

Peer Review File

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Reviewer A

The authors investigated the risk factors of prolonged air leak in the patients who underwent pulmonary segmentectomy. The result showed that the occurrence of PAL was associated with low preoperative carbon monoxide lung diffusion capacity (DLCO) ($p=0.003$) and the performance of complex segmentectomies as opposed to simple ones ($p=0.073$).

I believe that there are several essential issues to consider for publication.

Comment 1: What was new information in this study? Many previous reports have shown that low pulmonary function, such as DLCO, was a risk factor for PAL.

Reply 1: we think that exploring factors associated with PAL in the context of segmentectomies is still poorly analysed. In addition we found that complex segmentectomies are associated with increased rate of PAL which is a useful information especially for patient counselling.

Comment 2: How did the surgeons resect the intersegmental plane? Did they use only staplers or electrocautery for resection of each intersegmental plane? Also, the authors should clarify how the surgeons manage alveolar-pleural fistulas during surgery. For example, did they use fibrin glue or PGA sheets, or did they suture alveolar-pleural fistulas? Did the surgeons do pleurodesis therapy or not? Those factors affect the frequency of PAL.

Reply 2: We added the details on the segmental procedure and of the use of preventative measures in the Methods section as requested.

Reviewer B:

This is a retrospective observational study in a institute to address the risk factors of postoperative prolonged air leak following pulmonary segmentectomy. Authors identify low DLco and complex segmentectomy as significant predictors. Several issue should be added for further review.

Comment 1: The procedure of segmentectomy should be described in more detail. Is basal segmentectomy (S7-10) included in the present study? How did surgeons dissect inter-segmental plane? Using auto-stapler or combined use of stapler and cautery? Is fibrin glue or PGA sheet applied before chest closure?

Reply: We added details about the type of segmentectomies in a table. In addition, we added details on the segmental procedure and use of preventative measures in The Methods section as requested.

DLco could be influenced by the anemia or cardiac function. Hb or Ht and BNP could be included in patients' characteristics.

Reply 1: we thank the reviewer for this interesting comment. Unfortunately we do not have this information available in our dataset

Comment 2: Author should discuss more regarding the reason why DLCO rather than FEV1% is identified as a significant predictor for PAL.

Reply 3: we agree with this comments. This has been elaborated in the Discussion

Reviewer C:

The authors examined the risk of developing PAL after segmentectomy in a single institution. The risk extracted was DLCO, which is consistent with previous reports examining PAL in lobectomy or segmentectomy. It is unclear whether the complex segmentectomies are a statistically significant risk, since details of the multivariate analysis were not provided.

Major Comments

Comment 1: Are there any confounding factors in the factors included in the multivariate analysis behind the identification of complex segmentectomies as the second risk in the multivariate analysis?

Reply 1: we thank the reviewer for noting this missing information. We added all the variables which were tested for possible association with PAL in the Statistical paragraph. Those with a $p < 0.2$ at univariable analysis were included in a logistic regression analysis

Comment 2: Factors that may be involved in PAL include steroid use, smoking status, operation time, amount of blood loss, and presence of intrapleural adhesions, and it would be recommended to add these to the list of factors considered.

Reply 2: We have information about smoking status and pleural adhesions. We included this information in the analysis. Unfortunately, we do not have complete information about operation time and steroid use which prevented their use in the analysis.

Minor Comments

Comment 1. Please present information on which lobe the tumor was present in.

Reply 1: A table was added with the types of segmentectomies performed

Comment 2: How did you identify and divide the intersegmental planes?

Reply 2: This information was added in the Methods

Comment 3: Did you use any surgical sealants?

Reply 3: This information was added in the methods

Comment 4: Regarding the 4 deaths within 30 days, what was their cause of death?

Reply 4: the causes of death were added in the Results section

Comment 5: In the discussion, I think it would be better to focus on PAL rather than the overview of segmentectomy.

Reply 5: We have totally rewritten the discussion by focusing on the PAL in the context of segmentectomy

Reviewer D:

I would like to congratulate you on the nicely written observational study on air leaks after segmentectomies.

However, I need a few more clarifications, both for the future readers and myself

Comment 1: In line 152 you mentioned, "after adjusting for confounders." - what would those confounders be? Could you please name them?

Reply 1: We thank the reviewer for this comment. We added the details of all the variables tested for an association with PAL in the Statistical paragraph. In addition all variables are listed in table 2. Those resulting with a $p < 0.2$ at univariable analysis were used as factors in the logistic regression analysis

Comment 2: Nevertheless, "non-complex" segmentectomies failed to reach "the significance" of 0,05, both at simple inferential statistic tool (assumed MW Test) as well at LR, yet assumed to be a significant factor associated with PAL along with DLCO more than other factors. So it would be nice to see the other numbers, in a separate LR table. It would also be very good to see your comment on that in the discussion part, as that is what the discussion part is for (rather than lamenting the paper's significance or its aims, which have already partially been emphasized in the introduction part)

Reply 2: WE agree with this comment. The analysis was reperformed with adjustment for clustering within surgeons and complex segmentectomies resulted highly significant at multivariable regression. We added a new table (table 3) reporting the results of the logistic regression for clarity. The discussion was refocused to the main theme of the study. In addition we have totally rewritten the discussion by focusing on the PAL in the context of segmentectomy

Comment 3: What kind of segmentectomies have been performed? Were they be worthy of another table? How many of them were basal segmentectomies?

Reply 3: We added a table with the types of segmentectomies performed

Comment 4: Is there any difference between VATS and TT cohorts regarding PAL? What about VATS vs. TT plus conversions (despite the intention to treat - one could potentially argue for both variants)

Reply 4: this variable was tested for possible association with PAL and we did not find any statistical difference between MIS and open surgery. In addition we added

the results of the comparison between converted patients and those who were not converted in the Results section.

Comment 5: Lines 235 and 236 "The incidence of PAL was higher in AB cases than 25% vs. 10% with $p=0.005$ " is not that understandable. Could you please make it so

Reply 5: we thank the reviewer for spotting this confusing paragraph. We amended it to make it more clear and moved it to the results section.

Reviewer E:

The authors reported the incidence and risk factors of PAL.

As a result, low DLCO and complex segmentectomy was associated with an occurrence of PAL. The reviewer believe that the occurrence of PAL depends on the procedure for dissecting intersegmental plane and the procedure for intraoperative sealing of air leak. Unfortunately, the authors did not explain regarding how to dissect intersegmental plane and how to stop air leak intraoperatively. In their series, 19% of patients undergoing segmentectomy were complicated by PAL. In addition, 2.1% of patients undergoing segmentectomy died during hospitalization. Seven patients in 36 patients with PAL needed readmission to treat further complications. These results may be apparently worse than those resulted after lobectomy. The reviewer believe that some technical revision may be needed before evaluating real risk of PAL after segmentectomy.

Major comments

Comment 1: Please describe technical details for segmentectomy and stopping intraoperative air leak.

Reply 1: We added details about the type of segmentectomies in a table. In addition, we added details on the segmental procedure and use of preventative measures as requested.

Comment 2: Show us the tumor location or site of segmentectomy in overall patients.

Reply 2: We added a table with all types of segmentectomies

Comment 3: How to determine the intersegmental plane?

Reply 3: We added this detail in the Methods section

Reviewer F:

The authors have conducted a retrospective review of 191 segmentectomies performed in a single unit and analyzed PAL.

Overall the paper is well written and the topic is of great interest.

However there are some shortcomings to address:

Comment 1: On page 5 the 4 indications for segmentectomy is described. Please add a percentage for every indication. Only intentional is mentioned.

Reply 1: We added the number and percentage of each indication for segmentectomy

Comment 2: The suction was set for -8 cm H₂O. In relation to PAL it could be interesting with a discussion of influence of suction level.

Reply 2: this has been discussed in the Limitation

Comment 3: A maximal fluid threshold of 300-400 ml/d is conservative and not consistent with the ERAS guidelines. Please comment.

Reply 3: This is the current institutional protocol used by all consultants in the unit. The threshold of 400 ml/day is quite relaxed in our opinion compared to traditional cut offs of 150-200 ml/day. We do not think this is not consistent with our ERAS protocol

Comment 4: Page 6, line 123-26. Please explain why a basilar segmentectomy was not included in the simple segmentectomy group.

Reply 4: We thank the reviewer for spotting this oversight. The basilar segmentectomies were not listed in the definition of simple segmentectomies (Methods) but taken into account in the analysis. We now amended it in the text by including them in the definition of simple segmentectomies.

Comment 5: In the conclusion and throughout the text complex segmentectomies are attributed more PAL, however the P-values are >0.05. Please explain and correct in the relevant sections.

Reply 5: the analysis was performed again with adjustment for clustering within surgeons as suggested by another reviewer. After this adjustment, complex segmentectomies became a very significant risk factor for PAL ($p < 0.0001$). We added a table (table 3) reporting the results of the multivariable logistic regression as suggested.

Comment 6: Page 7 line 157-158. Difficult to understand this sentence and the P value is similar to line 151 $p = 0.13$. Please explain and correct.

Reply 6: we agree that p value is above 0.05, however it is below $p < 0.2$ which is the threshold we selected to include variables as independent factors in the regression analysis. Although there is no formal statistical significance there is a signal as the incidence of PAL is 8% higher after complex segmentectomies compared to simple. We detected a mistake in the percentages of air leak which was now corrected. This was then confirmed by the logistic regression showing a strong significance of this factor. This is now reported in the new table 3.

Comment 7: In the discussion section, I miss a discussion on the options to prevent and treat airleak, such as sealants, redo, blood pleurodesis ect.

Reply 7: This has now been added in the Limitation section

I enjoyed reviewing the paper and look forward to seeing the revision.

Reviewer G:

Gooseman et al, in their manuscript, “Prolonged air leak after segmentectomy: incidence and risk factors,” review their experience over 191 patients undergoing segmentectomy over a roughly 4 year period of time.

Comment 1: Results are noted in the Methods section of both the abstract and the text. This needs to be corrected. No results (number of patients, for instance), should be mentioned in the methods section.

Reply 1: we agree with this comment and moved the results listed in the Methods to the results section of both abstract and manuscript.

Comment 2: The listing of indications for segmentectomy (Lines 93-106) is unnecessary, unless this is to be examined as a variable of interest.

Reply 2: we respect the opinion of the reviewer but we think the indication for segmentectomy is a useful information for reader as it provides a snapshot of the type of population included in the study. We included this variable in the comparative analysis

Comment 3: The percentages cited in lines 149-151 are confusing. This makes it sound like 61% of patients in the complex segmentectomy group experienced PAL. Please reword.

Reply 3: we apologize for this confusing paragraph We have now corrected with the proper percentages (23% vs 15%)

Comment 4: Findings that are not statically significant (lines 150-151, line 154) should not be stated in a way that implies that they are.

Reply 4: we agree that p value is above 0.05, however it is below $p < 0.2$ which is the threshold we selected to include variables as independent factors in the regression analysis. Although there is no formal statistical significance there is a signal as the incidence of PAL is 8% higher after complex segmentectomies compared to simple. We detected a mistake in the percentages of air leak which was now corrected. This was then confirmed by the logistic regression showing a strong significance of this factor. This is now reported in the new table 3.

Comment 5: A very high number of patients were readmitted among patients who were discharged with a chest drain. This should be noted and discussed. Were patients sent home with a drain placed on antibiotics? The rate of empyema among these patients seemed high as well.

Reply 5: We have noted and discussed this finding in the Discussion

Comment 6: There are many word choice, phrasing, and syntax issues in the discussion section. This needs to read and edited. For instance, the use of “big” as an adjective (lines 178, 194). I will not cite all the problems here, but suffice it to say that the manuscript needs to be read and edited for clarity

Reply 6: the Discussion has been totally rewritten and focused on the PAL in the context of segmentectomy

Comment 7: Discussion of overall outcomes of segmentectomy (lines 219-226) is not very helpful. This is a study on prolonged postoperative air leak. On the flip side, there is very little discussion of the existing data on prolonged PAL. I would suggest you perform a more extensive review of the literature in your discussion, and place your findings in the context of this knowledge.

Reply 7: Discussion has been totally rewritten and re-focused as suggested

Comment 8: Can surgeon be analyzed a variable? There is a perfunctory analysis in the discussion section (lines 235-237). However (presumably) this is not entered in the logistic regression. This analysis should be formally performed, and documented in the Results section. The discussion section should be reserved for commentary on the findings of the study.

Reply 8: we agree with this comment. The surgeon element was taken into account in the analysis by adjusting the logistic regression for possible clustering within surgeons.

In addition any reference to this analysis in the discussion was moved to the Results section

Comment 9: COPD/smoking status and tumor staging should be included in Table 1. The technique (VATS, robotic, open) should be included in Tables 1 and 2. The location of the tumor would be useful to have as a variable as well (by lobe or even by upper/lower). The inclusion of CVD but not other comorbidities is puzzling – what is the justification for this?

Reply 9: we agree with this comment. We have now included smoking status, surgical access and site of resection as co-variables to test their association with PAL. These variables are reported in table 1. Table 1 and 2 have been merged now in a new table 2 and expanded with more variables. In addition, the types of segmentectomies and their site have been listed in table 1.

Comment 10: I am not sure that Table 3 or 4 are necessary. The differences between patients receiving complex vs simple segmentectomy is not relevant to the goals of the manuscript. Table 4 can likely be removed and the findings stated in the text of the results section.

Reply 10: we agree with this comment and removed table 4. Results have been reported as text in the Results section. However, considering the findings of the analysis we still think that knowing the baseline characteristics of patients receiving complex vs simple segmentectomies helps in the interpretation of the main findings. For this reason, we left table 3 as it is.

Comment 11: In fact, Table 1 and 2 should likely be combined: use three columns, first is all patients, 2nd is patients without PAL, 3rd is patients with PAL.

Reply 11: we agree with this suggestion and merged table 1 and 2 into a single table (now renamed table 2)

Reviewer H:

The authors investigated the rate of prolonged air leak in patients undergoing pulmonary segmentectomy. And they concluded that segmentectomy may be associated with a not negligible risk of prolonged air leak (PAL), especially in patients with compromised pulmonary function and after complex segmentectomies. I agree with their conclusion, however, the authors need some revisions before acceptance.

Comment 1: I consider the onset of PAL to be mainly a consequence of the technical aspects of segmentectomy. How did the authors dissect between segmental planes? Stapler or electrocautery? I believe that hilar node dissection also affects the occurrence of PAL. The authors should add the information about LN dissection in this cohort in the methods.

Reply 1: We added details about the type of segmentectomies in a table. In addition, we added details on the segmental procedure and use of preventative measures as requested.

Comment 2: The number of intentional and compromised indications in this cohort should be listed in Table1.

Reply 2: We added this information in table 2 (previous table 1)

Comment 3: After all, how long is the duration of drainage in the PAL and non-PAL groups?

Reply 3: this was added in the Results section

Comment 4: In this study, four patients died within 30 days of operation or while in hospital. What was the cause of death of these patients?

Reply 4: The main cause of death was respiratory failure and we added this detail in the Results section

Comment 5: In the results, complex segmentectomy was not significantly different in univariate analysis without the PAL group and with the PAL group. The multivariate analysis results also showed that complex segmentectomy was not a significant factor, but the authors also emphasized in the conclusion that complex segmentectomy was a factor affecting PAL, is that statement correct? In addition, the results of the multivariate analysis should be stated in another Table.

Reply 5: The analysis was performed again with adjustment for clustering within surgeons as suggested by another reviewer. After this adjustment, complex segmentectomies became a very significant risk factor for PAL ($p < 0.0001$). We added

a table (table 3) reporting the results of the multivariable logistic regression as suggested.