ILD after nonpulmonary surgeries.

This is the first study, to our knowledge, to evaluate the incidence and characteristics of PPCs in patients with ILD after variable types of surgical procedures, including nonpulmonary surgery. We also evaluated patient-related factors, such as underlying lung function, comorbidity, and respiratory symptoms, and procedure-related factors, including anesthesia time, EBL, type of surgery, and others. Pulmonologists are frequently called upon for preoperative consultations before major surgeries. ILD is problematic because there is still no consensus guideline for perioperative management of ILD patients. We have comprehensively reviewed the incidence and characteristics of PPCs in patients with ILD following various types of surgery, and our results may be useful to assist with perioperative management of ILD patients.

Our study has several limitations. First, it is a retrospective study. Second, we did not review chest CT scan results to evaluate the extent and severity of the ILDs. The patients in our study had several types of ILD and variable severity of fibrosis, which may have influenced the incidence and severity of the PPCs. Third, our study did not examine long-term survival data as we reviewed only in-hospital mortality.

In conclusion, the results suggest that the incidence of PPCs after all types of surgery is not as high as that after lung resection surgery alone in patients with underlying ILD, but the rate was higher than that reported in the general population. Lower BMI, emergency surgery, lung surgery, and longer anesthesia time were risk factors for PPCs in ILD patients. Our results emphasize that operation-related factors as well as lung function should be considered in preoperative planning and management for ILD patients undergoing major surgery.

Financial Disclosure and Conflicts of Interest

All authors have no financial or other potential conflicts of interest to disclose.

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