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Peer Review File

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Reviewer A

Dr. Yajima and colleagues submit an interesting retrospective study evaluating the risk factors for late onset pulmonary fistula after pulmonary segmentectomy. The large number of patients included in this study (N=396) and the sampling period (more than 10 years) is of special interest, although we must bear in mind that the results are very limited as come from a single institution. The work is well structured, the sections well explained and the discussion and conclusions correctly justified.

The article is understandable, with correct language and data well exposed. However, I think the number of tables and figures could be reduced. The photos included as Figure 2 do not provide useful information, likewise Table 3 and Supplemental Table 2 do not provide useful data to the reader.

It is evident that the study has some limitations, such as being retrospective, from a single center or with a single type of population. However, it is fair to say that the authors have carried out a very interesting analysis with results that can be extrapolated to clinical practice and can open the door for other groups to continue investigating. Prolonged air leak as well as onset pulmonary fistula are entities of great importance in thoracic surgery and it is vitally to improve the quality of the evidence on these pathologies, for this reason I believe that this work is of great interest and has the potential to be published.

Reply: We thank Reviewer A for the positive comment. According to your comment, we removed Figure 2, Table 3, and Supplemental Table 2.

Reviewer B

- definition of LOPF in this article is not consistent with the literature (occurring minimum 30d post-op), please clarify (range starts at 5d post-op; this is not late-onset) (only 50% of the declared LOPF patients actually meet the definition)

Reply: We thank Reviewer B for the time spent to review our manuscript. If it is BPF, as indicated, by the reviewer, the onset could be classified as early (1-7 days), intermediate (8-30 days), and late (>30 days). However, in this study, we analyzed LOPF and there is currently no clear definition in the literature regarding LOPF. For example, ‘A case of congenital cystic adenomatoid malformation with repeated pulmonary infections in adulthood and review of thirteen cases in Japan’ (The Journal of the Japanese Association for Chest Surgery; 2018 Volume 32 Issue 1 Pages 111-116) reported a LOPF within 14 days after surgery, and there have been cases reported as LOPF even at a relatively early stage. The cited reference

19 also does not give a clear definition of the onset of LOPF. We believe that there is no strict definition of LOPF, since the time of onset is not clear in each article. In the present study, we defined the onset time as the number of days after drain removal, rather than postoperative period.

- unclear inclusion: 'ALMOST all analyses were limited to segmentectomy'

Reply 2: According to your comment, we changed the phrase from 'ALMOST all analyses were limited to segmentectomy' to 'All analyses were limited to segmentectomy' (see page 4, line 96-97).

- why did the authors choose to exclude multiple segmentectomy, but include segmentectomy with subsegmentectomy? was this actually the case, as subsequently they declare 'single or multiple segments were classified according to the number of resected segments'

Reply 3: Segmentectomy involving multiple segments are included in this study (i.e. S⁸⁺⁹). The 'multiple segmentectomies' excluded in this study represent cases in which two separate segmentectomy were performed in a single operation (i.e., lingulectomy + S⁶ segmentectomy), and not the resection of several adjacent segments. In such cases, we excluded them from the same cohort because of the inability to identify which was the cause of the delayed pulmonary fistula and the longer operative time. According to your comment, we added the sentence (i.e., lingulectomy + S⁶ segmentectomy) .

- the grouping of intersegmental plane division is inconsistent, and raises doubts as to the validity of this work

Reply 4: The grouping of intersegmental plane division was classified according to the localization of the residual space and the orientation of the intersegmental plane.

The areas prone to leakage were analyzed in terms of CSFS and VSFS, since the residual space is located on the cranial side when standing or sitting, and on the ventral side when lying down.

Reviewer C

Kawatani and colleagues explored the risk factors for late onset pleural fistula by looking at their single-center cohort. This complication should be avoided with surgical countermeasures, thus the theme could interest thoracic surgeon. The authors focused on the procedure for lung division and the position of the residual space, which was a unique attempt. I have some comments.

1. I suppose whether some pleural reinforcement procedures (using fibrin glue, PGA sheet or self-tissue) were added or not during surgery can affect the outcome. The authors should address and discuss this issue.

Reply: We thank Reviewer C for the time spent to review our manuscript.

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‘Covering’ shown in Table 3 indicates the use of pleural augmentation. This factor was not significant.

2. In addition, presence or absence of broad pleural adhesion or past history of thoracic surgery should be also discussed as a potential risk factor for remaining pleural dead space and late pleural fistula.

Reply 2: We consider that the history of lung resection in Table 3 is similar to the discussion of the past history of thoracic surgery, and this factor was also not significant.

With regard to adhesions, we reviewed cases of late-onset pulmonary fistula and there were no adhesions in most cases; only few patients had acute prolonged pulmonary leakage and the lungs themselves were in relatively good condition.

3. Fissureless anatomy can be another risk factor which was not examined. This should be commented.

Reply 3: Similar to adhesions, there were no cases of severe incomplete lobulation in the LOPF group.

4. There is a substantially wide range in the length of the days between drain removal and LOPF development (5-190 days). I am interesting in the causes of early-onset and later-onset LOPF, which might be different. Could you comment that?

Reply 4: Since other reviewers pointed out the large range in the number of days to LOPF onset, we compared the two groups of early-onset and later-onset LOPF. First, we compared the BPF-oriented 30-day postoperative onset, and the only significant difference we found was in operative time (> 30-day group: 185.8 min vs. < 30-day group: 226.1 min, p=0.040). A comparison was also made at POD 14, but no significant difference was found between the two groups.

However, we cannot say that early onset after drain removal does not indicate acute pulmonary fistula, so we have added this as an additional limitation(see page 12, line 296-297).

5. Regarding the analyses in Table4, pulmonary function should be examined with % predicted value rather than actually measured volume.

Reply 5: We think preoperative lung status is more relevant for PAL and late-onset pulmonary fistula. and we think that actual measurement values are better for evaluation of pulmonary function.

Reviewer D

This manuscript is a very interesting research regarding risk factors for late-onset pulmonary fistula after pulmonary segmentectomy. Although it is a retrospective study at a single institution, the authors had considered this topic in detail. Segmentectomy has become very popular in recent years, and this paper would include useful

information for readers. However, there are several crucial issues in this manuscript, and the authors should resolve them to be accepted for JTD.

1. One of the largest issues in this paper is that most readers cannot understand how the surgeons selected the method for dividing the intersegmental plane. Although electrocautery dissection was established as an independent risk factor for LOPF as a result of multivariate analysis, the authors did not conclude that stapler dissection is recommended.

Reply: We deeply thank Reviewer D for the thorough review of our manuscript and the constructive comments regarding surgical data. We hope that the answer to the comments have reinforced the value of our manuscript. We assessed the pathogenesis of LOPF and classified them according to the localization of the residual lumen and the orientation of the intersegmental plane, as shown in Supplemental Table 1. The method for dividing the intersegmental plane vary considerably, even in the case of electrocautery, it depends on whether the electrocautery is used alone or in combination. (see page 11, lines 250-254). Staplers alone also do not completely prevent the creation of LOPF (see page 12, lines 279-288). The method for dividing the intersegmental plane was analyzed in various ways because it is complex and cannot be clearly categorized. As a result, the method for dividing the intersegmental plane was classified as shown here. This method has been selected according to the lung condition.

In addition, it was stated that the intersegmental plane was divided mainly by electrocautery, but the most frequent method for dividing the intersegmental plane was described as surgical stapler alone (45.7%), followed by electrocautery alone (19.4%). An explanation should be needed for this discrepancy.

Reply: We deleted ‘the intersegmental plane was divided mainly by electrocautery’. In addition, the percentages have been removed from Supplemental Table 2 because they are misleading.

2. The definition of segmentectomy grouping in Supplemental Table 1 could not be understand. For example, I don't understand why S1+3 resection was classified in the VSFS group. What was the definition of the “Other” group? I recommend to divide all cases into two groups, the CSFS or Other group.

Reply 2: The grouping of intersegmental plane division was classified according to the localization of the residual space and the orientation of the intersegmental plane.

The areas prone to leakage were analyzed in terms of CSFS and VSFS, since the residual space is located on the cranial side when standing or sitting, and on the ventral side when lying down.

For the S¹+S³ resection, both cranial and ventral side are created. For this analysis, we checked the actual images of lung after S1+S3 resection and found that they were rotated to the anterior side, so we categorized them in the VSFS group.

3. Another problem is that cases in which air leakage develops within 14 days after surgery were defined as late-onset pulmonary fistula cases. It is possible that the cause of air leakage occurred in the earlier period differs from that in the true late period. What were the postoperative drainage management method and criteria for drain removal? I recommend to perform additional analysis between the earlier and late-onset cases or to reconsider the targeted cases.

Reply 3: Postoperative drainage management is done by removing the chest tube on POD 2, after confirming that there is no leakage. Since there is currently no clear definition of LOPF in the literature, this review was conducted in patients readmitted to the hospital after discharge. Since other reviewers pointed out the large range in the number of days to LOPF onset, we compared the two groups of early-onset and later-onset LOPF. First, we compared the BPF-oriented 30-day postoperative onset, and the only significant difference we found was in operative time (> 30-day group: 185.8 min vs. < 30-day group: 226.1 min, p=0.040). A comparison was also made at 14 days, but no significant difference was found between the two groups.

However, we cannot say that early onset after drain removal does not indicate acute pulmonary fistula, so we have added this as an additional limitation. (see page 12, line 296-297)

4. In the Methods section, the authors said that factors shown to be significant using a univariate analysis with a p value of <0.1 were included in the multivariate analysis. However, in Table 4, FEV1 (p = 0.097) and Segmentectomy type (p = 0.050) with a p value of <0.1 were not included in the multivariate analysis (Table 5). I recommend to consult a statistician.

Reply 4: According to reviewer's comment, we changed the p-value from <0.1 to <0.05.

5. There were too many tables in the text. Supplemental Table 4 and 5 were far from the main topic, and I think that they are unnecessary together with Figure 2. In addition, please integrate Sup 1 and Sup 2.

Reply 5: According to the reviewer and other reviewers' comments, Figure 2, Table 3, and Supplemental Table 2 were removed. PAL is one of the most common early-phase complications after pulmonary segmentectomy. Supplemental Table 4 and 5 are considered necessary to clarify the differences between PAL risk factors. Supplemental Table 1 is important for the grouping of intersegmental plane division.

6. Please use the same text font consistently.

Reply 6: We apologize that text fonts were not standardized.

Reviewer E

-It is an article with the accumulation of the segmentectomy case of enough numbers,

but there must be considerably the progress of devices for 11 years. Does the frequency of the cutting method of the intersegmental plane to choose at the position of the segment to remove surgically not have the deflection? Is the effort of some kind of improvement not accomplished for 11 years? Some questions remain whether these statistics processing is appropriate.

Reply: We thank Reviewer E for the time spent to review our manuscript. The primary reason for the 11-year period was the frequency of late-onset pulmonary fistulas. We chose a longer period of 11-years because the number of incident was low. The same analysis was done for cases performed after 2015, but at that time the significant difference in intersegmental plane dissection by electrocautery was no longer seen. The reasons for this may be that energy devices are no longer used for intersegmental plane dissection, including ‘stapler in combination with electrocautery’, due to the experience of increased pulmonary fistula caused by the use of energy devices alone. Another reason may be the advancement and ingenuity of electrocautery techniques. However, CSFS remained a significant risk factor throughout the entire period of the study, both from 2010 and when limited to cases performed after 2015.

As the reviewer pointed out, there have been advances over the past 11 years (i.e., the ICG method of identification). Such technological changes have been added to the limitation.

-I think that Brinkmann Index is the index that is not so common in the world. You should switch to Pack-Year.

Reply 2: According to the reviewer’s comments, we converted the Brinkmann Index to Pack-Year.