Peer review file
Article information: http://dx.doi.org/10.21037/jtd-20-2436

Reviewer A

Comment 1: The authors described that the requirement for written consent in Methods. Generally, optout may be performed in such a case.

Reply 1: We omitted the description of the optout option; we have added that to the revised manuscript.

Changes: Page 7, line 5

The requirement for written consent was waived because of the retrospective nature of this study. Patients were notified of the study and given the option to optout.

Comment 2: Surgical details were unclear. You may show the detail such as anesthesia, position, port sizes, camera size, the length of thoracotomy and so on.

Reply 2: We have added the surgical details to the manuscript.

Changes: Page 7, line 11

A double-lumen endotracheal tube was inserted into the airway under general anesthesia, and surgery was performed during selective ventilation of the contralateral lung. Surgery was carried out with patients in the lateral position. The first choice for intervention at our institution was thoracoscopic surgery using a 5-mm, 30°video thoracoscope and 3 intercostal ports (5-12 mm) for access. The working ports were typically placed in the third intercostal space in the anterior and posterior axillary line, and the fifth intercostal space in the midaxillary line, but could be placed elsewhere depending on the requirements of the case. Thoracotomy (approximately 4-8cm) was an option when pleural adhesions prevented the safe use of thoracoscopy.

Comment 3: You performed various procedures such as bullectomy, bulla ligation, pleural cautery and pulmorrhaphy. The indication for each procedure should be shown.

Reply 3: We have added the surgical indications to the manuscript.

Changes: Page 8, line 8

The choice of surgical procedure was made by the surgeons after examining the preoperative CT findings and the immediate intraoperative findings. When bullae were numerous or their stalks were large, we opted for bullectomy. When bullae were small and few in number or their stalks were small, we performed bulla ligation. We performed pleural cautery when the origin of air leakage was not clear but the location was thought to be at the site of the inflammatory changes. We performed pulmorrhaphy when

bullectomy or bulla ligation were deemed difficult—for example, when the site of air leakage was near the hilum or when emphysematous changes were extremely prevalent.

Comment 4: You evaluated the SP including secondary SP (SSP). As you know, SSP has various underlying diseases such as COPD, IP, BHDS, LAM and so on. It is thought that the recurrence rate of these SSP is different. Therefore, you should show the detail for the underlying diseases.

Reply 4: There are many underlying diseases that can cause SSP, and the recurrence rate seems to vary accordingly. We have added a description of our patients' underlying diseases to the manuscript and supplied a new table: Supplemental Table 2.

Changes: Page 11, line 10 and Supplemental Table 2

The underlying diseases in patients with SSP included chronic obstructive pulmonary disease, interstitial pneumonia, and Birt-Hogg-Dubé syndrome (Supplemental Table 2).

Comment 5: The postoperative recurrences were compared using Fisher's exact test. However, the postoperative recurrence is time-dependent factor. Therefore, the evaluation may be performed by Kaplan-Meier method.

Reply 5: We agree that the rate of postoperative recurrence of pneumothorax seems to be time-dependent. Many recent reports use the Kaplan-Meier method to assess recurrence. We revised our manuscript to include univariate analysis using Fisher's exact test. This information is provided in the new Supplemental Table 3, and we have modified Table 3 (now Table 2) and Table 4 (now Table 3) accordingly.

Changes: Text and Table 2 (now Supplemental Table 3); Table 3 (now Table 2), Table4 (now Table 3).

【Abstract】

Page 4, line 10

A significant association with recurrence was noted for primary spontaneous pneumothorax, never smokers, thoracoscopic surgery, age younger than 30 years, operative time less than 100 minutes, and surgery by a resident surgeon. Patients younger than 30 years of age had a 5-year recurrence-free probability of 46.3%.

Page 4, line 19

Patients who underwent bulla ligation with pleural reinforcement using an absorbable polyglycolic acid sheet had a 4% recurrence rate and a 5-year recurrence-free probability of 90.0%.

【Manuscript Methods】

Page 9, line 18

We used recurrence-free probability (RFP),

Page 10, line 2

We calculated RFP using the Kaplan–Meier method.

【Manuscript Results】

Page 12, line 11

The 5-year RFP was 65.6% for all patients (Table 3 [now Table 2]). In patients younger than 20 years of age, the RFP was 44.2%, and in those between 20 and 29 years of age it was 48.5%.

Page 12, line 16

The 5-year RFP for patients undergoing bullectomy was 64.5%, and in patients undergoing bulla ligation it was 61.1% (P = 0.181; Table 4 [now Table 3]).

Page 13, line 1

The 5-year RFP for patients who underwent pleural reinforcement using ORC mesh was 56.7% (P = 0.281), and for those who underwent reinforcement with absorbable PGA sheets it was 86.4% (P = 0.261; Table 4 [now Table 3]).

Page 13, line 4

The recurrence rate for patients who underwent ligation with reinforcement using a PGA sheet was 4.0% (1/25 patients; P = 0.09) and the 5-year RFP was 90.0% (P = 0.459)

Page 13, line 6

Recurrence-free probability* and *Multivariate analysis of risk factors for recurrence

Page 13, line 8

Table 4 [now Table 3] shows that PSP (P < 0.001), never-smoker status (P < 0.001), left-sided pneumothorax (P = 0.049), thoracoscopic surgery (P = 0.008), operative time less than 100 min (P < 0.001), surgery by a resident surgeon (P = 0.008), and age younger than 30 years (P < 0.001) were significant risk factors for postoperative recurrence.

【Manuscript Discussion】

Page 15, line 15

The recurrence rate in our study was higher (28.8%), and 5- year RFP was lower (46.3%), in patients younger than 30 years of age.

Page 16, line 8

Our study demonstrates a trend toward a higher recurrence rate for bullectomy (5-year RFP, 64.5%) than for bulla ligation (5-year RFP, 61.1%; P = 0.181).

Page 17, line 4

we found that ligation with reinforcement using a PGA sheet may be an effective surgical method for preventing recurrence, with only a 4% recurrence rate and a 5-year RFP of 90.0%.

Comment 6: IPTW analysis was performed to discriminate the significant confounders. To my knowledge, Cox proportional hazards model is performed for same reason. I want to show the difference for two analyses. In addition, which results do you place emphasis on?

Reply 6: We evaluated factors using multivariate analysis and the IPTW method. Since this study was a retrospective analysis, we thought that the IPTW analysis would provide a more accurate analysis by eliminating bias. We did not use the Cox proportional hazards model: we have corrected this error in the manuscript.

Changes: Page 10, line 3

Cox regression analysis was used for multivariate analysis.

Comment 7: Do you select all factors on multivariate analysis? You should show the selected factors and reason clearly.

Reply 7: On our initial multivariate analysis, we used the factors that were found to be important on univariate analysis. Since we have now re-examined the data using the Kaplan–Meier method, we repeated the multivariate analysis using the important factors identified by the latter method.

Changes:

Page 13, line 12

Factors for multivariate analysis were selected based on the results of RFP analysis

Multivariate analysis (Table 4 [now Table 3]) indicated that age younger than 30 years (HR, 6.54; 95% CI, 1.34–32.1; P=0.021) was an independent predictor of recurrence.

Comment 8: In Discussion, the reports by Cho and Lee were referred. Did they evaluate PSP, SSP or SP?

Reply 8: Both reports evaluated primary spontaneous pneumothorax. We have clarified this in the Discussion section.

Changes: Page 15, line 6

Cho et al. (16) reported a 4.8% recurrence rate using absorbable ORC mesh coverage and fibrin glue in patients with PSP, while Lee et al. (17) reported a 3.9% recurrence rate using absorbable PGA sheets to widely cover the staple line and pleural abrasion in patients with PSP.

Comment 9. The cut-off point of age is 30 years in this study. It is 23 years for the report by Nakayama. You have to show the reason. If no reason, the ROC curve may be useful

to decide the point.

Reply 9: As you point out, Nakayama et al used the receiver operating characteristic (ROC) curve and established a cutoff point of 23 years of age for an increased risk of recurrence. However, when we examined our data (recurrence rate and RFP) by age group, we found that the recurrence rate was clearly higher and the RFP was clearly lower in patients younger than 30 years of age. We therefore used a cutoff of 30 years of age.

Comment 10. You argued that ligation with reinforcement using a PGA sheet may be an effective to prevent postoperative recurrence in Discussion. Why does the procedure have lower recurrence rate than others?

Reply 10: It is difficult to know why bulla ligation using a PGA sheet caused less recurrence, but we have added an educated guess to our Discussion section.

Changes:

Page 16, line 12

We speculate that, of the various surgical methods, bulla ligation is less stressful on the surgical site than bullectomy, and as a result, bulla neogenesis is less likely.

Page 16, line 17

Pleural reinforcement using ORC sheets prevents recurrence by thickening the visceral pleura near the surgical site. It also prevents adhesion formation between the surgical site and the chest wall. However, the mesh sheet may fall into the chest cavity. We speculate that this may cause recurrence more frequently than with the use of PGA sheets.

Page 17, line 4

It is very difficult to determine exactly why bulla ligation with the use of PGA sheets causes less recurrence, but it may be better for surgeons to combine methods that are less likely to lead to recurrence. Surgeons should think carefully about the surgical and pleural reinforcement methods used for each patient.

Comment 11. In Conclusion, the authors described that it was important to devise the novel methods to prevent postoperative recurrence. Recently, it is reported for the feasibility of dual covering method using ORC and PGA sheets for young patients with PSP aged <16, pleural coating by 50% glucose solution for SP and so on. You may refer these papers.

Reply 11: Many reports describe the usefulness of 50% glucose solution for patients with spontaneous pneumothorax. We have taken your advice and added this suggestion to the Discussion section as an option to reduce recurrence.

Changes: Page 17, line 8

One method of reducing postoperative recurrence is the use of 50% glucose solution for pleural reinforcement, as described by Fujino et al (19).

Comment 12. Table 2 is very complex. Because "PSP/SSP" is too much. You may revise it.

Reply 12: We have added a brief description of the different types of spontaneous pneumothorax to the text and have moved Table 2 to become Supplemental Table 1.

Changes: Table2→Supplemental Table1

(Tables 3-5 renumbered accordingly)

Comment 13. The factors such as pleural reinforcement and surgeon have several results for p-value in Table 4. Is it correct?

Reply 13: We have reviewed Table 4 (now Table 3) and we believe the information is presented correctly.

Comment 14. For Table 5, the factors such as Type of SP: Primary and Pleural Reinforcement: Yes have lower HR than one. Is it correct?

Reply 14: We have corrected the table to indicate SSP instead of PSP. In our revised manuscript, we have removed pleural reinforcement from this table because it was shown by RFP analysis not to be a significant factor.

Changes: Table 4 (now Table 3): Secondary

Comment 15. For Table 5, the results of Type of SP: Primary and Surgical Approach: Thoracoscopic Surgery didn't describe for IPTW Method. You may show the reason.

Reply 15: The use of thoracoscopic surgery could not be examined by ITPW analysis. Therefore, we added N/A to Table 5 (now Table 4) for this factor. We added the results of IPTW analysis for the type of spontaneous pneumothorax.

Changes: Table 5 (now Table 4)

Reviewer B

Comment 1: In the female patients, were there any cases of catamenial pnumothoracis cases?

Comment 2: Were there any assessment for genetic diseases such as Marfan's, Ehlar Danlos, Burt Hugg Dube syndrome?

Reply 1, 2: There were 5 cases of catamenial pnumothoracis cases in our study.
There were 8 cases of BHD syndrome cases and no cases of Marfan's nor Ehles Danlos in our study.
As Reviewer A asked us to provide details of the causes of SSP. we have added these to the manuscript and provided them in the new Supplemental Table 2
Changes: Page 11, line 10 and Supplemental Table 2
The underlying diseases in patients with SSP included chronic obstructive pulmonary disease, interstitial pneumonia, and Birt-Hogg-Dubé syndrome (Supplemental Table 2).

Comment 3: The application of Vanderschueren staging is attributed to high risk of recurrence, would this be a consideration by the author in addition to the confounding factors?

Reply 3: The use of Vanderschueren staging is not common in Japan and was not used in this study.

Comment 4: For the patients who are above 50 years, where there any radiological assessment to rule out the possibility of secondary spontaneous pneumothoracis?

Reply 4: We assessed the history of pulmonary disease, smoking habits, and preoperative CT findings in our patients over the age of 50 years. In those with no prior pulmonary history, a negative smoking status, and CT findings unlikely to indicate SSP, we were comfortable providing a classification of PSP. Add the following sentences.
Changes: Page 11, line 10
The type of spontaneous pneumothorax was categorized by comprehensively evaluating the preoperative CT findings, any history of pulmonary disease, and the patient's smoking history.

Comment 5: The data was not clear in regards to perioperative complications which can contribute to increased recurrence.

Reply 5: We made no mention of perioperative complications. However, we know that additional treatment required for prolonged air leakage may contribute to recurrence. We

have added this information to our manuscript.

Changes: Page 12, line 5

Additional treatment for prolonged air leakage, such as chemical pleurodesis, was performed in 30 patients.

Reviewer C:

Comment 1: The studied population is not clear. It is confusing that if all types of, or only primary spontaneous pneumothorax were included?

Reply 1: We examined patients with all types of pneumothorax. We chose to focus our manuscript on PSP because these patients had a large number of recurrences.

Comment 2: The recurrence rate is high (if for PSP). The average reported rate is 4-7 %.

Reply 2: We agree that the recurrence rate we noted for spontaneous pneumothorax is very high, at 17.6%. Kawamura et al report a high recurrence rate in patients younger than 23 years of age (5-yr recurrence-free progression, 78.1%).

We are not sure why our recurrence rate is so high, especially given the large number of surgeons included in our data. Our data show that patients with PSP have a higher rate of recurrence than those with SSP.

Comment 3: Did you perform pleural abrasions after the bullectomy or ligation? This will certainly affect the recurrence rate.

Reply 3: As a general rule, we did not perform pleural abrasion after bullectomy or bulla ligation. However, there were patients in whom additional treatment was performed, especially when it was difficult to treat all bullae (e.g., those with SSP). As the number of patients who underwent pleural abrasion was small, we did not examine the recurrence rate for this procedure. We believe that recurrence might be suppressed by performing abrasion of the surrounding pleural lesion after bullectomy or bulla ligation.

We have added a description of this possibility to the Discussion section.

Changes: Page 17, line 10

Abrasion of the surrounding pleural lesion after bullectomy or bulla ligation may also reduce recurrence.

Comment 4: In what condition you perform bulla ligation and not bullectomy?

Reply 4: As Reviewer A asked us to provide details of the choice of procedure. we have added these to the manuscript.

Changes: Page 8, line 8

The choice of surgical procedure was made by the surgeons after examining the preoperative CT findings and the immediate intraoperative findings. When bullae were numerous or their stalks were large, we opted for bullectomy. When bullae were small and few in number or their stalks were small, we performed bulla ligation. We performed pleural cautery when the origin of air leakage was not clear but the location was thought

to be at the site of the inflammatory changes. We performed pulmorrhaphy when bullectomy or bulla ligation were deemed difficult—for example, when the site of air leakage was near the hilum or when emphysematous changes were extremely prevalent.

Comment 5: Why recurrence rate is higher for bullectomy when compared with ligation?
Reply 5: Reviewer A asked this same question. we have added these to the manuscript.
Changes: Page 16, line 12
We speculate that, of the various surgical methods, bulla ligation is less stressful on the surgical site than bullectomy, and as a result, bulla neogenesis is less likely.

Comment 6: Did you perform CT scan preoperatively? This will certainly affect your surgical planning.
Reply 6: The findings of preoperative CT are very important in determining the appropriate surgical procedure. We performed preoperative CT in all patients. We have added this information to the manuscript.
Changes: Page 8, line 8
The choice of surgical procedure was made by the surgeons after examining the preoperative CT findings and the immediate intraoperative findings.

Comment 7; You article title should clearly state what type of pneumothorax you are going to study.
Reply 7: We evaluated patients with all types of pneumothorax. However, since we focused mainly on those with PSP, we changed the title to reflect that.
Revised title: Risk factors of postoperative recurrence of primary spontaneous pneumothorax