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Clinical Research

Impact of Postoperative Prolonged Air Leakage on Long-Term Pulmonary Function after Lobectomy for Lung Cancer

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Background: This study aimed to evaluate the long-term impact of postoperative prolonged air leak (PAL) on pulmonary function.
Methods: We enrolled 1,316 patients with pathologic stage I–III lung cancer who underwent lobectomy. The cohort was divided into 2 groups: those who experienced PAL (n=55) and those who did not (n=1,261). Propensity score matching was conducted at a 1:4 ratio, resulting in 49 patients in the PAL group and 189 in the non-PAL group. Changes in pulmonary function were compared among preoperative, 6-month postoperative, and 12-month postoperative measurements between the 2 groups.
Results: The variables used for propensity score matching included age, sex, smoking history, body mass index, baseline pulmonary function, pathologic stage, and surgical approach. All standardized mean differences were less than 0.1. Six months postoperatively, the PAL group showed a greater reduction in both forced expiratory volume in 1 second (FEV_1) (-13.0% vs. -10.0%, p=0.041) and forced vital capacity (FVC) (-15.0% vs. -9.0%, p<0.001) than the non-PAL group. In cases of upper lobectomy, there were no significant differences in FEV_1 changes between the PAL and non-PAL groups at both 6 and 12 months. However, in lower lobectomy, the PAL group demonstrated a more pronounced decrease in FEV_1 (-14.0% vs. -11.0%, p=0.057) and FVC (-20.0% vs. -13.0%, p=0.006) than the non-PAL group at 6 months postoperatively.
Conclusion: Postoperative PAL delayed the recovery of pulmonary function after lobectomy. These effects were markedly more pronounced after lower lobectomy than after upper lobectomy.

Keywords: Prolonged air leak, Postoperative pulmonary function, Pleurodesis

Introduction

Lung cancer is the leading cause of cancer-related death both in Korea and globally [1,2]. The standard treatment for non-small cell lung cancer (NSCLC) patients at clinical stages I and II, as well as for selected stage IIIA patients, is surgical resection. Although surgical interventions significantly enhance survival rates in early-stage lung cancer, the development of postoperative pulmonary complications is inevitable due to factors such as pre-existing lung disease, loss of lung parenchyma, and injury induced by one-lung ventilation [3,4]. Among these complications, postoperative prolonged air leak (PAL), defined as an air leak persisting beyond postoperative day 5, is the most frequent. While the definition of PAL varies in different studies, its reported incidence ranges from 8% to 26% [5].

Several studies have shown that forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) decrease substantially in the first 2–4 weeks after lung surgery and then gradually recover [6,7]. The decline in postoperative pulmonary function (PPF) can be attributed to various factors including old age, advanced disease stage, pre-existing poor pulmonary function, open thoracotomy, a high number of resected segments, or postoperative che-

motherapy [8-10]. Furthermore, while postoperative pulmonary complications can influence PPF, data on the long-term effects of PAL on PPF are limited. Nevertheless, PPF is a crucial determinant of postoperative quality of life, making it essential to understand the relationship between PAL and its long-term impact on PPF. Intraoperatively, all efforts should be directed towards minimizing PAL, and preoperatively, comprehensive patient counseling is particularly necessary for those with compromised lung function.

Therefore, this study aimed to identify the impact of PAL on long-term PPF in patients who underwent lobectomy for NSCLC.

Methods

Patients

This study enrolled patients who underwent a lobectomy for NSCLC between January 2011 and December 2020 and were classified within pathologic stages I–III. The exclusion criteria were the absence of pulmonary function test (PFT) data at either 6 or 12 months post-surgery, previous lung surgery, receipt of neoadjuvant therapy, or having undergone a right middle lobectomy and combined resection of other lobes. The study was approved by the Institutional Review Board (IRB) of Seoul National University Bundang Hospital (IRB approval no., B-2404-892-107). Due to the retrospective nature of the study, the requirement for informed consent was waived.

Definition of postoperative prolonged air leak and management

In this study, PAL was defined as an air leak persisting beyond postoperative day 5 or necessitating management through chemical pleurodesis or additional surgical interventions. Chemical pleurodesis was conducted using either fibrinogen, betadine, or both. The initial treatment involved pleurodesis with fibrinogen, with betadine used as a second option if pleurodesis was required more than once. Fibrinogen pleurodesis entails the instillation of a fibrinogen-rich solution into the pleural space to promote adhesion between the visceral and parietal pleurae, thereby obliterating the pleural space, stopping air leaks, and preventing fluid accumulation. For this procedure, 20 mL of 1% lidocaine hydrochloride (200 mg) is first instilled into the pleural cavity through the chest tube. This is followed by a solution containing 1 g of fibrinogen, 20 mL of calcium gluconate (2 g), and thrombin powder (5,000 IU). The chest tube is then elevated approximately 50 cm above the patient to retain the agent while allowing air to pass. The chest tube remains under thoracic suction, typically between -10 and -15 cmH_2O. The patient is repositioned every 10 minutes to ensure the solution uniformly contacts all pleural surfaces. Positions may include supine, prone, sitting, head-down, and lateral decubitus, in any sequence. The chest tube is lowered 1 hour later. If pain relief is necessary, non-steroidal anti-inflammatory drugs or acetaminophen are administered. For betadine pleurodesis, the procedural steps are identical, except for the agent used. A common dilution technique involves mixing 50 mL of betadine solution (10% povidone-iodine) with 450 mL of normal saline to achieve a final concentration of 1% povidone-iodine. Approximately 200 mL of this diluted solution is then introduced into the pleural cavity following the same steps as those for fibrinogen pleurodesis. The dilution concentration can be adjusted according to the surgeon's preference.

Changes in postoperative pulmonary function

Spirometry including FVC and FEV_1 was performed preoperatively and at 6 and 12 months after lobectomy. The percentage of postoperative functional changes in FVC and FEV_1 was calculated by the following formula: change in FVC or FEV_1 (%)=[postoperative FVC or FEV_1 (%)–preoperative FVC or FEV_1 (%)]/preoperative FVC or FEV_1 (%). Changes in FVC or FEV_1 were expressed as median (%) (interquartile range).

Propensity score matching

Propensity score matching (PSM) was conducted at a 1:4 ratio, with the caliper set to 0.1. The variables used for matching included age, sex, smoking history, body mass index (BMI), baseline pulmonary function, pathologic stage, and surgical approach. The standardized mean difference (SMD) was utilized to assess the balance of covariates between the 2 groups.

Statistical analyses

The primary outcome of this study was to compare the changes in FEV_1 and FVC at 6 and 12 months postoperatively between the 2 groups. The secondary outcome was the differential impact of PAL on PPF, depending on which lobe was resected. Correlations between clinicopathologi-

cal variables in the PAL group and the non-PAL group were analyzed using the chi-square test or the Fisher exact test for categorical variables, and the Mann-Whitney U test for continuous variables. Statistical analyses were performed using IBM SPSS ver. 22.0 for Windows (IBM Corp., Armonk, NY, USA) and R statistical software ver. 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Basic characteristics before propensity score matching

A total of 1,316 patients were selected and divided into 2 groups: those who experienced PAL (n=55, 4%) and those who did not (n=1,261) (Fig. 1). The overall characteristics of the patients in the 2 groups of the unmatched cohort are presented in Table 1. Significant differences were observed

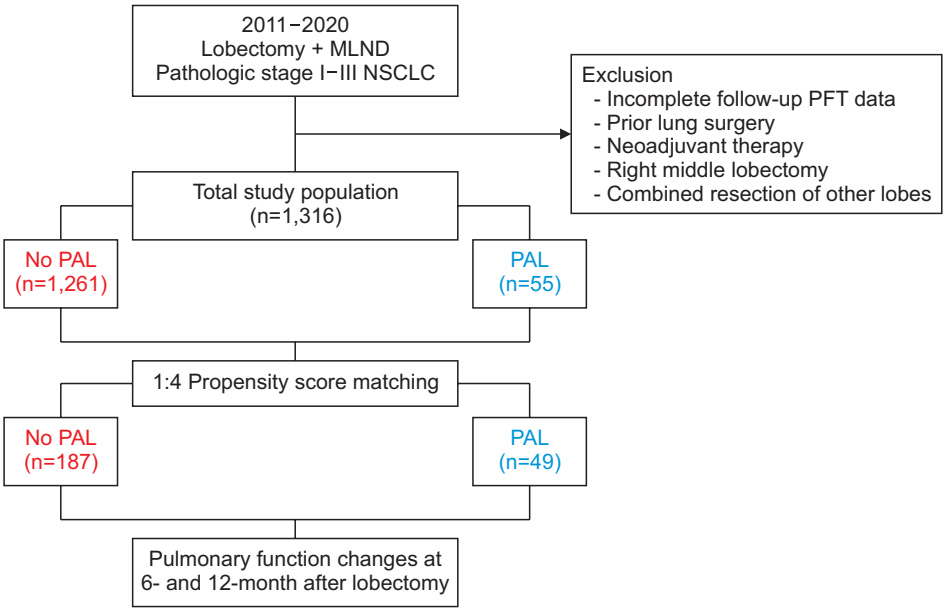


Fig. 1. Study design. MLND, mediastinal lymph node dissection; NSCLC, non-small cell lung cancer; PFT, pulmonary function test; PAL, prolonged air leak.

Table 1. Overall patients' characteristics compared between the PAL and non-PAL groups

Characteristic	Non-PAL group (n=1,261)	PAL group (n=55)	p-value
Age (yr)	64.1±10.1	67.2±10.0	0.026
Sex (male)	483 (38.3)	37 (67.3)	0.001
Smoking (ever)	430 (34.1)	31 (56.4)	0.001
Smoking amount (pack year)	33.6±22.6	39.3±18.7	0.173
Body mass index (kg/m^2)	24.2±0.3	22.8±3.1	0.001
Cardiovascular disease	157 (12.5)	4 (7.3)	0.251
Chronic obstructive pulmonary disease	8 (0.6)	2 (3.6)	0.012
Interstitial lung disease	23 (1.8)	4 (7.3)	0.005
Tuberculosis	83 (6.6)	4 (7.3)	0.840
Forced vital capacity (%)	106.3±19.0	104.6±19.6	0.528
Forced expiratory volume in 1 second (%)	102.4±15.2	104.1±12.8	0.414
Video-assisted thoracic surgery	1,230 (97.5)	49 (89.1)	0.001
TNM staging			0.272
Stage I	956 (75.8)	46 (83.6)	
Stage II	147 (11.7)	6 (10.9)	
Stage III	158 (12.5)	3 (5.5)	

Values are presented as mean±standard deviation or number (%).
PAL, prolonged air leak; TNM, tumor-node-metastasis.

between the groups in terms of age, gender, smoking history, BMI, presence of chronic obstructive pulmonary disease (COPD), interstitial lung disease, and the proportion of patients undergoing video-assisted thoracic surgery (VATS). However, there were no differences in preoperative pulmonary function, including FVC and FEV_1, or in pathologic staging. Among the patients who experienced PAL, 52 (95%) underwent chemical pleurodesis, with an average of 2 treatments administered (range, 1–6). The agents used for chemical pleurodesis were fibrinogen alone (n=40) and a combination of fibrinogen and betadine (n=12).

Overall characteristics after propensity score matching

All SMDs in the matched variables were less than 0.1. PSM was conducted at a 1:4 ratio, with 49 patients in the PAL group and 187 in the non-PAL group. Table 2 presents the baseline characteristics following PSM. After matching, all differences between the 2 groups were statistically insignificant.

Changes in pulmonary function in the matched cohorts

At 6 months after surgery, FEV_1 decreased significantly more in the PAL group than in the non-PAL group (-13.0% [-20.0% to -6.0%] versus -10.0% [-17.0% to -2.0%], p=0.041) and this difference was statistically significant. Similarly, the FVC decreased more in the PAL group than in the non-PAL group (-15.0% [-23.0% to -8.0%] versus -9.0% [-16.0% to -2.0%], p<0.001) and this difference was also statistically significant. At 12 months after surgery, the PAL group exhibited decreases in FEV_1 (-11.0% [-20.0% to -6.0%] versus -10.0% [-18.0% to -1.0%], p=0.198) and FVC (-12.0% [-16.0% to -4.0%] versus -6.0% [-14.0% to 1.0%], p=0.030). In all matched patients, the difference in FVC between the 2 groups was consistently statistically significant at both periods (Fig. 2).

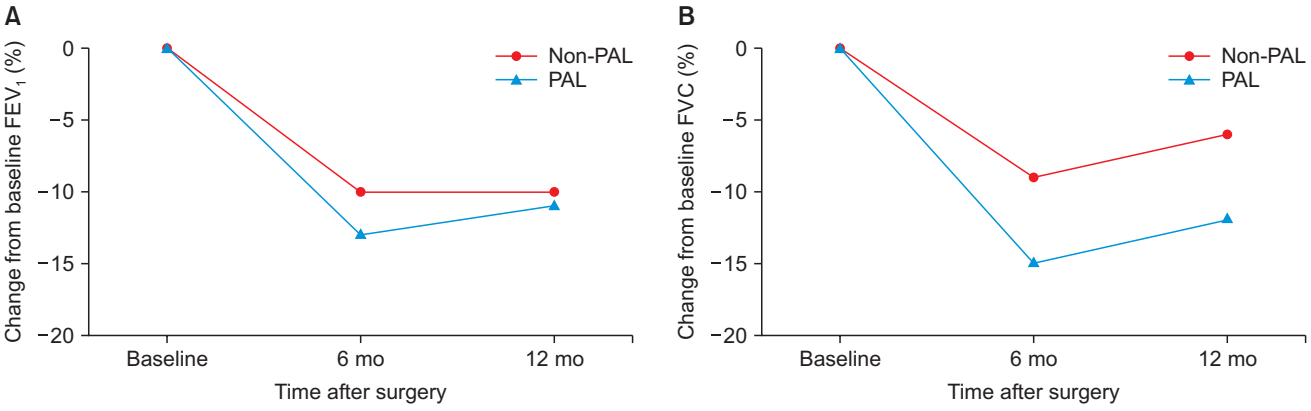
Changes in pulmonary function according to the resected lobe in the matched cohort

We further analyzed the changes in PPF according to the resected lobe to investigate whether differences existed in this regard between the upper and lower lobes. First, in upper lobectomy, the changes in FVC and FEV_1 at 6 and 12 months after surgery showed no significant differences between the PAL and non-PAL groups, except for FVC at 6 months (Fig. 3). The PPF in the PAL group became almost the same as that in non-PAL group after upper lobectomy. In contrast, in patients who underwent lower lobectomy, at 6 months after surgery, the FEV_1 decreased in the PAL group more substantially than in the non-PAL group (-14.0% [-20.0% to -10.0%] versus -11.0% [-17.0% to -3.0%], p=0.057), with a marginally statistically significant difference. At 12 months, the PAL group exhibited a decrease in

Table 2. Comparison of characteristics between the PAL and non-PAL groups after propensity score matching

Characteristic	Non-PAL group (n=187)	PAL group (n=49)	p-value
Age (yr)	66.3±8.6	66.2±10.0	0.937
Sex (male)	93 (49.7)	26 (53.1)	0.001
Smoking (ever)	79 (42.2)	24 (48.9)	0.001
Smoking amount (pack year)	36.6±20.6	37.3±18.8	0.463
Body mass index (kg/m^2)	24.2±2.3	23.8±3.1	0.281
Cardiovascular disease	10 (5.3)	4 (7.3)	0.151
Chronic obstructive pulmonary disease	8 (0.6)	1 (2.0)	0.092
Interstitial lung disease	13 (6.9)	3 (6.1)	0.785
Tuberculosis	16 (8.6)	4 (7.3)	0.340
Forced vital capacity (%)	102.5±15.4	101.7±14.0	0.681
Forced expiratory volume in 1 second (%)	104.3±20.7	102.9±21.8	0.573
Video-assisted thoracic surgery	173 (92.5)	45 (91.8)	0.566
TNM staging			0.791
Stage I	148 (79.1)	41 (83.6)	
Stage II	22 (11.8)	6 (10.2)	
Stage III	23 (12.3)	3 (6.1)	

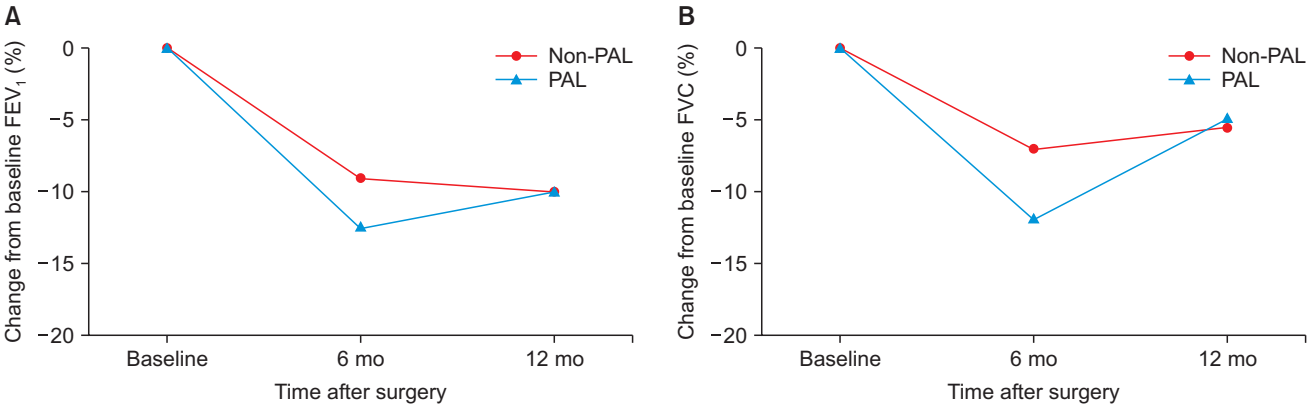
Values are presented as mean±standard deviation or number (%).
PAL, prolonged air leak; TNM, tumor-node-metastasis.



FEV_1 (%)	Non-PAL (n=189)	PAL (n=49)	p-value
6 mo	−10.0 (−17.0 to −2.0)	−13.0 (−20.0 to −6.0)	0.041
12 mo	−10.0 (−18.0 to −1.0)	−11.0 (−20.0 to −6.0)	0.198

FVC (%)	Non-PAL (n=189)	PAL (n=49)	p-value
6 mo	−9.0 (−16.0 to −2.0)	−15.0 (−23.0 to −8.0)	<0.001
12 mo	−6.0 (−14.0 to −1.0)	−12.0 (−16.0 to −4.0)	0.03

Fig. 2. (A, B) In the matched patients, the forced vital capacity (FVC) in the prolonged air leak (PAL) group was statistically significantly lower at both 6 and 12 months. FEV_1, forced expiratory volume in 1 second.



FEV_1 (%)	Non-PAL (n=189)	PAL (n=49)	p-value
6 mo	−9.0 (−17.8 to −1.0)	−12.5 (−19.2 to −2.8)	0.295
12 mo	−10.0 (−19.0 to −0.2)	−10.0 (−20.0 to −5.8)	0.672

FVC (%)	Non-PAL (n=189)	PAL (n=49)	p-value
6 mo	−7.0 (−14.0 to −1.0)	−12.0 (−18.2 to −5.0)	0.022
12 mo	−5.5 (−11.8 to −3.0)	−5.0 (−12.8 to −1.5)	0.502

Fig. 3. (A, B) The forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) in the prolonged air leak (PAL) group at 12 months became almost the same as those in the non-PAL group after upper lobectomy.

FEV_1 (-15.0% [-20.0% to -7.0%] versus -10.0% [-17.0% to -1.0%], p=0.114); however, this difference was not statistically significant. Nonetheless, the changes in FVC between the 2 groups were markedly different. The FVC at 6 months decreased more in the PAL group than in the non-PAL group (-20.0% [-27.0% to -14.0%] versus -13.0% [-18.0% to -6.5%], p=0.006), and at 12 months, the FVC decreased significantly more in the PAL group than in the non-PAL group (-14.0% [-22.0% to -12.0%] versus -9.0% [-17.0% to -2.0%], p=0.011) (Fig. 4).

Discussion

In this study, PAL was found to influence the recovery of PPF at 6 months following surgery, with effects persisting for 12 months, particularly in FVC. The changes in PPF varied depending on the resected lobe; both FVC and FEV_1 showed less recovery in the lower lobectomy group compared to the upper lobectomy group.

The reasons why lung function recovery is slower in the PAL group compared to the non-PAL group include common postoperative findings such as pleural effusion, pleu-

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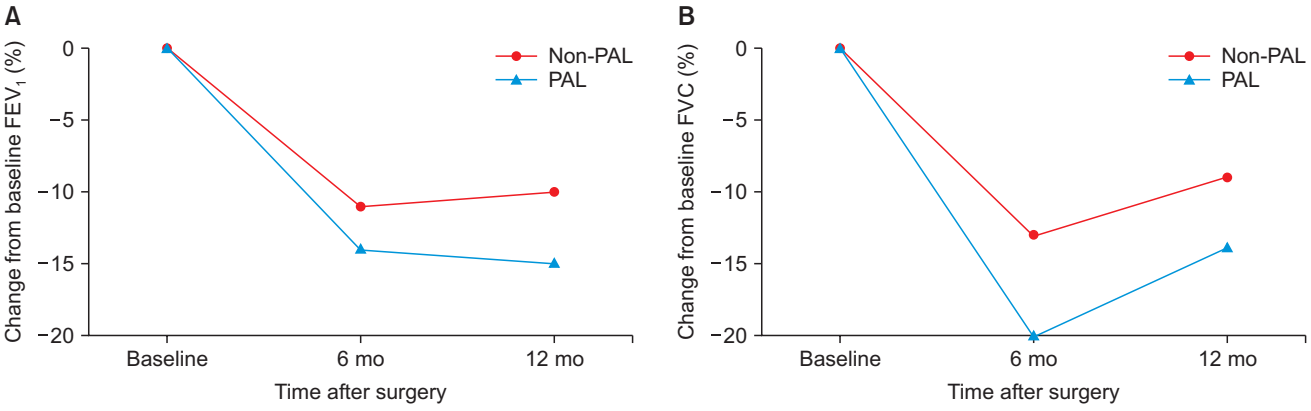

FEV_1 (%)	Non-PAL (n=189)	PAL (n=49)	p-value
6 mo	−11.0 (−17.0 to −3.0)	−14.5 (−20.0 to −10.0)	0.057
12 mo	−10.0 (−17.0 to −1.0)	−15.0 (−20.0 to −7.0)	0.114

FVC (%)	Non-PAL (n=189)	PAL (n=49)	p-value
6 mo	−13.0 (−18.0 to −6.5)	−20.0 (−27.0 to −14.0)	0.006
12 mo	−9.0 (−17.0 to −2.0)	−14.0 (−22.0 to −12.0)	0.011

Fig. 4. (A, B) The forced vital capacity (FVC) in the prolonged air leak (PAL) group was lower than that in non-PAL group after lower lobectomy at both 6 and 12 months. FEV_1, forced expiratory volume in 1 second.

ral thickening, and empyema in the PAL group. PAL is the most common postoperative pulmonary complication, occurring in 5% of cases in this study, which is slightly lower than reported in the literature. PAL is closely associated with a higher rate of pleural empyema, which was 8.2% in patients with empyema compared to 0% in those without PAL [11]. Most cases of PAL were treated with chemical pleurodesis, and the agents used are believed to induce pleural inflammation, pleural symphysis, and sealing of the visceral pleura [12]. These findings suggest that PAL itself causes pleural thickening in the remaining lung, which then prevents its re-expansion after surgery. Furthermore, pleural thickening and adhesion following chemical pleurodesis could lead to significant loss of pulmonary function [9]. In this study, chemical pleurodesis was typically performed 1–2 times as a treatment for PAL. At our institution, fibrinogen pleurodesis is most commonly used to cover the visceral pleura, and betadine is also used to create symphysis between the visceral and parietal pleura. This symphysis may impact long-term pulmonary function. Maeyashiki et al. [13] reported that the gap between postoperative and preoperative pulmonary function was larger in the chemical pleurodesis group than in the non-chemical pleurodesis group. This difference was significant in FVC compared to FEV_1 (FVC, -21.1% and -20.8% at 6 and 12 months; FEV_1, -19.1% and -19.6% at 6 and 12 months) [13]. There were no data on whether different chemical agents would have varying effects on PPF. A recent study involving talc, OK-432, 50% glucose, minocycline, or autologous blood patch demonstrated that a decline in FVC was slightly greater in patients who underwent pleurodesis with talc [14].

This study demonstrated varying degrees of recovery in PPF depending on the resected lobe. In patients who underwent lower lobectomy, FEV_1 and FVC were significantly lower in the PAL group compared to the non-PAL group. Interestingly, after upper lobectomy, there was no significant difference in FVC and FEV_1 between the 2 groups at 12 months. Although it is challenging to determine the exact mechanism, 2 contrasting observations must be considered. First, the lung volume reduction effect following upper lobectomy is noteworthy. Conditions such as emphysema, COPD, or other inflammatory lung diseases predominantly affect the upper lobe. Not only does the presence of these conditions not contribute to pulmonary function, but it also impedes the expansion of the remaining lung tissue before surgery. However, after upper lobectomy for lung cancer, the remaining lobes may expand more effectively and contribute positively to PPF. This effect is evident regardless of the presence of PAL and may even be more pronounced in the PAL group [15]. PPF following lung volume reduction surgery typically peaks between 3 to 6 months after the procedure, with benefits potentially lasting from 1 to 2 years [16]. Similarly, at 12 months, there was no significant difference in FVC or FEV_1 between the non-PAL and PAL groups. Second, PAL is more likely to occur after upper lobectomy in patients with underlying emphysematous lungs. As noted, postoperative air leaks, whether spontaneous or induced by chemical pleurodesis, prevent effective lung expansion. Therefore, it can be inferred that

the positive and negative effects in the PAL group after lobectomy result in no significant differences in PFTs at both 6 and 12 months between the PAL and non-PAL groups.

In contrast, FVC and FEV_1 were lower in the PAL group after lower lobectomy. To interpret the results of this study accurately, we need to understand the mechanisms similar to those observed in upper lobectomy. Factors such as the absence of a lung volume reduction effect, different underlying diseases, and the larger lung volume of the lower lobe were considered. After a significant loss of volume, PPF following lower lobectomy relies solely on the expansion of the remaining lung tissue. Therefore, PAL, which causes pleural thickening or restricted lung expansion, is more closely associated with PPF, and this effect persists for 12 months after surgery.

The effect of PAL was greater on FVC than on FEV_1. In all cohorts, both FVC and FEV_1 at 6 months after surgery were lower in the PAL group. The difference in FEV_1 between the 2 groups was statistically marginal ($p=0.041$), but the difference in FVC was statistically significant ($p< 0.001$). Twelve months after lobectomy, only FVC remained lower in the PAL group. In the lower lobectomy cohort, there was no difference in FEV_1 between the 2 groups at 6 and 12 months, although statistical differences were observed in FVC at both 6 and 12 months, and in FEV_1 at 6 months. These findings are consistent with those seen in restrictive lung diseases such as inflammatory lung disease and interstitial lung disease. Echoing previous mechanisms, the most common complication was an air leak, which was managed by chemical pleurodesis. Pleural adhesion and pleural thickening contributed to the remaining lung being restricted.

Limitations

Several limitations of this study must be acknowledged. First, as this is a retrospective single-center study, selection bias was a significant issue. This was primarily because some patients who experienced severe postoperative pulmonary complications, including PAL, were not included in the study due to the absence of PFT data. To address this, we employed PSM to mitigate the differences between the 2 groups; however, unaccounted biases may still be present. Second, this study included both VATS and open surgical methods. Although the majority of surgeries in both groups were performed using VATS, there was a slight difference in the frequency of VATS usage, which was marginally lower in the PAL group. This variation could potentially influence PPF. Third, the results of the diffusion capacity of carbon monoxide (DLCO) were not included in this study due to the complexity of administering the test in an outpatient setting. Subjective symptoms such as dyspnea on exertion are closely associated with DLCO levels. Consequently, patients may report subjective dyspnea even when FEV_1 and FVC values are normal or within acceptable ranges. Fourth, it is unclear whether the reason for the greater decline in lung function in patients with PAL than in patients without PAL is due to PAL itself or pleurodesis. In this study, 52 of the PAL patients underwent pleurodesis, while 3 did not; however, the 3 patients who did not undergo pleurodesis after PSM were excluded and a further analysis could not be performed.

Conclusions

Postoperative PAL that occurs after lobectomy in NSCLC patients can harm long-term pulmonary function. This impact is notably more pronounced after lower lobectomy than after upper lobectomy. Therefore, efforts to prevent PAL during the surgical and perioperative periods are particularly important when performing lower lobectomy. Preventing PAL is the best treatment for air-leak complications and reduced long-term pulmonary function. Thoracic surgeons can minimize the occurrence of PAL through meticulous closure of parenchymal and pleural defects and the reinforcement of suture and stapled lines.

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Conflict of interest

No potential conflict of interest relevant to this article was reported.

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