Peer Review File
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Reviewer A

Thank you for good work about comparing covering and pleurectomy. This article is good, but it would be better with some revisions.

Comment 1: *Prospective study design was applied, but the process of allocation or blindness were not stated fully. Please add on such information.*

Reply: Thank you for the suggestion. We have modified and added following text based on the Reviewer's comment.

Additional surgical procedures for bullectomy were not randomized and were determined according to the surgeon's preference for each case. In addition, patients, surgeons, and the study administrator were not blinded." (page 6, lines 96–98)

Comment 2: *The number of patients were limited, so to overcome the limits, you could compare the total cost of two groups including those of staplers or coverings, pain medications used during hospitalization. And with the same reasons, you could gather more QOL questionnaire till Dec. 2022*

Reply: We thank the reviewers for evaluating our manuscript and agree with your concern regarding the limited number of participating patients. Regarding the total cost of each procedure, the two groups were basically the same up to the bullectomy suggesting that the number of staplers might be comparable, although the number of staplers was not investigated in this study unfortunately. The use of pain medications was also identical because we used the same clinical pathway for pneumothorax surgery. The PGA sheets used in the covering group cost 16,700 yen each and is considered a cost advantage in the pleurectomy group. In terms of the number of patients recruited in this study, we had already terminated recruiting for this survey by the end of April 2018. However, we consider estimating a more appropriate sample size for the next study based on the data obtained, such as the mean values and standard deviations of the EQ5D VAS.

Comment 3: Some questions about surgery. Pleura abrasion would show similar outcomes with pleurectomy. Why did you use pleurectomy only? Why did you use 3 ports, not two or single? Did you use no adhesive for coverings? Your method could fix coverings tightly but for only small lesions. However, coverings with adhesive materials could apply on more wide lesions. You could refer the article. [1]

Reply: We thank you for your insightful comments. Among several options for surgery of pneumothorax, the surgical procedure has been mainly determined by the chief surgeon at the time in our institution, although we

agree that pleural abrasion is also effective. Similarly, only a three-port VATS has been performed in our institution. As you indicated, reducing the number of ports may contribute to an improvement in patient-reported outcomes/QOL. Regarding the adhesive materials, we used fibrin glue with covering only in patients with secondary pneumothorax, but not in patients with primary spontaneous pneumothorax. We added new text regarding pleural abrasion and adhesive materials as follows:
"We neither performed parietal pleural abrasion nor used fibrin glue." (Page 8, lines 142–143)

Comment 4: *As you know, age could influence the patients' QOL. Could consider the age during the QOL analysis? You could refer this. [2, 3]*

Reply: Thank you for the important comment and interesting references. We recognized the study of Kim D et al. assessing psychological distress as a study of patient-reported outcomes in patients with pneumothorax. They evaluated psychological distress in patients with pneumothorax at different age groups at the time of discharge and reported that older adult patients experienced more psychological distress compared with younger patients. According to their findings, we performed the analysis to evaluate an influence of age on anxiety/depression. No significant difference was noted in the proportion of respondents who reported slight or more anxiety/depression between two age groups (40< and ≥40 years). We have modified the text in the Introduction section and added new text in the Result and Discussion sections as follows:
"In addition, a study investigated whether psychological distress in patients with spontaneous pneumothorax differed by age group, which could be generally considered an observational study of PROs (6)." (Page 5, lines 71–73)
"%). Additionally, in terms of relationship between psychological distress and age, we analyzed a proportion of respondents who reported slight or more anxiety/depression and two age groups (40< and ≥40 years). The proportion of anxiety/depression at each time point were as follows: 40<:≥40 (%) Pre; 37.5:50.0, POD1; 58.3:71.4, POD3; 27.5:42.9, POD5; 20.5:14.3, POM1; 14.6:25.0. No significant difference was noted at each time point (p-value: Pre: POD1: POD3: POD5: POM1=0.390: 0.419: 0.342: 0.583: 0.389, respectively)." (Page 10, lines 216–222)
"No significant difference in proportion of respondents who reported slight or more anxiety/depression between two age groups (40< and ≥40 years) in terms of psychological distress, although a study reported that older adult patients with pneumothorax are associated with higher psychological distress (6)." (Page 13, lines 286–291)

Comment 5: *Smoking could have a robust effect on the recurrences. So, you should consider it to analyze the recurrence rate. You could refer this. [4]*

Reply: We thank the reviewer for the important comment. We analyzed the relationship between postoperative recurrence and smoking. Preoperative smoking history was not a significant factor in our cohort (recurrence rate: never smoker 9.0%, former or current smoker 5.6%, p=0.570). However, assessing the risk factor of postoperative recurrence would be out of the scope of this study. We prefer not to add new text

regarding this issue.

Comment 6: *At last, you could change the conclusions. Covering process showed similar outcomes with less operative time, So, authors could recommend covering, not a pleurectomy.*

Reply: We appreciate your suggestions. We have added new text regarding our preferred procedure based on our result in the Discussion section as follows:
“Our own preferred technique is the covering method based on the results of this study. The main reason is an ease of adaptation to the technique even for a younger trainee. However, we consider the use of artificial material and cost of the materials are still an issue.” (Page 13, lines 291–294)

1. Kim, S. W., and D. Kim. "Management of Long-Term Persistent Air Leakage Developed after Bullectomy for Giant Bullous Lung Disease Associated with Neurofibromatosis Type 1." J Thorac Dis 8, no. 1 (2016): E140-3.

2. Kim, D., H. J. Shin, S. W. Kim, J. M. Hong, K. S. Lee, and S. H. Lee. "Psychological Problems of Pneumothorax According to Resilience, Stress, and Post-Traumatic Stress." Psychiatry Investig 14, no. 6 (2017): 795-800.

3. Nam, S. H., K. W. Kim, S. W. Kim, S. W. Kim, J. M. Hong, and D. Kim. "Fate of Spontaneous Pneumothorax from Middle to Old Age: How to Overcome an Irritating Recurrence?" J Thorac Dis 11, no. 11 (2019): 4782-89.

4. Kim, D., J. H. Lee, S. W. Kim, J. M. Hong, S. J. Kim, M. Song, J. M. Choi, S. Y. Lee, H. Yoon, and J. Y. Yoo. "Quantitative Measurement of Pneumothorax Using Artificial Intelligence Management Model and Clinical Application." Diagnostics (Basel) 12, no. 8 (2022).

Reviewer B

Comment: *This is a well-written and well-conducted study that compared a parietal pleurectomy and a visceral pleural covering as an additional method during VATS bullectomy to reduce the recurrence of pneumothorax. It seems to be difficult to choose one between the two aforementioned treatments because the number of enrolled patients was somewhat small. Nonetheless, it would be acceptable even if the authors suggested subjective opinions sufficiently.*

Reply: We are sincerely grateful to you for your time and effort in reviewing our manuscript and providing these valuable comments. We completely agree with the Reviewer’s concern regarding the small number of

enrolled patients. Although we believe that further studies would be required to determine the optimal additional procedure, we have added new text regarding our preferred procedure based on our result in Discussion section as follows:
“Our own preferred technique is the covering method based on the results of this study. The main reason is an ease of adaptation to the technique even for a younger trainee. However, we consider the use of artificial material and cost of the materials are still an issue.” (Page 13, lines 291–294)

Reviewer C

1. Abstract:
Comment 1: *‘Distant period’ as the time for telephone or mail survey is vague. Will you switch to the specific time period for these surveys?*

Reply: Thank you for this comment. We have added the following text based on the Reviewer’s comment”
“Recurrences and postoperative symptoms in the distant period were investigated cross-sectionally by telephone and mail surveys in February 2020.” (Page 3, line 34–35)
In addition, we have added a new text in the Methods section as follows:
“We performed a long-term postoperative survey in February 2020 on persisting symptoms associated with surgery, smoking habits, and recurrence via telephone and mail.” (page 8, line 168)
“Postoperative median follow-up time was 38 months for all cases, 35 months in the covering group, and 42 months in the pleurectomy group.” (Page 11, lines 227–229)

Comment 2: *Please clarify why reporting visual analog scale score then stating no significant difference in PROs in the next sentence.*

Reply: We thank the reviewer for evaluating our manuscript and apologize for the confusing text. The visual analog scale score (Figure 2) indicates the best imaginable health status for the patient, and we found a difference between the two groups on only POD1. In contrast, the frequency of PROs shown in the next paragraph refers to a descriptive system with five dimensions–five levels including pain and other dimensions (Figure 3), and no significant difference between the two groups was found.

Comment 3: *Please report long term outcome in abstract.*

Reply: Thank you for this valuable comment. The recurrence rate and presence of residual symptoms, shown in the last sentence of the Results section, are the long-term outcome results. To improve clarity, we have added the following text:
“There was no significant difference in the recurrence rate and frequency of residual symptoms, e.g., chest discomfort in the long-term outcomes.” (Page 3, lines 40–42)

2. Introduction:

Comment 4: *The first sentences states bullectomy is the critical component, but many patients do not have an identifiable hole and most require pleurodesis. Stating pleurodesis is the critical component is just as accurate.*

Reply: We thank the reviewer for the insightful comments. We agree with the Reviewer's comment that additional treatment is also important. Based on the Reviewer's comment, we have modified and added following text:

"Although the main component of surgery for primary spontaneous pneumothorax (PSP) is regarded as resection of the bulla/bleb (bullectomy), which causes air leakage resulting from its rupture, an additional procedure inducing pleural adhesion has an important role in reducing postoperative recurrence, and various methods have been attempted." (Page 4, lines 51–54)

3. Hypothesis:

Comment 5: *While PROs in the short term are important, the goal of pleurodesis is prevention of recurrence. I would recommend adding long term outcomes to the primary endpoint of this study.*

Reply: We would like to thank the reviewer for evaluating our manuscript and for their important comments. We agree with the Reviewer's comment that long-term postoperative outcomes, including recurrence rates, are also important endpoints. We have modified and added the following text:

"Based on our clinical experience, we hypothesized that PRO, including postoperative pain, and surgical outcomes, including recurrence rates, would be comparable between the two procedures." (Page 5, lines 79–81)

4. Results:

Comment 6: *The statistical significance of CRP on POD4 between covering and pleurectomy is likely not clinically meaningful especially since no difference is noted on POD2 or after discharge. I would recommend deemphasizing this finding in the manuscript.*

Reply: Thank you for this valuable comments. We agree with the Reviewer's concern that the difference in CRP would be a clinically meaningless difference. We will revise the text to de-emphasize the differences in CRP as follows:

The trajectory of perioperative CRP levels is shown in Figure 1. Although the pleurectomy group had a significantly lower CRP level at POD4 than the covering group (3.2 vs. 5.5 mg/dL, $p = 0.003$), those at other time points were comparable. (Page 10, lines 201–203)

Comment 7: *The better score for pleurectomy on POD1 may reflect multiple, statistical comparisons rather than a true finding. Did you correct for multiple comparisons? Similar to above, this finding is likely not clinically meaningful since no differences were noted on POD3, 5, or POM1.*

Reply: We thank the reviewer for evaluating our manuscript and for the insightful comments. We did not use the mixed effects model for repeated measures including the time variable as a factor with the unstructured covariance matrix. However, we further performed a multiple regression analysis on VAS at POD1 with clinical factors. The pleurectomy was identified as a significant factor predicting better VAS value at POD1 (data not shown). Regardless of our additional analysis, interpreting our data definitively without the minimum important difference (MID) of EQ5D VAS in patients with pneumothorax and further investigation are required on this matter. As we consider that we have already been sufficiently modest in the interpretation of our results, we prefer not to add new text regarding this issue.

Comment 8: *Other than one patient, were long term chest radiographs evaluated to determine recurrence? Surveys were answered in 11 and 13 patients, but how many patients did the surgeons reach by phone?*

Reply: We appreciate your questions and important comments. We noticed that the number of patients with long-term survey in the manuscript was incorrect. The number of patients in Table 3 is correct. Twenty-five patients in the covering group and 27 patients in the pleurectomy group responded to the long-term postoperative survey. Regarding how we determined the recurrence, only one patient who came to the hospital with symptoms was X-rayed for evaluation of recurrence, and evaluation of recurrence for the others was done by telephone or by mail. Only one patient in the covering group responded through mail, and all others were confirmed via telephone by the surgeon. We have corrected the number of patients and modified and added a new text as follows:
"The numbers of patients who answered the survey were 25 and 27 in the covering and pleurectomy groups, respectively. Only one patient in the covering group responded through mail; all others were confirmed via telephone by the surgeon." (page 10, lines 225–227)

Comment 9: *Did the surgeons query whether the patients presented with recurrent symptoms to any medical facility? The recurrences are reported in the last paragraph of the results, but the methods of detection and the management are not reported. This outcome may be the most important of this paper. Will you describe in detail these findings?*

Reply: Thank you for this valuable comment. We agree with you regarding the detection of recurrence. Yes, we asked the patients whether they had a medical visit for chest discomfort or pain or dyspnea and whether they had been diagnosed with pneumothorax postoperatively. Moreover, we instructed the patients postoperatively to visit the medical facilities when they have any chest symptoms. We have added new text regarding the survey as follows:
"For detection of recurrence, we asked the patients whether they had a medical visit for chest discomfort or pain or dyspnea and whether they had been diagnosed with pneumothorax postoperatively." (Page 9, lines 170–172)

Comment 10: *Similarly, the recurrences are all within the post-op period. Were any long term recurrences*

noted? Also, were the chest tubes removed too soon? They are removed based on volume, but should a standard time on such be performed to prevent recurrence?

Reply: We thank the reviewer for the insightful comments. In this study, the image-confirmed recurrence was only in the perioperative period, and no symptomatic long-term recurrence was observed. Although our criteria for chest drain removal are described in the manuscript, we performed a clamp test to confirm no air leakage when a slight air leakage was suspected. We added new text as follows:
"When a slight air leakage was suspected, we performed a clamp test of the chest drain to confirm no air leakage." (Page 8, lines 148–149)