



# Postpneumonectomy syndrome related to the thickness of the fat tissue in the anterior mediastinum: a retrospective observational study

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**Background:** Postpneumonectomy syndrome (PPS) is a life-threatening condition characterized by the extrinsic compression of the mainstem bronchus after pneumonectomy, causing rapidly progressive dyspnea. Information regarding the predictive factors of this condition is limited. Thus, the current study aimed to identify the predictive findings that can help prepare the treatment of PPS in advance.

**Methods:** The present study is a retrospective observational study. We reviewed the medical records of 12 consecutive patients who underwent pneumonectomy for lung cancer or tuberculosis between 2009 and 2020. The anatomical findings evaluated via computed tomography scan, nutritional status assessed using laboratory data, respiratory function, intraoperative variables between PPS and non-postpneumonectomy-syndrome patients were compared.

**Results:** There were two female patients who presented with left PPS (PPS 1 and PPS 2 aged 73 and 55 years, respectively). The median age of 10 non-postpneumonectomy-syndrome patients (n=6, men and n=4 women) was 66 (range, 54–76 years). Four and six patients underwent right and left pneumonectomy, respectively. The fat tissue thickness in the anterior mediastinum was significantly thinner in PPS than in non-postpneumonectomy-syndrome patients. However, the body mass index (BMI) and other nutritional parameters did not differ between PPS and non-postpneumonectomy-syndrome patients. The median vital capacity was higher in PPS than in non-postpneumonectomy-syndrome patients. The decrement of respiratory function and body weight after pneumonectomy did not differ between two groups. The intraoperative variables did not also differ between two groups.

**Conclusions:** The fat tissue in the anterior mediastinum between the bilateral lungs is an anchor that can help maintain the normal position of the mediastinum after pneumonectomy. Thus, the fat tissue thickness between the bilateral lungs can be a predictive factor for the occurrence of PPS before surgery.

**Keywords:** Pneumonectomy; postpneumonectomy syndrome (PPS); lung cancer; mediastinum

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## Introduction

Postpneumonectomy syndrome (PPS) is a rare life-threatening condition characterized by extrinsic compression of the trachea and mainstem bronchus after pneumonectomy.

Several mechanisms associated with the condition have been reported (1,2). First, an excessive shift of the heart and mediastinum toward the side of the pneumonectomy is observed. Second, there is a significant rotation of the great

vessels. Third, hyperinflation of the remaining lung occurs. The trachea and/or main bronchus are compressed against the vertebral column or aorta. Consequently, patients develop progressive dyspnea, inspiratory stridor, and recurrent pneumonia at least 6 months after surgery and the condition can be fatal if left untreated.

There are several treatments for PPS. That is, the position of the shifted mediastinum can be treated with surgery, intrapleural gas injection therapy, or intrathoracic tissue expander (3-5). Another option is the placement of expandable stents at the compressed portion of the airway (6,7).

PPS causes severe asphyxia and even death. In this study, two adult patients died of this condition, which rapidly developed to progressive dyspnea. To identify predictive factors that can help prepare the treatment of PPS in advance, we assessed the data of 12 adult patients who underwent pneumonectomy, including two who presented with PPS in our institution.

We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/jtd-20-2370>).

## Methods

### Patients

The present study is a retrospective observational study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Committee for Protection of Human Subjects, the local institutional review board of National Hospital Organization, Kanagawa National Hospital approved this study (The approval number of Institutional Review Board of Kanagawa Hospital: R2-3). Because of the retrospective nature of the study, patient informed consent or ethical statement was not required. All patients who underwent pneumonectomy for lung cancer or tuberculosis at our institution between January 2009 and March 2020 were identified from a maintained surgical database of our institution. All patients or families were contacted, and they agree to provide information about their clinical courses.

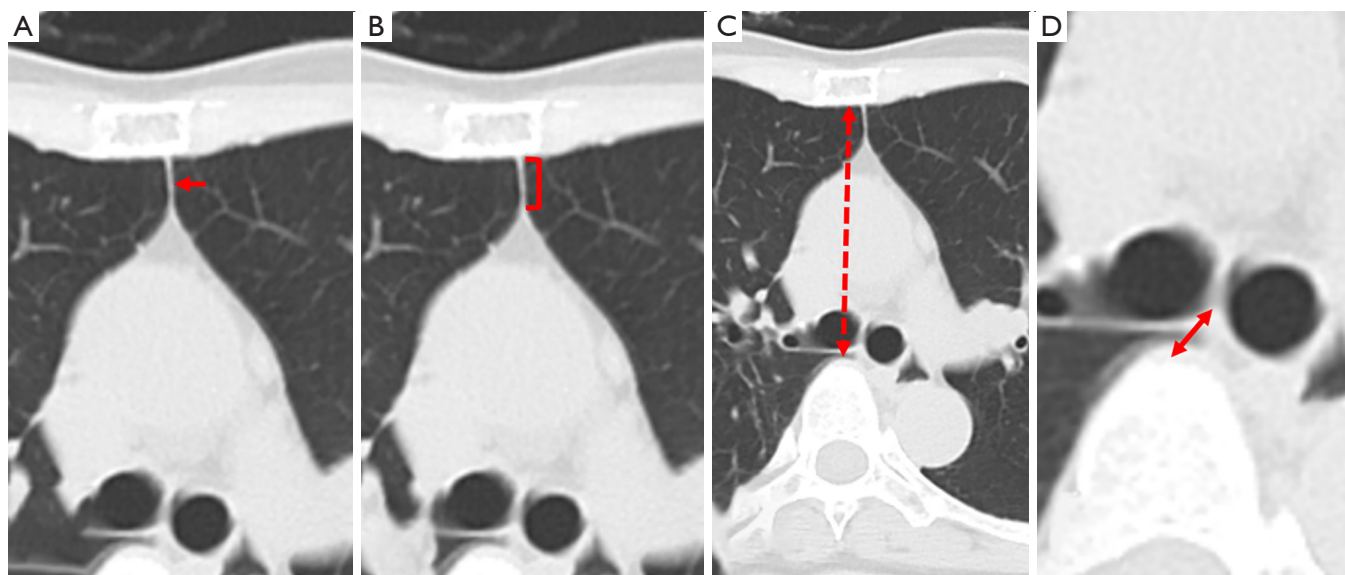
### Data collection

We analyzed the medical records from three viewpoints.

First, we assessed some mediastinum structures using computed tomography (CT) scan images. Second, the respiratory function of the patients before surgery were compared. Third, nutritional status was assessed using laboratory information obtained before surgery. Data, such as height, body weight, blood examination results, CT images, chest radiography images, presenting signs and symptoms, surgical approach used, date of surgery, interval between pneumonectomy and the development of PPS, preoperative and postoperative radiographic and pulmonary function test results, operation time, the amount of blood loss, the presence of adhesion between thoracic wall and lung, postoperative morbidity, and mortality and last follow-up visit or date of death, were obtained from the medical records of the patients. The patients were followed up every three or four months after surgery by five years in principle. There was not missing patient in the observation period.

### Definition of parameters

The parameters in the axial images of CT scan conducted before surgery, which may indicate the stability of the mediastinal organs, were assessed (*Figure 1*). The thinnest portion of the fat tissue between bilateral thoracic cavities in the anterior mediastinum at the level of the carina was referred to as T (*Figure 1A*). The length of the fat tissue between the bilateral thoracic cavities in the anterior mediastinum at the level of the carina, with a thickness  $\leq 1$  mm, was referred to as  $L_A$  (*Figure 1B*). The length between the sternum and the vertebra at the level of the carina was referred to as  $L_B$  (*Figure 1C*). The length between the carina and the vertebra at the level of the carina was referred to as  $L_C$  (*Figure 1D*). The area of the fat tissue in the anterior mediastinum at the level of the carina was evaluated. To assess nutritional status, the body mass index (BMI), prognostic nutritional index (PNI), neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR) of the patients were evaluated (8-10). BMI was defined as weight in kilograms divided by height in meters squared.  $\Delta BW$  was defined as the decrement of body weight in the first 6–12 months after pneumonectomy. PNI was calculated based on the serum albumin concentration and peripheral blood lymphocyte count. Based on the respiratory function test before surgery, vital capacity (VC) and forced expiratory volume in



**Figure 1** (A) The thinnest portion of the fat tissue between the bilateral thoracic cavities in the anterior mediastinum at the level of the carina was referred to as T. (B) The length of the fat tissue between bilateral the thoracic cavities in the anterior mediastinum at the level of the carina, with a thickness  $\leq 1$  mm, was referred to as  $L_A$ . (C) The length between the sternum and the vertebra at the level of the carina was referred to as  $L_B$ . (D) The length between the carina and vertebra was referred to as  $L_C$ .

1 second (FEV1) were assessed. The predicted postoperative VC (ppo-VC) and predicted postoperative FEV1 (ppo-FEV1) were calculated using the following formula: ppo-VC or ppo-FEV1 = preoperative VC or ppo-FEV1  $\times$  (No. of segments remaining/total No. of segments) (11).  $\Delta$ VC was defined as the decrement of VC the first 6–12 months after pneumonectomy.  $\Delta$ FEV1 was defined as the decrement of FEV1 the first 6–12 months after pneumonectomy.

### Statistical analysis

Continuous non-normal data were expressed as medians with range (minimum and maximum). In univariate analysis for the two groups, categorical variables were compared using the  $\chi^2$  test or Fisher's exact test, while Student *t*-test was used to compare normally distributed continuous variables, and non-normal data were tested with Mann-Whitney U test with IBM SPSS Statistics version 25 (IBM, Armonk, NY, USA). A P value  $<0.05$  was considered statistically significant.

### Results

There were 12 patients undergone pneumonectomy

between January 2009 and March 2020 in our institution. PPS occurred in 2 patients and did not occur in 10 patients. Of the 12 patients in this study, 6 were men and 6 were women. In total, 10 patients underwent pneumonectomy for lung cancer and 2 for tuberculosis empyema with fistula. Two patients with lung cancer received neo-adjuvant chemotherapy, and anti-tuberculosis agents (rifampicin, isoniazid, pyrazinamide, and ethambutol) were administered in two patients with tuberculosis empyema before and after surgery (Table 1).

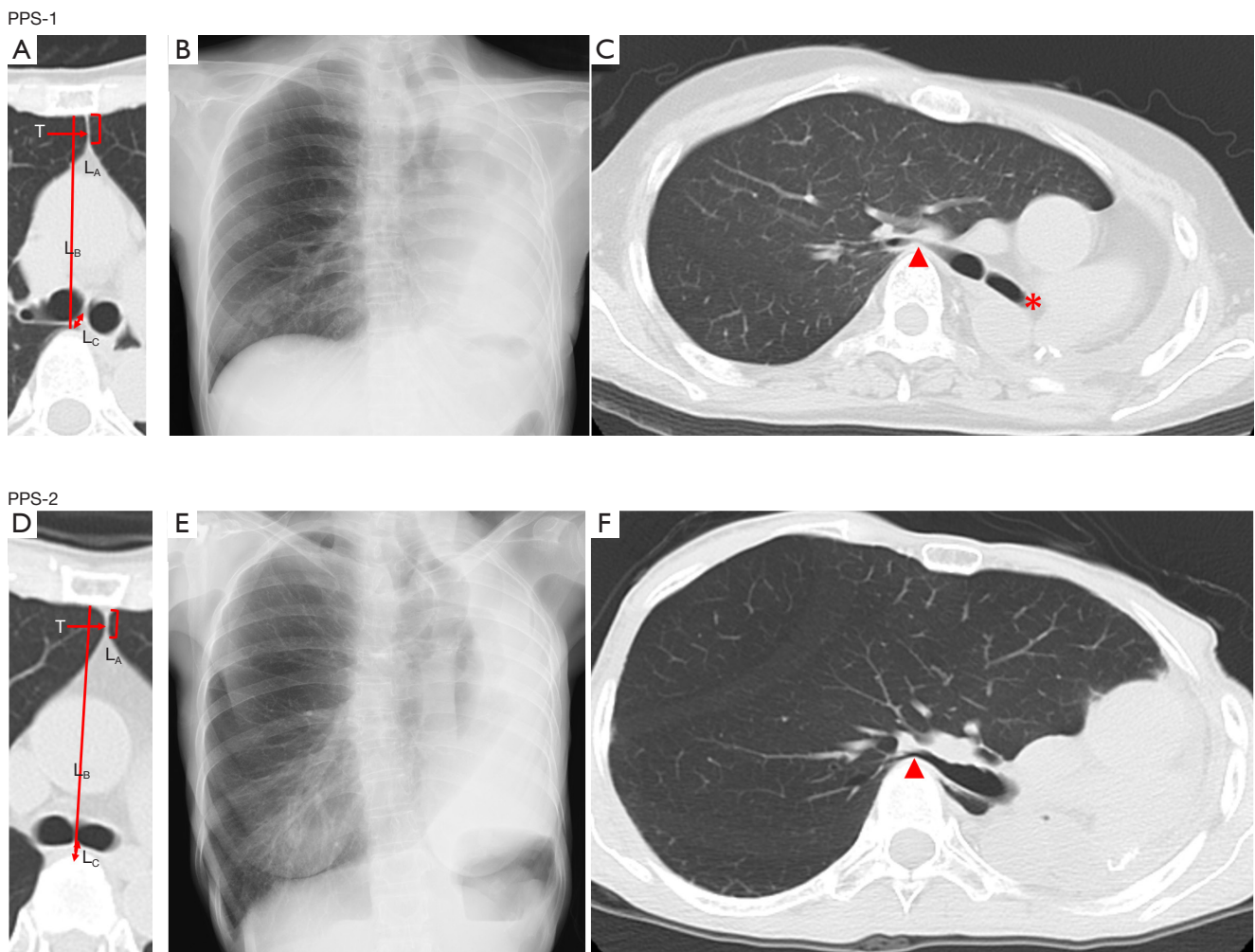
There were two female patients who presented with PPS [PPS-1 (Figure 2A,B,C) and PPS-2 (Figure 2D,E,F)] aged 73 and 55 years, respectively. The two patients underwent left pneumonectomy, and PPS-1 and PPS-2 died 31 and 21 months after surgery, respectively. In both cases, dyspnea, which particularly occurred when they stooped down, gradually developed 6 months after surgery. They suddenly presented with severe hypoxia, which is an emergency condition. Respiratory support via intubation and bag ventilation exacerbated hypoxia and resulted in death. There was no clinical evidence to deteriorate pulmonary function other than PPS.

The median age of 10 non-PPS patients (n=6, men

**Table 1** Characteristics of the patients

Characteristic	PPS-1	PPS-2	Non-PPS	P value
Age (years)	73	55	66 [54–76]	0.914
Gender (cases)	Female	Female	Female: 4, male: 6	0.224
Affected side (cases)	Left	Left	Left: 6, right: 4	0.079
Indication for pneumonectomy	Lung cancer	Lung cancer	Lung cancer: 8, tuberculosis: 2	
Neoadjuvant chemotherapy (cases)	No	No	2	
Adjuvant chemotherapy (cases)	CDDP + PEM: two courses	S-1	4	

Preoperative characteristics of the patients who underwent pneumonectomy. PPS, postpneumonectomy syndrome; CDDP, cisplatin; PEM, pemetrexed; S-1, tegafur-gimeracil-oteracil.



**Figure 2** (A,B,C) are images of PPS-1, and (D,E,F) are images of PPS-2. (A and D) are the CT scan at the level of the carina before surgery. B and E are the chest radiography image after PPS. (C and F) are the CT scan at the level of the carina after PPS. Chest radiography image (B and E) showed hyperinflation of the right lung, shift of the trachea and the mediastinum. CT scan image (C and F) showed that the right lung compressed the right main bronchus on the vertebra. The arrowhead indicates the compressed and narrowed right main bronchus. The asterisk indicates the stump of the left main bronchus. PPS, postpneumonectomy syndrome; CT, computed tomography.

**Table 2** Comparison of the CT scan findings, nutritional status, respiratory function and intraoperative variables between PPS patients and non-PPS patients

Variable	PPS-1	PPS-2	Non-PPS, median [range]	P value
T (mm)	1	1	8.5 [1–16]	0.061
L <sub>A</sub> (mm)	13	14	0 [0–8]	0.030
L <sub>B</sub> (mm)	78	77	86.4 [70–99]	0.273
L <sub>C</sub> (mm)	9	4	9 [4–23]	0.505
Area of the connective tissue (mm <sup>2</sup> )	16.0	103.1	42.1 [18.5–209.4]	0.721
BMI	17.7	19.1	15.9 [14.0–17.0]	0.173
PNI	54.8	47.6	47.4 [29.6–52.3]	0.136
PLR	108.9	137.2	188.4 [136.8–595.8]	0.142
NLR	1.26	2.18	3.24 [0.85–17.73]	0.962
ΔBW (kg)	–1.0	1.0	1.25 [–1–1]	0.130
VC before surgery (L)	3.00	2.82	2.42 [1.75–4.40]	0.411
FVC before surgery (L)	2.79	2.78	2.42 [1.63–4.03]	0.412
FEV1 before surgery (L)	1.92	1.98	1.97 [1.21–3.12]	0.636
ppo-VC (L)	1.57	1.01	1.27 [0.89–2.10]	0.296
ppo-FEV1 (L)	1.48	1.04	1.03 [0.63–1.49]	0.620
ΔVC (L)	1.66	N/E	1.03 [0.48–1.60]	N/E
ΔFEV1 (L)	1.78	N/E	1.29 [0.44–1.81]	N/E
Operation time (min)	363	284	333 [232–703]	0.244
Amount of blood loss (g)	2,950	90	850 [140–2,700]	0.510
Adhesion (presence or absence)	Absence	Absence	Presence: 7, absence: 3	0.209

PPS, postpneumonectomy syndrome; T, thinnest fat tissue between the bilateral lungs in the anterior mediastinum; L<sub>A</sub>, length of the T, with a thickness ≤1 mm; L<sub>B</sub>, length between the sternum and the vertebra at the level of the carina; L<sub>C</sub>, the length between the carina and the vertebra at the level of the carina; BMI, body mass index; PNI, prognostic nutritional index; PLR, platelet-lymphocyte ratio; NLR, neutrophil-lymphocyte ratio; ΔBW, the decrement of body weight in the first 6–12 months after surgery; VC, vital capacity; FEV1, forced expiratory volume in 1 second; ppo-VC, predicted postoperative vital capacity; ppo-FEV1, predicted postoperative forced expiratory volume in 1 second; ΔVC, the decrement of VC the first 6–12 months after pneumonectomy; ΔFEV1, the decrement of FEV1 the first 6–12 months after pneumonectomy; N/E, not examined.

and n=4, women) was 66 (range, 54–76) years. Both PPS-1 and PPS-2 were female. In total, four and six patients underwent right and left pneumonectomy, respectively. The two groups, which are PPS patients and non-PPS patients, did not differ significantly in age, gender and affected side. The median follow-up time was 35.5 months.

The results of comparison of the CT scan findings, nutritional status, respiratory function, and intraoperative variables between PPS patients and non-PPS patients were shown in *Table 2*. Based on the CT scan images before surgery, the T of PPS-1, PPS-2 and the median T of non-PPS patients

were 1, 1, and 8.5 (range, 1–16) mm, respectively. The L<sub>A</sub> of PPS-1, PPS-2 and the median L<sub>A</sub> of non-PPS patients were 13, 14, and 0 (range, 0–8) mm, respectively. The L<sub>B</sub> of PPS-1, PPS-2 and the median L<sub>B</sub> of non-PPS patients were 78, 77, and 86.4 (range, 70–99) mm, respectively. The L<sub>C</sub> of PPS-1, PPS-2 and the median L<sub>C</sub> of non-PPS patients were 9, 9, and 9 (range, 4–23) mm, respectively. The area of the fat tissue of PPS-1, PPS-2 and the median value of non-PPS patients were 16.0, 103.1, and 42.1 (range, 18.5–209.4) mm<sup>2</sup>, respectively. The L<sub>A</sub> significantly differed between PPS and non-PPS patients (P=0.030). The T has also a tendency to be thinner in

PPS patients ( $P=0.61$ ). This result indicated that the partition between the bilateral thoracic cavities was thin in PPS patients.

The BMI of PPS-1, PPS-2 and the median BMI of non-PPS patients were 17.7, 19.1, and 15.9 (range, 14.0–17.0), respectively. The PNI were 54.8, 47.6, and 47.4 (range, 29.6–52.3), respectively. The PLR were 108.9, 137.2, and 188.4 (range, 136.8–595.8), respectively. The NLR were 1.26, 2.18, and 3.24 (range, 0.85–17.73), respectively. The  $\Delta$ BW of PPS-1, PPS-2 and the median  $\Delta$ BW of non-PPS patients were  $-1.0$ ,  $1.0$  and  $1.25$  (range,  $-1.0$  to  $14.0$ ) kg, respectively. The two groups did not differ significantly in BMI, PNI, PLR, NLR and  $\Delta$ BW. These results indicated that the nutrition status of PPS patients was not inferior to that of non-PPS patients.

The VC of PPS-1, PPS-2 and the median VC of non-PPS patients were 3.00, 2.82, and 2.42 (range, 1.75–4.40) L, respectively. The FEV1 of PPS-1, PPS-2 and the median FEV1 of non-PPS patients were 1.92, 1.98, and 1.97 (range, 1.21–3.12) L, respectively. The ppo-VC of PPS-1, PPS-2 and the median ppo-VC of non-PPS patients were 1.57, 1.01 and 1.27 (range, 0.89–2.10) L, retrospectively. The ppo-FEV1 of PPS-1, PPS-2 and the median ppo-FEV1 of non-PPS patients were 1.48, 1.04, and 1.03 (range, 0.63–1.49), retrospectively. The  $\Delta$ VC of PPS-1, PPS-2 and the median  $\Delta$ VC of non-PPS patients were 1.66, not examined, and 1.03 (0.48–1.60) L, respectively. The  $\Delta$ FEV1 of PPS-1, PPS-2 and the median  $\Delta$ FEV1 of non-PPS patients were 1.78, not examined, and 1.29 (0.44–1.81) L, respectively. The two groups did not differ significantly in VC before surgery, FEC before surgery, FEV1 before surgery, ppo-VC, ppo-FEV1, VC and FEV1. The VC and FVC of PPS patients was higher than the median of non-PPS patients. The ppo-FEV1 of PPS patients was higher than the median of non-PPS patients. The  $\Delta$ VC and  $\Delta$ FEV1 were more than the median of non-PPS patients.

The operation time of PPS-1, PPS-2 and the median operation time of non-PPS patients were 363, 284, and 333 (range, 232–703) minutes, respectively. The amount of blood loss of PPS-1, PPS-2 and the median amount of blood loss of non-PPS patients were 2,950, 90, and 850 (range, 140–2,700) g, respectively. In PPS-1 and PPS-2, the adhesion between thoracic wall and lung was absence. In 7 non-PPS patients, adhesion was presence. On the other hand, in 2 non-PPS patients, adhesion was absence. The

two groups did not differ significantly in the operation time, the amount of blood loss and adhesion.

## Discussion

Dyspnea develops rapidly after the development of PPS, and this condition is fatal if left untreated. Several treatments for this condition have been reported. One is repositioning of the mediastinum via surgery and filling of the postpneumonectomy space with a non-absorbable material (3-5). Another option is endobronchial intervention (6,7). However, the treatments must be prepared before the development of PPS. Grillo *et al.* also mentioned that occurrence of the syndrome is unpredictable. The incidence would seem to be rare enough so that prophylactic steps that might add complexity to pneumonectomy do not appear to be justified (12). Therefore, whether PPS occurs before progressive dyspnea should be predicted and investigation for the predictive factors of the occurrence of postpneumonectomy is worth.

Mehran *et al.* described that risk factors for the PPS include age and sex of the patient. Elasticity of the mediastinal tissues is one of the risk factors. Women, in general, and young patients can shift more than elderly patients (1). We focused on the anatomical structures around the mediastinum, which maintain the normal position of the mediastinum after pneumonectomy.

From an anatomical viewpoint, the  $L_A$  significantly differed between PPS and non-PPS patients ( $P=0.030$ ). The T has also a tendency to be thinner in PPS patients ( $P=0.61$ ). This result indicated that the partition between the bilateral thoracic cavities in the anterior mediastinum was thin in PPS patients. The density of the tissue in the anterior mediastinum on CT scan in non-PPS patients was compatible with the fat density, with an average CT value of  $-83.6$ . However, the BMI of the two PPS patients were 17.1 and 19.1, and the median BMI of non-PPS was 15.9. This result indicated that the PPS patients were not thinner than non-PPS patients in physical constitution. Regarding to the nutritional parameters, the NLR, PLR and PNI did not significantly differ between PPS cases and non-PPS patients. In terms of BMI, NLR, PLR and PNI, no significant difference was observed between PPS and non-PPS patients. This result indicated that the fat tissue thickness in the anterior mediastinum is not correlated

to nutritional status and the physical constitution of the patients. Moreover, the decrement of body weight after surgery also did not correlated to the occurrence of PPS. The fat tissue in front of the mediastinum could be an anchor that can help maintain the normal position of the mediastinum after pneumonectomy. These findings suggested that the change of respiratory function and body weight after pneumonectomy could not be predictive factors and the diet after surgery to increase body weight might not be effect to prevent PPS.

In terms of respiratory function before surgery, the VC of PPS patients was higher than the median of non-PPS patients. The FEV1 was similar between PPS and non-PPS patients. By contrast, in the ppo-VC, the PPS-1 case was higher and the PPS-2 case was lower than the median of non-PPS cases. Some studies showed that hyperinflation of the residual lung was a factors of PPS (1,2). However, the fat tissue between the bilateral thoracic space is a partition that can prevent the residual lung to hyperinflate toward the thoracic cavity after pneumonectomy.

Regarding to the affected side, PPS occurs more commonly after the right-sided pneumonectomy than the left-sided pneumonectomy in several reports (1,3,12). Shen *et al.* reported 18 PPS patients, which developed after right pneumonectomy in 13 patients and after left pneumonectomy in 5 patients. Grillo *et al.* reported PPS, which followed right pneumonectomy in 7 patients and left pneumonectomy in 4 patients. Mehran *et al.* described that most cases of PPS have occurred after right pneumonectomy, because the powerful negative pressure of the involved hemothorax and the overexpansion of the remaining lung create a vacuum, moving the mediastinum toward the right side. According to these literatures, the occurrence of the left-sided PPS may be less than right-sided PPS. However, the left-sided pneumonectomy might be performed more often than right-sided pneumonectomy because right-sided pneumonectomy is often avoided in respiratory function.

The fat tissue thickness between the bilateral lungs can be a predictive factor for occurrence of PPS before surgery. By contrast, the changes of respiratory function and body weight after surgery did not differ in the two groups. To find the occurrence of PPS as soon as possible after surgery, the shift of the anterior mediastinum should be observed

in the patients with the thin fat tissue in the anterior mediastinum before pneumonectomy.

The limitation of this study is small size retrospective cohort in one single institution, because pneumonectomy is becoming rarer due to several efforts made to reduce the numbers of pneumonectomy for the treatment of lung cancer. Therefore, it is difficult to collect the adequate patients undergone pneumonectomy. On the other hand, no similar observations to explore the predictive factors of PPS have been published, to our best knowledge. More studies with larger cohorts are needed in multi institutions, because the frequency of the pneumonectomy for lung cancer is decreasing due to the development of the other treatments.

## Conclusions

In conclusion, the fat tissue in the anterior mediastinum between the bilateral lungs is an anchor that can help maintain the normal position of the mediastinum after pneumonectomy. Thus, the fat tissue thickness between the bilateral lungs can be a predictive factor for occurrence of PPS before surgery.

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## Footnote

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*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/jtd-20-2370>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by our institutional review board (Approval number, R2-3). Because of the retrospective nature of the study, patient informed consent or ethical statement was not required.

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