Observational Study

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Analysis of factors predicting the application of chemical pleurodesis for pneumothorax

An observational study

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Abstract

Chemical pleurodesis is performed in pneumothorax patients to treat nonresolving air leakage or prevent recurrence. However, factors that might predict the need for chemical pleurodesis remain unknown. Therefore, this study investigated predictive factors for the application of chemical pleurodesis for pneumothorax.

We retrospectively analyzed 401 adult pneumothorax patients who underwent chest tube drain insertion during hospitalization at Fukujuji Hospital from January 2016 to December 2020. The patients were divided into 3 groups: the pleurodesis group, comprising 89 patients treated with chemical pleurodesis; the nonpleurodesis group, comprising 206 patients treated without chemical pleurodesis; and the surgical group, comprising 106 patients treated surgically. Data for patients in the pleurodesis group were compared to those in the nonpleurodesis or surgical group, and a predictive score of the application of chemical pleurodesis for pneumothorax was developed.

Compared with the nonpleurodesis group, in the pleurodesis group, patient age was higher ($P < .001$), emphysema (n = 33 (37.1%) vs 70 (34.0%), $P = .045$), and interstitial pneumonitis (n = 19 (21.3%) vs 19 (9.2%), $P = .022$) were more common causes, and chest tube suction was more common (n = 78 (87.96%) vs n = 123 (59.7%), $P < .001$). Similar results were found between the pleurodesis and surgical groups. We developed a score for predicting the application of chemical pleurodesis for pneumothorax, including the following factors: age ≥55 years; presence of emphysema and/or interstitial pneumonitis; and use of chest tube suction. The score for the pleurodesis group showed a high area under the receiver operating characteristic curve compared with that for the nonpleurodesis group (0.776 [95% confidence interval]: 0.725–0.827). With a score of 2 as the cutoff value, the sensitivity was 91.0% and the specificity was 52.4%. In a comparison between the pleurodesis and surgical groups, the predicting score showed the high AUC of 0.904 (95% confidence interval: 0.863–0.945).

This study reveals predictive factors for the application of chemical pleurodesis and provides a predictive score including 3 factors.

Abbreviations: AUC = area under the ROC curve, CI = confidence interval, CRP = C-reactive protein, IP = interstitial pneumonitis, IQR = interquartile range, NTM = nontuberculous mycobacteria, ROC = receiver operating characteristic.

Keywords: chemical pleurodesis, chest tube drainage, pneumothorax, predicted score

1. Introduction

Chemical pleurodesis is performed in patients with pneumothorax to treat nonresolving air leakage or prevent recurrence.[1,2] Several chemical agents have been used, such as talc, OK-432, minocycline, 50% glucose, and autologous blood.[2] Generally, since surgical options are more effective, chemical pleurodesis should only be used as a postsurgical treatment[2] or if a patient is either unwilling or unable to undergo surgery.[1] Surgical therapy can be considered in patients with pneumothorax greater than or equal to 50% in size[3]; however, there have been no reports comparing the characteristics of patients who underwent surgical therapy with those of patients who underwent chemical

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The study was approved by the Institutional Review Board of Fukujuji Hospital, and the requirement for patient consent was waived. The decisions made by this board were based on and in accordance with the Declaration of Helsinki (Study number: 2103).

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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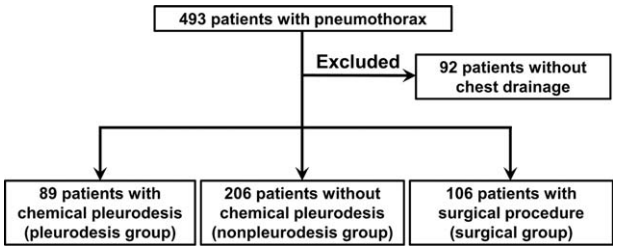


Figure 1. Flowchart of the study.

pleurodesis. Additionally, while chemical agents for pleurodesis have been reported to successfully improve pneumothorax even without a surgical procedure,[4–6] it is unknown what factors could predict the need for chemical pleurodesis. Therefore, this study investigated predictive factors for the application of chemical pleurodesis for pneumothorax.

2. Materials and methods

2.1. Study design and setting

We retrospectively collected the data of 493 adult patients (age ≥18 years old) with pneumothorax who were hospitalized at Fukujuji Hospital from January 2016 to December 2020. The flowchart of the study is in Figure 1. Ninety two patients who did not require chest drainage were excluded. In total, 89 patients treated with chemical pleurodesis (pleurodesis group), 206 patients treated without chemical pleurodesis (nonpleurodesis group), and 106 patients treated with a surgical procedure (surgical group) were reviewed. The pleurodesis group comprised patients who underwent chemical pleurodesis for pneumothorax, and the nonpleurodesis group comprised patients who did not undergo chemical pleurodesis or a surgical procedure. The surgical group comprised patients who underwent a surgical procedure, such as wedge resection of bullae, lobectomy, pleurectomy/pleural abrasion, or coverage with absorbable mesh, without chemical pleurodesis preoperatively, as well as patients who underwent chemical pleurodesis postoperatively. Data regarding symptoms, laboratory test results, radiological findings, and other relevant findings were collected. The study was approved by the Institutional Review Board of Fukujuji Hospital, and the requirement for patient consent was waived. The decisions made by this board were based on and in accordance with the Declaration of Helsinki (Study number: 2103).

2.2. Definition of causes of pneumothorax and complications of chemical pleurodesis

The causes of pneumothorax in this study were emphysema, interstitial pneumonitis (IP), nontuberculous mycobacteria, or bronchiectasis according to the medical history and/or chest computed tomography findings of the patients. Bullae were diagnosed by chest computed tomography scan and/or thoracoscopy.

Complications of chemical pleurodesis, including fever, infection, drain obstruction, and pleural effusion, were defined as developing within a week after chemical pleurodesis was performed. The causative agent of a complication was defined as the last agent applied before the appearance of the complication.

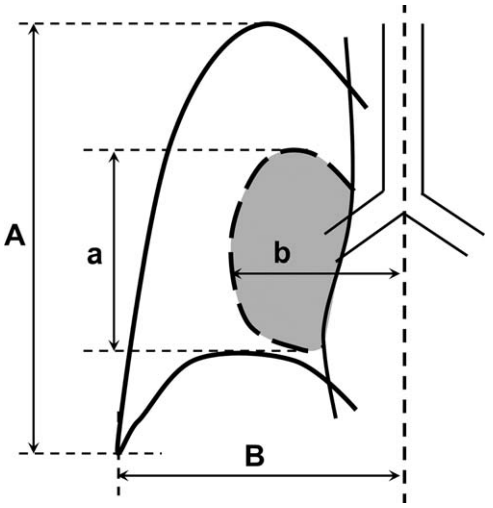


Figure 2. The size of the pneumothorax on the chest X-ray was calculated according to the following formula: (pneumothorax size) = {1 − (a × b)/(A × B)} × 100 (%).

2.3. Pneumothorax size

The size of the pneumothorax detected on chest X-ray was subtracted from the area of the hemithorax and was calculated according to the formula below (Fig. 2).[7]

$$(\text{pneumothorax size}) = \{1 - (a \times b)/(A \times B)\} \times 100\,(\%)$$

Regarding bilateral pneumothorax, the size of the pneumothorax was determined based on the side with the larger pneumothorax. Lesions ≥50% in size were defined as extensive, while those <50% in size were defined as small/moderate.[3]

2.4. Statistical methods

All data were analyzed and processed using EZR, version 1.53.[8] The Kruskal–Wallis test was used to compare data among the pleurodesis group, nonpleurodesis group, and surgical group, and Bonferroni correction was used for comparative testing. Student *t* test, the Mann–Whitney *U* test, Fisher exact test, and binomial logistic regression analysis were used for group comparisons. The sensitivity, specificity, and odds ratio were calculated. A receiver operating characteristic (ROC) curve was constructed, and the area under the ROC curve (AUC) was calculated for each predictive model. The ROC curves were used to determine the cutoff values. The AUC was used as an accurate measure of the predictive capability of each model. The level of statistical significance was set at $P = .05$ (2-tailed).

3. Results

3.1. Comparison between the pleurodesis group and the nonpleurodesis or surgical group

The baseline characteristics of the study subjects are shown in Table 1. Patients in the pleurodesis group were older than those in the nonpleurodesis group (median interquartile range (IQR): 74 years (65–80) vs 63.5 years (34–77), $P < .001$) and those in the

Table 1

Baseline characteristics of the study subjects.

	Pleurodesis group (n = 89)	Nonpleurodesis group (n = 206)	*P* value	Surgical procedure (n = 106)	*P* value
Age, median (IQR), years	74 (65–80)	63.5 (34–77)	<.001	25 (19–48)	<.001
Sex (male/female)	71/18	162/44	1.000	91/15	1.000
Body weight, median (IQR), kg[*]	49.5 (42.5–56.6)	51.7 (44.7–60.7)	.093	54.5 (50.1–61.2)	<.001
Comorbidity, n (%)[†]	79 (88.8)	130 (64.0)	<.001	66 (64.1)	<.001
History of pneumothorax, n (%)[†]	21 (23.6)	49 (24.1)	1.000	52 (50.5)	<.001
Smoking history, n (%)[‡]	70 (87.5)	129 (69.0)	.004	44 (44.9)	<.001
Duration of hospitalization, median (IQR), day	29 (18–41)	10 (7–19)	<.001	10 (7–13)	<.001
Mortality, n (%)	3 (3.4)	14 (6.8)	.873	0 (0.0)	.010
Laboratory findings					
WBCs, median (IQR), cells/μL[§]	7790 (6115–9990)	7540 (5890–9370)	.732	6835 (5928–8123)	.013
CRP, median (IQR), mg/dL[‖]	0.57 (0.24–2.31)	0.35 (0.07–1.67)	.021	0.07 (0.02–0.30)	<.001
Albumin median (IQR), mg/dL[¶]	3.85 (3.52–4.14)	4.15 (3.49–4.60)	.004	4.51 (4.15–4.80)	<.001
Radiographic findings					
Right pneumothorax, n (%)	47 (52.8)	114 (55.3)	1.000	56 (52.8)	1.000
Left pneumothorax, n (%)	38 (42.7)	85 (41.3)	1.000	48 (45.3)	1.000
Bilateral pneumothorax, n (%)	4 (5.0)	7 (5.8)	1.000	2 (1.9)	1.000
Size of pneumothorax, median (IQR), %[#]	38.7 (25.3–51.0)	33.8 (21.9–49.0)	.486	44.4 (29.8–63.9)	.045
Size of pneumothorax ≥50%, n (%)	25 (28.4)	46 (22.7)	.905	44 (41.5)	.212
Use of chest tube suction, n (%)	78 (87.6)	123 (59.7)	<.001	60 (56.6)	<.001
Cause of pneumothorax					
Bullae, n (%)	19 (21.3)	70 (34.0)	.110	91 (85.8)	<.001
Emphysema, n (%)	33 (37.1)	47 (22.8)	.045	7 (6.6)	<.001
IP, n (%)	19 (21.3)	19 (9.2)	.022	3 (2.8)	<.001
Emphysema + IP, n (%)	8 (9.0)	3 (1.5)	.011	0 (0.0)	.005
NTM/BE, n (%)	6 (6.7)	12 (5.8)	1.000	0 (0.0)	.025
Trauma, n (%)	0 (0.0)	19 (9.2)	.004	0 (0.0)	1.000
Others, n (%)	4 (4.5)	18 (8.7)	.709	2 (1.9)	1.000
Uncertain, n (%)	0 (0.0)	19 (9.2)	.004	3 (2.8)	.756
Bronchial occlusion with EWS, n (%)	11 (12.4)	8 (3.9)	.027	2 (1.9)	.011

Other causes of pneumothorax included 9 cases of infectious lung disease, 5 cases of Birt-Hogg-Dube syndrome, 3 cases of lung malignancy, 3 cases of catamenial factor, 2 cases of Marfan syndrome, and 1 case of sarcoidosis, along with 1 case caused by an iatrogenic factor.

BE = bronchiectasis, CRP = C-reactive protein, EWS = endobronchial Watanabe spigot, IP = interstitial pneumonia, IQR = interquartile range, LDH = lactate dehydrogenase, NTM = nontuberculous mycobacteria, WBCs = white blood cells.

[*] Medical pleurodesis, n = 88; without pleurodesis, n = 197; surgical procedure, n = 106.

[†] Medical pleurodesis, n = 89; without pleurodesis, n = 203; surgical procedure, n = 103.

[‡] Medical pleurodesis, n = 80; without pleurodesis, n = 187; surgical procedure, n = 98.

[§] Medical pleurodesis, n = 87; without pleurodesis, n = 205; surgical procedure, n = 106.

[‖] Medical pleurodesis, n = 87; without pleurodesis, n = 203; surgical procedure, n = 104.

[¶] Medical pleurodesis, n = 87; without pleurodesis, n = 201; surgical procedure, n = 105.

[#] Medical pleurodesis, n = 88; without pleurodesis, n = 203; surgical procedure, n = 106.

surgical group (25 years [19–48], $P < .001$). Regarding laboratory findings, patients in the pleurodesis group showed higher C-reactive protein (CRP) levels (median (IQR): 0.57 mg/dL [0.24–2.31] vs 0.35 mg/dL [0.07–1.67], $P = .021$) and lower serum albumin levels (median [IQR]: 3.85 mg/dL [3.52–4.14] vs 4.15 mg/dL [3.49–4.60], $P = .004$). Comparison between the pleurodesis group and the surgical group showed similar results (the surgical group: CRP levels median 0.07 mg/dL (IQR 0.02–0.30), $P < .001$; and albumin levels median 4.51 mg/dL [IQR 4.15–4.80], $P < .001$). More patients in the pleurodesis group required chest tube suction (the pleurodesis group n = 78 (87.6%); vs the nonpleurodesis group n = 123 (59.7%), $P < .001$; vs the surgical group n = 60 (56.6%), $P < 0.001$). Regarding the cause of pneumothorax, patients in the pleurodesis group were more likely to have emphysema (the pleurodesis group n = 33 [37.1%]; vs the nonpleurodesis group 47 [22.8%], $P = .045$; vs the surgical group n = 7 [6.6%], $P < .001$), IP (the pleurodesis group n = 19 [21.3%]; vs the nonpleurodesis group 19 [9.2%], vs the surgical group n = 3 [2.8%], $P = .022$), and combined emphysema with IP (the pleurodesis group n = 8 [9.0%]; vs the nonpleurodesis group 3 [1.5%], $P = .011$; the surgical group n = 0 [0.0%], $P = .005$). There was no significant difference in body weight (median [IQR]: 49.5 kg [42.5–56.6] vs 51.7 kg [44.7–60.7], $P = .093$) or a history of pneumothorax (n = 21 [23.6%] vs n = 49 [24.1%], $P = 1.000$) between the pleurodesis group and the nonpleurodesis group. However, compared to patients in the surgical group, patients in the pleurodesis group showed a lower body weight (the surgical group; median 54.5 kg (IQR 50.1–61.2), $P < .001$), and fewer patients in the pleurodesis group had a history of pneumothorax (the surgical group; n = 52 [50.5%], $P < .001$).

3.2. Development of a predictive score for the application of chemical pleurodesis

The results of the binomial logistic regression analysis of factors for predicting the application of chemical pleurodesis in the pleurodesis and nonpleurodesis groups are shown in Table 2. The cutoff value for age, CRP, and serum albumin were determined

Table 2

Binomial logistic regression analysis of predictive factors for the application of chemical pleurodesis.

		95% Confidence interval		
	Odds ratio	Upper limit	Lower limit	*P* value
Age≥55 years old	5.13	1.72	15.3	.003
Presence of emphysema and/or IP	2.32	1.26	4.27	.007
CRP > 0.2 mg/dL	1.47	0.72	3.01	.288
Alb ≤ 4.2 g/dL	1.57	0.73	3.40	.247
Use of chest tube suction	4.63	2.23	9.63	<.001

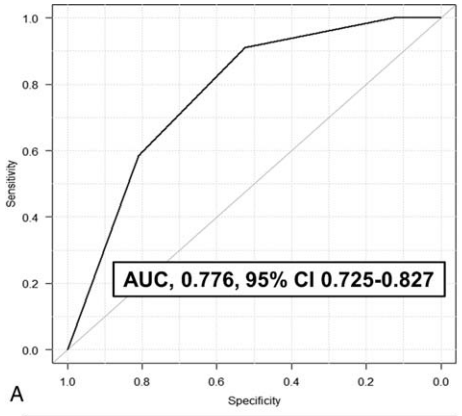
Alb = albumin, CRP = C-reactive protein.

by ROC curve analysis. An age of 55 years or older showed the highest odds ratio of 5.13 (95% confidence interval [CI]: 1.72–15.3, $P = .003$). A high odds ratio was also found to be significant for patients with emphysema and/or IP (2.32 [95% CI: 1.26–4.27], $P = .007$) or chest tube suction (4.63 [95% CI: 2.23–9.63], $P < .001$). We developed a predictive score for the application of chemical pleurodesis, including the following factors: age ≥55 years; presence of emphysema and/or IP; and use of chest tube suction, which showed significant difference in the binomial logistic regression analysis. Each variable was assigned a value of 1 point, with the score therefore totaling 3 points. The ROC curve of the score demonstrated a high AUC of 0.776 (95% Cl: 0.725–0.827) (Fig. 3A). A score of 2 or more was regarded as the cutoff, and the sensitivity, specificity, and odds ratio were 91.0%, 52.4%, and 8.82 (95% Cl: 4.25–20.2), respectively. If the cutoff was 3 points, the sensitivity was 58.4%, and the specificity was 81.1%.

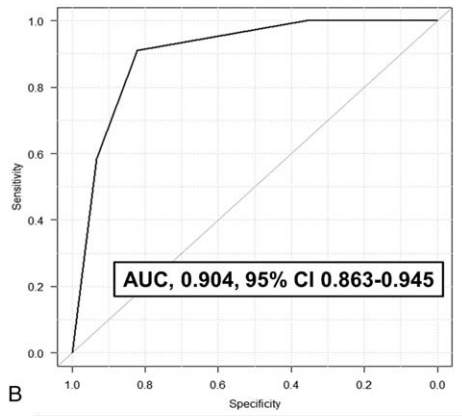
If the predictive score was adapted for a comparison between the pleurodesis group and the surgical group, the AUC was remarkably high at 0.904 (95% Cl: 0.863–0.945) (Fig. 3B). With a score of 2 as the cutoff value, the sensitivity was 91.0%, and the specificity was 82.1%.

3.3. Various pleurodesis agents and complications

Various pleurodesis agents were administered, including OK-432 in 35 patients (39.3%), 50% glucose in 35 patients (39.3%), minocycline in 23 patients (25.8%), autologous blood in 27 patients (30.3%), and talc in 2 patients (2.2%). Sixteen of the 23 patients who received minocycline (69.6%) also received OK-432. When 50% glucose was administered, it was combined with either OK-432 or minocycline in each patient. Autologous blood and talc were used alone. The average number of pleurodesis procedures performed in each patient was 1.97 (range: 1–9), and the pleurodesis agent was changed to another agent in 20 patients (22.5%). Complications of chemical pleurodesis occurred in 44 of 89 patients (49.4%), including fever in only 28 patients (31.5%), infection such as empyema, pleuritis, and pneumonia in 12 patients (13.5%), drain obstruction in 5 patients (5.6%), and pleural effusion in 2 patients (2.2%). Fever was observed mainly in patients administered OK-432 (n = 24, 68.3%). Infection was observed in 6 patients administered 50% glucose (16.7%) and 5 patients administered autologous blood (18.5%). Drain obstruction and pleural effusion were observed only in patients administered autologous blood and OK-432, respectively.



Cutoff value	Sensitivity (%)	Specificity (%)
1	100	12.6
2	91.0	52.4
3	58.4	81.1



Cutoff value	Sensitivity (%)	Specificity (%)
1	100	35.8
2	91.0	82.1
3	58.4	93.4

Figure 3. The ROC curve of the predictive score for the application of chemical pleurodesis in the pleurodesis group versus the nonpleurodesis group (A) or the surgical group (B). The predictive score included the following factors: age ≥55 years; presence of emphysema and/or IP; and use of chest tube suction. Each variable was assigned a value of 1 point, with the score therefore totaling 3 points. ROC = receiver operating characteristic.

4. Discussion

We demonstrate the characteristics of patients who required chemical pleurodesis. Patients in the pleurodesis group were older, more commonly had emphysema and IP, had higher CRP levels and lower serum albumin levels, and were more likely to require chest tube suction than those in the nonpleurodesis group or the surgical group. While there were no differences in the incidence of extensive pneumothorax among the three groups, a previous study reported that extensive pneumothorax was a factor to consider in surgical therapy.[3] We developed a predictive score for the application of chemical pleurodesis including three factors. The score showed a high AUC. These results could be useful for identifying patients with pneumothorax who require chemical pleurodesis.

Elderly patients and patients with emphysema or IP are at a high risk for thoracic surgical procedures.[9] Elderly patients are likely to have underlying comorbidities, and patients with emphysema or IP have decreased spirometry metrics, such as forced expiratory volume in one second and diffusing capacity for carbon monoxide.[9] These patients have a high risk of postoperative complications; therefore, surgical procedures often should be avoided.[9,10] Furthermore, regarding the treatment of pneumothorax by aspiration, previous studies have reported a reduced success rate in patients aged >50 years as well as in patients with chronic lung disease.[1] Therefore, advanced age and the presence of emphysema and/or IP might predict the need for chemical pleurodesis, which is similar to the results of our study. In our study, the use of chest tube suction was also a predictive factor for the application of chemical pleurodesis. Generally, chest tube suction is used in patients without successful lung re-expansion under water seal,[11] yet there are few data regarding the utility of applying suction to chest tubes.[12] Experts have suggested that there is no role for the immediate use of suction in all cases; however, some patients may benefit from the application of suction in the case of ongoing air leakage.[12] Lung re-expansion is achieved in up to 70% of patients treated with chest tube drainage alone by day 3 without suction.[12] It might be possible to predict the application of chemical pleurodesis through our predictive score within 3 days after the insertion of a chest tube for drainage.

Our score can also be adapted to predict the application of chemical pleurodesis compared with surgery because of very high AUC of the ROC curve; therefore, it would be easy to distinguish between patients who require chemical pleurodesis and those who can tolerate surgery. In terms of distinguishing between the pleurodesis group and the nonpleurodesis group, chemical pleurodesis was very likely if the score was 3 points because of the high specificity of 81.1%. If the score was 0-1 points, treatment with chest tube drainage alone or a surgical procedure could be expected because of the very high sensitivity. A score of 2 points was more predictive of an internal medicine approach rather than a surgical procedure; however, the need for chemical pleurodesis remained uncertain because the specificity was 52.4%. Determining the indications for chemical pleurodesis is important because complications of chemical pleurodesis can be severe in some cases, such as pneumonia, hemothorax, and acute respiratory distress syndrome, among others.[13] Our results suggest that chemical pleurodesis is required in patients with pneumothorax who fail to achieve successful lung re-expansion after chest drainage without suction, and these patients are likely elderly and suffer from emphysema or IP, which might make it difficult to perform surgical procedures. Additionally, as each chemical agent showed different complications in our study, chemical agents for pleurodesis should be selected under consideration of risk for those complications.

This investigation has several limitations. The study was conducted retrospectively at a single center, some medical data were not recorded, and some patients underwent treatment with several types of chemical agents. There was no definition for an indication of undergoing chemical pleurodesis, surgical procedure, or chest tube suction use in our study.

5. Conclusion

The study demonstrates predictive factors for the application of chemical pleurodesis and provides a predictive score, including the following factors: age ≥55 years; presence of emphysema and/or IP; and use of chest tube suction.

Author contributions

Conceptualization: Masafumi Shimoda, Yoshiaki Tanaka.
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Validation: Masafumi Shimoda.
Visualization: Masafumi Shimoda.
Writing – original draft: Masafumi Shimoda.
Writing – review & editing: Masafumi Shimoda, Yoshiaki Tanaka.

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