

Peer review file

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Reviewer A

Comment 1:

1. Authors should perform some statistical test for clinical characteristics. For example, affected side must show some statistical difference.
2. In table 2, authors should perform statistical analysis.

Reply1:

Thank you for your comments.

We added statistical analysis in Table 1 and Table 2.

There was not significant difference between postpneumonectomy syndrome (PPS) patients and non-postpneumonectomy-syndrome (nonPPS) patients in the characteristics (Table 1). On the other hand, in Table 2, there was the significant difference between PPS and nonPPS patients in the parameter of L_A (p -value: 0.030). (See table 1 and 2, Page 11 line168-170)

Reviewer B

Comment 1:

Your work however has major problems. You did not mention how many patients were in the non postpneumonectomy group, even if you stated that you analyzed all patients up to 2020.

Reply 1:

Thank you for your comments.

We have modified our text as advised to elucidate how many patients were in the non-postpneumonectomy group. (see Page 10, line 139-140 and Table 1)

Comment 2:

You do mention predicted postoperative lung functions, but non effective postoperative lung function data. Generally patients after pneumonectomy receive at least once postoperatively a pneumologic assessment. Especially when respiratory symptoms worsen.

Reply 2:

We added the data about postoperative lung function data. We compared the decrement of respiratory function after pneumonectomy in vital capacity (VC) and forced expiratory volume in 1 second (FEV1). We defined ΔVC as the decrement of VC after pneumonectomy, and $\Delta FEV1$ as the decrement of FEV1 after pneumonectomy, respectively. The postoperative respiratory function was examined in the first 6 – 12 months after surgery. However, in PPS-2, respiratory function was not examined after surgery. The ΔVC and $\Delta FEV1$ of PPS-1 was more than the median ΔVC and $\Delta FEV1$ of non-PPS patients. (See Table 2, Page 9, line 128-130, Page 12, line 186-193, Table 2)

Comment 3:

You fail to address other possible reasons for deteriorating pulmonary function.

Reply 3:

We modified our text as advised to address other possible reasons for deteriorating pulmonary function. There was no clinical evidence to deteriorate pulmonary function other than PPS, because computed tomography did not show any findings of interstitial pneumonia, emphysema, pneumothorax, pleural effusion and so on.

(See Page 11, line 152-153)

Comment 4:

Your data is not significant to reach any conclusion, but you omit already published works in your discussion. It might be useful to add this in the discussion especially if postulate that mediastinal fat tissue is a sort of mediastinal midline anchor.

Reply 4:

We added the discussion the reason why mediastinal fat tissue could be anchor.

The motivation of the present study was based on our experience that two postpneumonectomy patients could not be saved. 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. Therefore, we believe that investigation for the predictive factors of the occurrence of postpneumonectomy syndrome was worth.

Mehran et al. described that risk factors for the postpneumonectomy syndrome 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.

We focused on the anatomical structures around the mediastinum, which maintain the normal position of the mediastinum after pneumonectomy. The present study concluded that the fat tissue thickness between the bilateral lungs can be a predictive factor for occurrence of postpneumonectomy syndrome before surgery. (See Page 14 line 207-217)

Comments 5:

In summary your paper needs a major rework to be a meaningful addition to the literature and therefore be suitable for publication.

Reply 5:

We modified our text as advised.

First, we added the data of respiratory function and the body weight after surgery. The two groups did not differ significantly in the changes of respiratory function and body weight.(See Table 2, Page 9 line 121-122, Page9 line 128-130, Page12 line 176-178, Page12 line 186-193) Second, we added the data of intraoperative variables, which were the operation time, the amount of blood loss and the presence of adhesion between thoracic wall and lung. The two groups did not differ significantly in them. (See Page 8 line 99, 103-104, Page 13 line 194-201) Third, we added our thoughts based on the experience we gained and our recommendations based on the data and findings. The changes of respiratory function and body weight after pneumonectomy could not be predictive factors. Thus, the diet after surgery to increase body weight might not be effect to prevent PPS. 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. (See Page14 line 207-240, Page 16 line 253-258) Forth, we discussed the risk factor of PPS and the frequency of left-sided or right-sided PPS based on the literatures. (See Page16 line 241-252)

Reviewer C

Comment 1:

Indeed, postpneumonectomy syndrome is very morbid and potential fatal long term complication of Pneumonectomy.

Although very interesting and supported by data you provided, I believe that this report fall under case report/ case series. It might benefit also from more sound review of the literature which is lacking in the current version.

Your discussion should be revised and I recommend to add your thoughts based on the experience you gained and your recommendations based on the data and findings you described.

Reply 1:

Thank you for your comments.

The sample size of the present study is small, 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 cause of postpneumonectomy syndrome have been published so far. Investigation for the predictive factors of the occurrence of postpneumonectomy syndrome is worth. (See Page17 line 259-265)

We added our thoughts based on the experience we gained and our

recommendations based on the data and findings.

According to the present study, the fat tissue in front of the mediastinum could be an anchor that can help maintain the normal position of the mediastinum after pneumonectomy. However, the thickness of the fat tissue in the anterior mediastinum did not correlated the nutritional status and constitution of patients. Moreover, the decrement of body weight after surgery also did not correlated to the occurrence of PPS. These findings suggested that the diet after surgery to increase body weight might not be effect to prevent PPS. 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. (See Page14 line 207-240, Page 16 line 253-258)

Reviewer D

Comment 1:

Interesting study but as the authors pointed out, the sample size was really small, only two patients. This should be emphasized more.

Reply 1:

Thank you for your comments.

We modified our text as advised to elucidate that the sample size of the present study is small. 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 cause of postpneumonectomy syndrome have been published so far. Investigation for the predictive factors of the occurrence of postpneumonectomy

syndrome is worth. (See Page 14 line 207-212, Page 17 line 259-265)

Comment 2:

I noticed from figure 2A and 2D that in the two cases of PPS, the carina were very close to the spine before surgery. Please measure this distance in the PPS and non-PPS patients and compare. That may be a more important predictor of PPS because in the two cases of PPS shown, the airway was severely compressed onto the spine. Maybe, the distance between the carina and spine is a predictor.

Reply 2:

We analyzed the distance between the carina and vertebra at the level of the carina, which was referred to as L_C . The value of L_C of PPS-1 and PPS-2 was 9 and 4 mm, respectively. The median value of L_C of the non-PPS patients was 9 mm. There was not significant difference. We added these data. (See Figure 1, Table 2, Page 8 line 115-116, Page 11 line 165-166, Page 21 line 324-325)

Comment 3:

Corrections need to be made in legend of Figure 2. It should be:

A-C are images of PPS-1, and D-F are images of PPS-2. A and D (not C) are the CT scan at the level of the carina before surgery. B and E (not D) 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 [not D]) showed hyperinflation of the right lung, shift of the trachea and the mediastinum.

Reply 3:

We corrected our text as advised. (See Page 21 line 327-334)

Comment 4:

In the conclusion, the following change would be more appropriate:

By contrast, in the ppo-VC ('and ppo-FEV1 of PPS' should be crossed out because this was not supported by the results), the PPS-1 case was higher and the PPS-2 (not PPS-1) case was lower than the median of nonPPS cases.

Reply 4:

We corrected our text as advised. (See Page15, line 233)

Reviewer E**Comment 1:**

1. The authors bring up an important and potentially helpful idea. It would be useful to be able to predict which patients may be at risk for post-pneumonectomy syndrome preoperatively. But this is very difficult to do with only 12 patients, and only 2 who developed the syndrome. Did the authors consider using a national administrative database in addition to their cohort? Although some variables like fat tissue diameter may not be present, it may be a more conclusive study.

Reply 1:

Thank you for your comments.

We agree that the sample size of the present study is small. 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. We did not consider using a national administrative database, but, now, we hope to collect more pneumonectomy cases with multiple institutions. (See

Comment 2:

2. How do the authors explain that the syndrome was more common in left-sided than right-sided procedures in their study? Once again, this finding may be secondary to a low number of patients.

Reply 2:

Shen et al. reported 18 postpneumonectomy syndrome patients, which developed after right pneumonectomy in 13 patients and after left pneumonectomy in 5 patients. On the other hand, Grillo et al. reported postpneumonectomy syndrome, which followed right pneumonectomy in 7 patients and left pneumonectomy in 4 patients. Mehran et al. described that most cases of postpneumonectomy syndrome 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 literature, left-sided postpneumonectomy may be not common. (See Page16 line 241-252)

Comment 3:

3. Female gender is a known risk factor, and both patients who developed the syndrome in the study were female. But some perioperative factors may also be related. In particular, women who undergo a protracted postoperative course and lose a significant amount of weight may be at higher risk. Was weight loss in the first 6 months after surgery available in their records? That would be interesting to note.

Reply 3:

We added the data about postoperative body weight data. We compared the decrement of body weight after pneumonectomy. We defined Δ BW as the decrement of body weight after pneumonectomy. The patients were weighed in the first 6 – 12 months after surgery. The Δ BW of PPS-1 and PPS-2 was 1.0 kg and -1.0 kg, respectively. Surprisingly, in PPS-2, the body weight increased after surgery. On the other hand, the median Δ BW of nonPPS was 2.2 kg (range: -1kg – 14kg). From the analysis of the loss of body weight, there was not significant difference. (See Table 2, Page 9 line 121-122, Page12 line 176-178, Page15 line 227-228)

Comment 4:

4. Were there any intraoperative variables which correlated with developing the syndrome? For example, did operations which took longer, had more blood loss, etc. lead to a higher likelihood of developing the syndrome?

Reply 4:

We added the data about postoperative intraoperative variables. We compared the operation time, the amount of blood loss and presence/absence of adhesion between the thoracic wall and the lung. The operation time was 363 minutes and 284 minutes in PPS-1 and PPS-2, respectively. The amount of blood loss of PPS-1 and PPS-2 were 2950 g and 90 g, respectively. Operation time and the amount of blood loss of PPS-1 were more than the median of non-PPS, but of PPS-2 were less than the median of non-PPS. Regarding to the adhesion, in the both of PPS-1 and PPS-2, adhesion was absence. In non-PPS, adhesion was presence in 7cases and absence in 2 cases. The two groups did not differ significantly in the operation time, the amount of blood loss and adhesion. (See Page 8 line 99, 103-104, Page 13 line 194-201)

Comment 5:

This is an interesting idea but a larger cohort is needed.

Reply 5:

The sample size of the present study is small, 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 cause of postpneumonectomy syndrome have been published so far. We hope that 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. (See Page17 line 259-265)