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ORIGINAL ARTICLE

The influence of pleurodesis on the outcome of primary spontaneous pneumothorax in children

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Abstract

Background: Primary spontaneous pneumothorax (PSP) has a high rate of recurrence, and pleurodesis has been shown to decrease the rate of recurrence in adult PSP. For pediatric PSP patients, there are only a few case series available and evidence on the benefits of pleurodesis is insufficient. This study aimed to analyze the outcome of pleurodesis among pediatric PSP patients via a nationwide population-based cohort in Taiwan.

Methods: The hospitalization data from the pediatric intensive care sampling file of the National Health Insurance Research Database from January 1 to December 31, 2010, were retrieved and analyzed. Children aged 0-18 years with a discharge diagnosis of PSP (ICD-9: 512, 512.0, and 512.8) were enrolled in the study. Demographic data, management strategies, and clinical outcomes were recorded and analyzed as well.

Results: A total of 1005 hospitalization cases were identified and divided into the pleurodesis (409 hospitalizations) and nonpleurodesis (596 hospitalizations) groups. In the univariate analysis, thoracoscopic surgery for PSP decreased the incidence of recurrence (hazard ratio [HR], 0.46; 95% CI, 0.32-0.67) and the need for further surgical intervention (HR, 0.29; 95% CI, 0.18-0.47); however, conventional open surgery did not. A lesser incidence of PSP recurrence (HR, 0.53; 95% CI, 0.37-0.78) and fewer subsequent surgical interventions (HR, 0.32; 95% CI, 0.20-0.52) were found in the pleurodesis group in comparison with the nonpleurodesis group. A multivariate Cox regression analysis revealed that pleurodesis was the only significant factor capable of decreasing the incidence of PSP recurrence (HR, 0.57; 95% CI, 0.38-0.86) and the need for further surgical intervention (HR, 0.40; 95% CI, 0.23-0.69).

Conclusion: Pleurodesis reduces the rate of recurrence and the need for further surgical intervention in pediatric PSP. It may be considered as the method of choice for the management of PSP in children.

Keywords: Child; Pleurodesis; Pneumothorax; Recurrence

1. INTRODUCTION

Primary spontaneous pneumothorax (PSP) is defined as spontaneous pneumothorax (SP) without underlying disease or secondary cause.[1] There are two peaks of incidence for SP, namely, in the younger (15-34 years) and older (55+ years) age groups.[2] Although treatment success is easy to achieve, the high recurrence rate remains a difficult clinical problem.

There is a lower incidence of PSP in the pediatric population than in the adult population (2.68-3.41 per 100 000 children vs 18-28 per 100 000 men and 1.2-6 per 100 000 women).[3,4] However, the recurrence rate among children is higher than that among the adults (50%-61% vs 30%).[5–8] Thus, seeking an adequate management strategy to reduce the high recurrence rate of PSP in the pediatric population is an urgent and important issue.

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Initially, some studies tried to apply primary pleurodesis in patients who only underwent tube thoracotomy to prevent recurrence.[9,10] Subsequently, pleurodesis was successfully performed during thoracoscopic operation for PSP in order to reduce the likelihood of recurrence in comparison to conventional open surgery.[11,12] Pleurodesis has been proven as a safe and effective procedure to reduce the recurrence of SP regardless of the chemical or surgical methods in the adult population.[12–19] However, there are only few studies on pleurodesis focusing on the pediatric population.[20] Consequently, whether or not performing pleurodesis on pediatric patients to reduce the incidence of recurrence becomes a frequently asked clinical question.

The aim of the present study was to investigate which factors or treatments, particularly pleurodesis, can reduce the recurrence of PSP or the need for further surgical intervention in the pediatric population. We conducted a cohort study with the use of a nationwide population-based database in Taiwan in 2010, and hospitalization cases were divided into the pleurodesis and control (nonpleurodesis) groups to determine any differences in clinical outcomes, particularly the incidence of recurrence.

2. METHODS

2.1. Data source

Since 1999, the Taiwan National Health Insurance Research Database (NHIRD) has been providing the claims data in an electronic form containing the demographic and medical information of insured residents after deidentification and encryption. Several reports on children's disease utilizing data from Taiwan's NHIRD have been published.[21–24] We used the special request sampling files that consisted of the total population of patients in 2010 who were ever admitted to the pediatric intensive care unit (ICU) since birth. The study was approved by the Institutional Review Board of Taipei Veterans General Hospital (VGHIRB No. 2012-06-017A).

2.2. Study population

Hospitalized patients aged 3 months to 18 years with a discharge diagnosis of SP (International Classification of Diseases, Ninth Revision [ICD-9]: 512, 512.0, or 512.8) in 2010 were included in the study. Patients with invasive or noninvasive ventilator use (reimbursement code: 57001B, 57002B, 57023B, or 57029C); intubation (reimbursement code: 47031C); tracheostomy (reimbursement code: 56003C, 56004C, 56022C, 66006B); respiratory failure (ICD-9: 518.81, 518.83, 518.84, or 518.85); related diagnoses of secondary pneumothorax such as neoplasm (ICD-9: 140-239), tuberculosis (ICD-9: 011-), asthma (ICD-9: 493-), *Pneumocystis jirovecii* pneumonia (ICD-9: 136.3), lung abscess (ICD-9: 513.0), Marfan syndrome (ICD-9: 759.82), Ehlers-Danlos syndrome (ICD-9: 756.83), polymyositis (ICD-9: 710.4), dermatomyositis (ICD-9: 710.3), foreign body aspiration (ICD-9: 934-), secondary SP (ICD-9: 512.82), or sarcoidosis (ICD-9: 135); and those with a disposition code of referral without further hospitalization data were excluded from the study. We also combined the data of hospitalizations wherein the admission date is within 1 day after the date of previous discharge.

The information on each hospitalization, including five leading diagnoses coded using ICD-9 diagnostic codes, patient's age and sex, clinician's specialty of admission and discharge, days of hospitalization and ICU stay, region and level of the hospital, management strategies, time to recurrence, time to subsequent surgery for pneumothorax, and days of oxygen use, was recorded. The management strategies included thoracocentesis (procedure code 29012B), tube thoracotomy (procedure code 56010B), open or thoracoscopic surgery for pneumothorax, pleurodesis, and intrapleural minocycline use (ATC code J01AA08). Recurrence is defined as readmission due to pneumothorax 7 days after the date of previous discharge.[1,25] The intervals between the pneumothorax event in 2010 and the next hospitalization due to pneumothorax were compared in our study. Pleurodesis comprises surgical pleurodesis or medical pleurodesis by minocycline. Open or thoracoscopic surgery for pneumothorax consists of the following: lung segmental resection (procedure code 67010B), open or thoracoscopic wedge partial resection (procedure codes 67011B, 67051B), open or thoracoscopic lobectomy (procedure codes 67023B, 67050B), bilobectomy (procedure code 67042B), open or thoracoscopic pneumonectomy (procedure codes 67024B, 67049B), and open or thoracoscopic pleurodesis (procedure codes 67034B, 67048B). The specialties of the clinicians are further divided into pediatric and nonpediatric specialties as well as surgical and nonsurgical specialties. The region of the hospital is determined according to the region of the insurance bureau (see Supplementary Appendix).

2.3. Statistical analysis

The software Microsoft® SQL Server® 2008 R2 was used for retrieving datasets from NHIRD. Microsoft Office Excel 2016 (Microsoft Corporation, Redmond, Washington, WA) and SPSS version 19.0 (SPSS Inc., Chicago, IL) were used for data analysis. Continuous variables are presented as mean with SDs and nominal variables as frequencies with associated percentages. For two-group comparisons, the two-sample independent t-test for continuous variables and chi-square test for nominal variables were used. For comparing two sample proportions, the two-sample z-test was used. The Kaplan-Meier method was utilized to estimate the overall PSP recurrence and the need for further surgical intervention. The log-rank test was performed to determine the difference in PSP recurrence and the need for further surgical intervention between the two patient groups. Univariate and multivariate Cox regression analyses were conducted, and the results were presented in terms of hazard ratio (HR) with a 95% CI. Univariate factors with a p value of <0.05 were included in the multivariate Cox regression calculation. Univariate factors that highly correlated with pleurodesis (r > 0.8) were excluded in the multivariate Cox regression analysis in order to avoid collinearity. A p value of <0.05 was considered significant, and all the tests were two tailed. Graphs were made using Stata 12.0 (StataCorp LLC, College Station, TX).

3. RESULTS

3.1. Demographic data of hospitalizations due to PSP

A total of 1005 hospitalization data were retrieved from the datasets of 2010. The median age (interquartile range [IQR]) was 16.9 (1.8) years, mainly adolescent age. An extremely male predominance was revealed (male:female = 12.8:1). Nearly 50% of the hospitalizations were admitted for and discharged from thoracic surgery. Pediatric cases accounted for one-sixth of the hospitalizations, being the second most common hospitalized patient group. The duration of the hospitalizations was mostly within a week (5.6 ± 2.0 days) with an extremely short ICU stay (0.3 ± 1.0 days). Most of the hospitalizations were at medical centers (47.1%), followed by regional hospitals (42.4%). Slightly <50% of the hospitalizations involved the operation for pneumothorax (46.1%), which mostly consisted of thoracoscopic surgery (44.5%). A short and variable duration of oxygen use was noted (2.35 ± 2.69 days). Around 40% of hospitalization cases had pleurodesis, and 11% had intrapleural minocycline use. Tube thoracotomy was performed for 70% of hospitalizations, and nearly 5% of hospitalizations had thoracocentesis. The recurrence rate of hospitalization was 13.4%, and 10.4% of hospitalizations had a subsequent operation for pneumothorax during follow-up (Table 1).

3.2. Comparisons between the pleurodesis and nonpleurodesis groups

We further divided hospitalization cases into the pleurodesis (409 hospitalizations) and nonpleurodesis (596 hospitalizations) groups. The patients in the pleurodesis group were older than those in the nonpleurodesis group (median [IQR], 16.7 [1.6] vs 16.4 [1.6] years, p = 0.043), and both showed adolescent predominance without differences in sex. The discharge specialties were significantly different between the groups, showing a greater application of pleurodesis in surgery-related specialties, particularly thoracic surgery, than in nonsurgical specialties (p < 0.001). The duration of hospitalization was longer in the pleurodesis group (pleurodesis vs nonpleurodesis, 7.1 ± 3.9 vs 4.6 ± 4.0, p < 0.001). There was a greater application of pleurodesis in medical centers (pleurodesis vs nonpleurodesis, 51.3% vs 44.1%, p = 0.025) than in other hospital levels. More pleurodesis procedures were performed in the southern region (pleurodesis vs nonpleurodesis, 15.4% vs 9.9%, p = 0.011) than in the northern region (pleurodesis vs nonpleurodesis, 13.4% vs 19.5%, p = 0.009), whereas there was no difference between these two groups in other regions. There is a large difference in the operation for pneumothorax between the groups in that more operations were performed in the pleurodesis group, specifically thoracoscopic operations (pleurodesis vs nonpleurodesis, 96.1% vs 9.1%, p < 0.001). Intrapleural minocycline was used in 26.7% of hospitalizations in the pleurodesis group. More tube thoracotomy (pleurodesis vs nonpleurodesis, 95.4% vs 53.0%, p < 0.001) and less thoracocentesis procedures (pleurodesis vs non-pleurodesis, 2.0% vs 6.7%, p = 0.001) were

Table 1

Demographic data of patients receiving pleurodesis or not

	Nonpleurodesis (n = 596)	Pleurodesis (n = 409)	p^a	Total
Age[b]	16.8 (1.8)	17 (1.6)	0.043	16.9 (1.8)
Infant (3 mo to 1 y)	3 (0.5%)	0 (0%)	0.15	3 (0.3%)
Children (1-12 y)	12 (2.0%)	0 (0%)	0.004	12 (1.2%)
Adolescent (12-18 y)	581 (97.5%)	409 (100%)	0.001	990 (98.5%)
Gender			0.5	
Male	550 (92.3%)	382 (93.4%)		932 (92.7%)
Female	46 (7.7%)	27 (6.6%)		73 (7.3%)
Discharge specialty			<0.001	
Pediatric surgery	14 (2.3%)	27 (6.6%)	0.002	41 (4.1%)
Pulmonology	105 (17.6%)	10 (2.4%)	<0.001	115 (11.4%)
Thoracic surgery	199 (33.4%)	306 (74.8%)	<0.001	505 (50.2%)
Pediatrics	150 (25.2%)	19 (4.6%)	<0.001	169 (16.8%)
Surgery	72 (12.4%)	26 (6.4%)	0.001	100 (10%)
Total hospital day	4.6 ± 4.02	7.06 ± 3.88	<0.001	5.60 ± 2.00
ICU day	0.27 ± 0.97	0.23 ± 0.95	0.57	0.25 ± 0.96
Hospital level			0.08	
Local hospital	67 (11.2%)	39 (9.5%)	0.382	106 (10.5%)
Regional hospital	266 (44.6%)	160 (39.1%)	0.082	426 (42.4%)
Medical center	263 (44.1%)	210 (51.3%)	0.025	473 (47.1%)
Region of the hospital[c]			0.008	
Middle	133 (22.3%)	99 (24.2%)	0.485	232 (23.1%)
North	116 (19.5%)	55 (13.4%)	0.009	171 (17%)
Taipei	194 (32.6%)	141 (34.5%)	0.531	335 (33.3%)
East	15 (2.5%)	4 (1%)	0.064	19 (1.9%)
South	59 (9.9%)	63 (15.4%)	0.011	122 (12.1%)
Kaohsiung/Pingtung	79 (13.3%)	47 (11.5%)	0.392	126 (12.5%)
Emphysematous bleb	6 (1%)	32 (7.8%)	<0.001	38 (3.8%)

Data are presented as mean ± SD in continuous variables and number (ratio) in nominal variables, except age.

ICU = intensive care unit.

[a]Compare between pleurodesis group and nonpleurodesis group.

[b]Data are presented as median (interquartile range), and *p* value was compared between pleurodesis and nonpleurodesis groups via Mann-Whitney *U* test.

[c]The region of the hospital is defined by the region of the insurance bureau and divisions.

noted in the pleurodesis group. More hospitalizations associated with emphysematous bleb were observed in the pleurodesis group (pleurodesis vs non-pleurodesis, 7.8% vs 1.0%, $p < 0.001$; Tables 1 and 2).

Within 1 year, 97 (16.3%) hospitalization cases had recurrence in the nonpleurodesis group, whereas 38 (9.3%) had recurrence in the pleurodesis group ($p = 0.001$). Furthermore, 85 (14.3%) cases required surgical intervention for pneumothorax in the nonpleurodesis group compared with 20 (4.9%) cases in the pleurodesis group ($p < 0.001$). Using the Kaplan-Meier curve, less PSP recurrence (log-rank test, $p = 0.001$) and less need for subsequent surgery (log-rank test, $p < 0.001$) were found in the pleurodesis group (Fig. 1).

3.3. Analysis of risk factors for the recurrence of pneumothorax

Using the univariate Cox regression analysis, some factors were found to significantly influence the recurrence of PSP. A discharge specialty of thoracic surgery had a trend of less recurrence (HR, 0.70; 95% CI, 0.50-0.99). There was no difference in time to recurrence between surgical specialties and nonsurgical specialties or between pediatric specialties and nonpediatric specialties. There was a higher incidence of recurrence in East Taiwan (HR, 2.86; 95% CI, 1.10-7.43). A tremendously lesser incidence of recurrence was observed when a patient underwent thoracoscopic operation (HR, 0.46; 95% CI, 0.32-0.67) for pneumothorax compared with patients who had not undergone surgical intervention; however, undergoing nonthoracoscopic operation for pneumothorax had no beneficial effect on recurrence. Pleurodesis significantly reduced the incidence of recurrence (HR, 0.53; 95% CI, 0.37-0.78), but there was no difference with regard to intrapleural minocycline use. No differences in recurrence were noted among the different hospital levels, including local hospitals, regional hospitals, and medical centers. Undergoing tube thoracotomy or thoracocentesis did not affect the recurrence of PSP. Moreover, the duration of hospitalization, ICU stay, or oxygen use had no influence on recurrence. The presence of emphysematous bleb did not affect PSP recurrence as well (Table 3).

In the multivariate Cox regression model, we included factors such as age, sex, thoracic surgery as discharge specialty, regions of hospitals, and pleurodesis. We did not include operation for pneumothorax due to its high correlation with pleurodesis ($r > 0.8$). Only pleurodesis remained a significant factor reducing the recurrence of PSP after multivariate analysis (adjusted HR, 0.57; 95% CI, 0.38-0.86).

3.4. Analysis of risk factors for proceeding to surgery for pneumothorax

Through the univariate Cox regression analysis, several factors were identified that significantly influenced the need for further surgical intervention after PSP diagnosis. Longer hospitalization contributed to less surgery in the following period (HR, 0.91; 95% CI, 0.85-0.97). Thoracoscopic operation for pneumothorax reduced the possibility of further surgical intervention (HR, 0.29; 95% CI, 0.18-0.47), but not the open surgery for PSP. Pleurodesis also prolonged the time to next surgery (HR, 0.32; 95% CI, 0.20-0.52) and so did intrapleural minocycline use (HR, 0.24; 95% CI, 0.08-0.75). There is no difference with regard to age, sex, specialty of discharge, duration of ICU stay and oxygen use, hospital level, region of the hospital, thoracocentesis, tube thoracotomy, or the presence of emphysematous bleb (Table 4).

In the multivariate Cox regression model, we selected the following factors: age, sex, hospitalization day, intrapleural minocycline use, and pleurodesis. We did not include thoracoscopic

Table 2

Treatment and outcome of patients receiving pleurodesis or not

	Nonpleurodesis (n = 596)	Pleurodesis (n = 409)	p^a	Total
Thoracoscopic surgery			<0.001	
No operation	537 (90.1%)	8 (2%)	<0.001	545 (54.2%)
Thoracoscopic operation	54 (9.1%)	393 (96.1%)	<0.001	447 (44.5%)
Not thoracoscopic operation	5 (0.8%)	8 (2%)	0.126	13 (1.3%)
Oxygen day	2.36 ± 2.56	2.34 ± 2.86	0.93	2.35 ± 2.69
Intrapleural minocycline use	0 (0%)	109 (26.7%)	<0.001	109 (10.8%)
Thoracocentesis	40 (6.7%)	8 (2%)	0.001	48 (4.8%)
Tube thoracotomy	316 (53%)	390 (95.4%)	<0.001	706 (70.2%)
Next recurrence	97 (16.3%)	38 (9.3%)	0.001	135 (13.4%)
Next surgery	85 (14.3%)	20 (4.9%)	<0.001	105 (10.4%)
Recurrence-free day	311.2 ± 5.6	339.2 ± 5.5	0.001	159.1 ± 104.4
Surgery-free day	318.7 ± 5.3	356.2 ± 4.1	<0.001	162.3 ± 104.4

Data are presented as mean ± SD in continuous variables and number (ratio) in nominal variable.
[a]Compare between pleurodesis group and nonpleurodesis group.

operation for pneumothorax, due to its high correlation to pleurodesis. Only pleurodesis significantly reduced the possibility of further surgical intervention after multivariate analysis (adjusted HR, 0.40; 95% CI, 0.23-0.69).

4. DISCUSSION

This study is one of the large nationwide database analyses on the management of PSP in the pediatric population. We analyzed the hospitalizations due to PSP in 2010 among patients under the age of 19 years who were admitted to the ICU, comprising mostly adolescents with an extremely male predominance similar to previous epidemiology reports and reviews.[1,8,26–28] Our first major finding is that pleurodesis can not only decrease the recurrence of PSP but also reduce the need for further surgical intervention. Additionally, the thoracoscopic operation for PSP can reduce recurrence and the need for subsequent surgery, but not the nonthoracoscopic operation for PSP. The recurrence of PSP or the need for subsequent surgery will not be affected whether emphysematous blebs or bullae are detected or not. Moreover, hospitalizations to the surgical versus nonsurgical team or pediatric versus nonpediatric team showed no difference in PSP recurrence or the need for further surgical intervention.

For decades, to prevent the high recurrence rate of PSP, clinicians developed several management methods varying from oxygen inhalation, simple aspiration, and closed-tube drainage to invasive strategies. Pleurodesis emerged as one of the promising methods. Since the 1980s, a randomized trial comparing simple aspiration, tube drainage with talc pleurodesis, and tube drainage with tetracycline pleurodesis showed that adjunctive pleurodesis groups had less recurrence rates than simple drainage groups.[9] Chemical pleurodesis alone, a less invasive method for decreasing PSP recurrence, had become an alternative treatment to surgery and can even be conveniently performed in an outpatient setting. Although chemical pleurodesis reduced the recurrence rate compared with tube thoracotomy only, the incidence of recurrence was still higher than that among patients who underwent surgery.[10] Moreover, a randomized controlled study by Chen et al.[18] demonstrated that simple aspiration and drainage followed by minocycline pleurodesis is a safer and more effective treatment than simple aspiration and drainage alone. A German retrospective study showed that video-assisted thoracoscopic surgery (VATS) with additional mechanical pleurodesis decreased the recurrence rate compared with VATS alone and had no additional disadvantages and worsening postoperative symptoms reported.[12] Due to the fact that pleurodesis is less effective than surgery in reducing recurrence, it remained only as an adjunctive therapy for pneumothorax among adult patients.[12–14,16,19,29] However, a Korean study showed that the recurrence rate after wedge resection in patients aged ≤16 years was much higher than that in older patients, which meant that surgery was less effective in preventing recurrence in the pediatric group than in adults.[8] Consequently, the only retrospective pediatric study on pleurodesis we could find was that by Bialas et al.[20] who concluded that VATS with blebectomy plus chemical pleurodesis appeared to have a low risk of ipsilateral recurrence among patients aged 13 to 20 years. Nevertheless, neither the British Thoracic Society nor the American College of Chest Physicians guideline had recommendations about pleurodesis, especially for pediatric patients.[30,31] Our study confirmed the

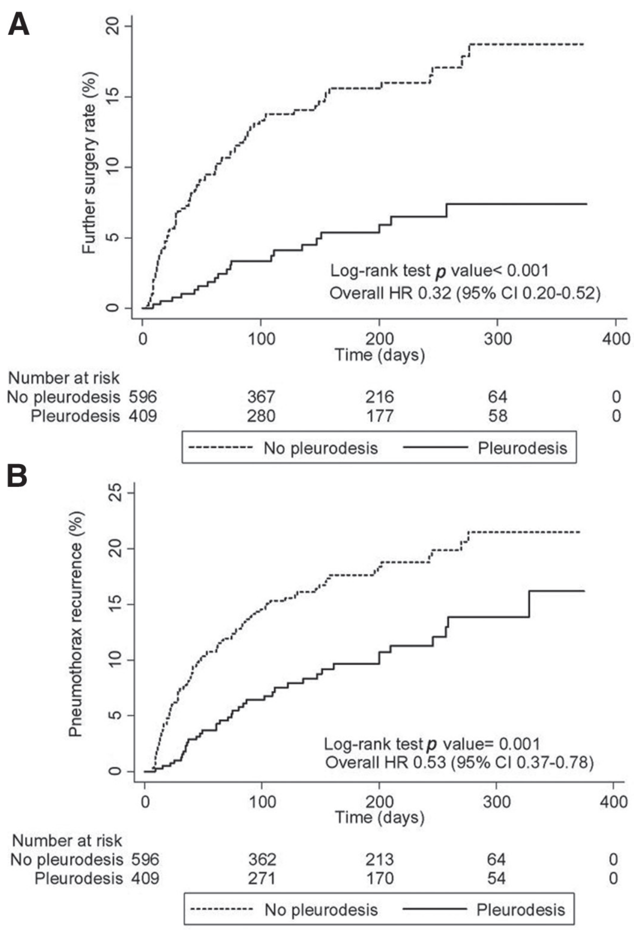

Fig. 1 A, Kaplan-Meier curves of free from pneumothorax recurrence in the pleurodesis vs nonpleurodesis group. Overall = 365 d. B, Kaplan-Meier curves of free from surgery for primary spontaneous pneumothorax in the pleurodesis vs nonpleurodesis group. Overall = 365 d. HR = hazard ratio.

Table 3

Univariate and multivariate Cox regression analysis for recurrence

	Univariate		Multivariate	
Variable	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Age	0.98 (0.91-1.05)	0.502	0.99 (0.92-1.06)	0.690
Gender(male vs female)	1.58 (0.74-3.38)	0.240	1.71 (0.78-3.73)	0.177
Discharge specialty				
Pulmonology	1.08 (0.63-1.84)	0.789		
Thoracic surgery	0.70 (0.50-0.99)	0.042	0.95 (0.30-2.98)	0.930
Pediatrics	1.03 (0.66-1.60)	0.891		
Pediatric surgery	1.48 (0.73-3.03)	0.279		
Surgery	1.34 (0.80-2.22)	0.263		
Nonsurgery vs surgery	1.13 (0.79-1.63)	0.496		
Pediatric vs nonpediatric	1.13 (0.76-1.69)	0.534		
Total hospitalization day	0.95 (0.90-1.00)	0.057		
ICU day	0.96 (0.79-1.16)	0.685		
Hospital level				
Medical center	1			
Local hospital	1.07 (0.61-1.87)	0.825		
Regional hospital	1.02 (0.71-1.46)	0.917		
Region of the hospital				
Kaohsiung/Pingtung	1		1	
North	0.87 (0.43-1.76)	0.696	0.73 (0.36-1.50)	0.394
Taipei	1.40 (0.77-2.52)	0.270	1.42 (0.78-2.56)	0.250
Middle	1.06 (0.56-2.01)	0.860	1.01 (0.53-1.93)	0.977
East	2.86 (1.10-7.43)	0.032	2.20 (0.83-5.83)	0.114
South	1.38 (0.69-2.75)	0.363	1.63 (0.81-3.29)	0.175
Thoracoscopic surgery[a]				
No operation	1			
Thoracoscopic operation	0.46 (0.32-0.67)	<0.001		
Not thoracoscopic operation	0.35 (0.05-2.54)	0.302		
Oxygen day	0.96 (0.90-1.03)	0.220		
Intrapleural minocycline use[b]	0.51 (0.25-1.05)	0.067		
Pleurodesis[b]	0.53 (0.37-0.78)	0.001	0.57 (0.38-0.86)	0.008
Thoracocentesis[b]	0.72 (0.29-1.75)	0.462		
Tube thoracotomy[b]	0.89 (0.62-1.29)	0.546		
Emphysematous bleb[c]	0.91 (0.37-2.23)	0.844		

HR = hazard ratio; ICU = intensive care unit.

[a]In multivariate model, pleurodesis had high correlation to operation for pneumothorax ($r > 0.8$). Only pleurodesis remained a significant factor after multivariate analysis ($p = 0.008$).

[b]Use vs not use.

[c]Presented vs not presented.

importance of pleurodesis in decreasing PSP recurrence rate and the need for subsequent operation in pediatric patients.

In the past decades, open thoracotomy with pleurectomy was the mainstay of treatment for PSP. As conventional operation is highly invasive, VATS pleurectomy was developed and became the most common and definite treatment for PSP in adults. However, open thoracotomy with pleurectomy remains the procedure with the lowest recurrence rate according to the consensus and the recent guideline for adults.[30,31] Moreover, Barker et al.[32] gathered randomized controlled trial data in adult patients for analysis and concluded that thoracoscopic surgery with pleurodesis had a four times higher recurrence rate than the open procedure. However, Vohra et al.[33] conducted a meta-analysis demonstrating that VATS pleurectomy resulted in shorter hospital stay, less analgesic requirements, decreased postoperative pulmonary dysfunction, and a similar recurrence rate compared to open pleurectomy. Although there exist several studies among the adult population, there are only a few pediatric studies comparing the effect of pleurectomy between VATS and open thoracotomy. In our study, thoracoscopic operation for pneumothorax reduced the incidence of recurrence and the need for subsequent surgery significantly, but conventional open surgery did not. Notably, this is the first study demonstrating that VATS operation had superior results in terms of recurrence in comparison with open surgery in the pediatric population. Thus, if surgical treatment is indicated, we suggest thoracoscopic surgery instead of open surgery.

For years, surgeons have been searching for a strong and reliable predictor of PSP recurrence, which can be used as an indication for primary VATS pleurectomy although surgery is recommended only when PSP recurs or air leak persists after tube thoracotomy according to the guideline.[1,30,31] Blebs and bullae frequently occur in patients with SP.[34] On computed tomographic (CT) images, they are termed as emphysema-like changes (ELCs). In adults, several studies showed that ELCs detected by CT or thoracotomy have no predictive value on pneumothorax recurrence, except one study that revealed increased ipsilateral recurrence or contralateral PSP.[5,9,34–36] We demonstrated that emphysematous blebs have no significant influence on recurrence and reoperation in pediatric patients.

There is no difference in PSP recurrence and further need for PSP surgery between different regions or different hospital levels in our study. Although almost 50% of the hospitalizations occurred in medical centers in the northern part of Taiwan, the recurrence rate and subsequent surgical rate did not correlate to the volume of patients. Even though there is quite a small volume of patients in the eastern part of Taiwan (1.9%) and in local hospitals (10.5%), there is no significant difference in clinical outcome by multivariate Cox regression analysis, indicating that pediatric PSP can be treated adequately at every hospital level and region in Taiwan.

Although this study is one of the largest pediatric PSP studies and also one of the nationwide population-based studies exclusively focusing on the pediatric population, there are a

Table 4

Univariate and multivariate Cox regression analysis for need for next surgery

	Univariate		Multivariate	
Variable	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Age	1.00 (0.91-1.10)	0.953	1.00 (0.91-1.11)	0.930
Gender(male vs female)	1.71 (0.70-4.19)	0.244	1.74 (0.70-4.32)	0.233
Discharge specialty				
Pulmonology	1.21 (0.67-2.16)	0.528		
Thoracic surgery	0.75 (0.51-1.10)	0.135		
Pediatrics	0.98 (0.59-1.63)	0.940		
Pediatric surgery	1.43 (0.63-3.27)	0.393		
Surgery	1.04 (0.56-1.94)	0.900		
Nonsurgery vs surgery	1.15 (0.76-1.73)	0.511		
Pediatric vs nonpediatric	1.08 (0.68-1.70)	0.751		
Total hospital day	0.91 (0.85-0.97)	0.006	0.96 (0.90-1.03)	0.230
ICU day	0.91 (0.71-1.16)	0.433		
Hospital level				
Medical center	1			
Local hospital	1.26 (0.70-2.28)	0.446		
Regional hospital	0.92 (0.61-1.39)	0.695		
Region of the hospital				
Kaohsiung/Pingtung	1			
North	1.29 (0.57-2.92)	0.539		
Taipei	1.71 (0.83-3.52)	0.147		
Middle	1.30 (0.60-2.83)	0.504		
East	2.92 (0.90-9.47)	0.075		
South	1.60 (0.69-3.69)	0.273		
Thoracoscopic surgery[a]				
No operation	1			
Thoracoscopic operation	0.29 (0.18-0.47)	<0.001		
Not thoracoscopic operation	0.42 (0.06-3.02)	0.389		
Oxygen day	0.95 (0.88-1.03)	0.219		
Intrapleural minocycline use[b]	0.24 (0.08-0.75)	0.014	0.51 (0.15-1.73)	0.279
Pleurodesis[b]	0.32 (0.20-0.52)	<0.001	0.40 (0.23-0.69)	0.001
Thoracocentesis[b]	0.95 (0.39-2.33)	0.911		
Tube thoracotomy[b]	0.77 (0.52-1.15)	0.206		
Emphysematous bleb[c]	0.71 (0.22-2.23)	0.553		

HR = hazard ratio; ICU = intensive care unit.

[a]In multivariate model, pleurodesis had high correlation to operation for pneumothorax. Only pleurodesis remained a significant factor after multivariate analysis ($p = 0.001$).

[b]Use vs not use.

[c]Presented vs not presented.

few limitations to be acknowledged. First, we used a selected NHIRD database that consisted of the total patient population aged <19 years in 2010, who were admitted to the pediatric ICU. Selection bias, however, cannot be avoided. Moreover, the insurance database does not provide the results of diagnostic exams. Diagnosis codes were our only diagnostic criteria for pneumothorax. To avoid overdiagnosis of pneumothorax from the outpatient department and emergency room, we analyzed hospitalized patient data exclusively. This may also result in underestimation of the actual incidence and recurrence rate. Second, most of the follow-up periods were <1 year. A short follow-up period resulted in a lower recurrence rate compared with other studies. Lastly, there is a large difference in the demographic data between the pleurodesis and control groups. This is a retrospective study, so we used multivariate Cox regression analysis to adjust for baseline differences.

In conclusion, this study demonstrated that pleurodesis decreases the recurrence rate and the need for subsequent surgical intervention among pediatric patients with PSP. Thus, pleurodesis may be considered as an adjunctive therapy to standard treatment for pediatric PSP.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1097/JCMA.0000000000000073.

REFERENCES

1. Sahn SA, Heffner JE. Spontaneous pneumothorax. *N Engl J Med* 2000;**342**:868–74.
2. Gupta D, Hansell A, Nichols T, Duong T, Ayres JG, Strachan D. Epidemiology of pneumothorax in England. *Thorax* 2000;**55**:666–71.
3. Melton LJ 3rd, Hepper NG, Offord KP. Incidence of spontaneous pneumothorax in Olmsted County, Minnesota: 1950 to 1974. *Am Rev Respir Dis* 1979;**120**:1379–82.
4. Dotson K, Timm N, Gittelman M. Is spontaneous pneumothorax really a pediatric problem? A national perspective. *Pediatr Emerg Care* 2012;**28**:340–4.
5. Schramel FMNH, Postmus PE, Vanderschueren RGJRA. Current aspects of spontaneous pneumothorax. *Eur Respir J* 1997;**10**:1372–9.
6. Seguier-Lipszyc E, Elizur A, Klin B, Vaiman M, Lotan G. Management of primary spontaneous pneumothorax in children. *Clinical Pediatrics* 2011;**50**:797–802.

7. Butterworth SA BG, LeBlanc JG, Skarsgard ED. An open and shut case for early VATS treatment of primary spontaneous pneumothorax in children. *Can J Surg* 2007;**50**:171–4.
8. Noh D, Lee S, Haam SJ, Paik HC, Lee DY. Recurrence of primary spontaneous pneumothorax in young adults and children. *Interact Cardiovasc Thorac Surg* 2015;**21**:195–9.
9. Almind M, Lange P, Viskum K. Spontaneous pneumothorax: comparison of simple drainage, talc pleurodesis, and tetracycline pleurodesis. *Thorax* 1989;**44**:627–30.
10. Alfageme I, Moreno L, Huertas C, Vargas A, Hernandez J, Beiztegui A. Spontaneous Pneumothorax. *Chest* 1994;**106**:347–50.
11. Schramel FM, Sutedja TG, Janssen JP, Cuesta MA, van Mourik JC, Postmus PE. Prognostic factors in patients with spontaneous pneumothorax treated with video-assisted thoracoscopy. *Diagn Ther Endosc* 1995;**2**:1–5.
12. Horio H, Nomori H, Kobayashi R, Naruke T, Suemasu K. Impact of additional pleurodesis in video-assisted thoracoscopic bullectomy for primary spontaneous pneumothorax. *Surg Endosc* 2002;**16**:630–4.
13. Chen JS, Hsu HH, Kuo SW, Tsai PR, Chen RJ, Lee JM, et al. Effects of additional minocycline pleurodesis after thoracoscopic procedures for primary spontaneous pneumothorax. *Chest* 2004;**125**:50–5.
14. Chen JS, Hsu HH, Chen RJ, Kuo SW, Huang PM, Tsai PR, et al. Additional minocycline pleurodesis after thoracoscopic surgery for primary spontaneous pneumothorax. *Am J Respir Crit Care Med* 2006;**173**:548–54.
15. Alayouty HD, Hasan TM, Alhadad ZA, Omar Barabba R. Mechanical versus chemical pleurodesis for management of primary spontaneous pneumothorax evaluated with thoracic echography. *Interact Cardiovasc Thorac Surg* 2011;**13**:475–9.
16. Chen JS, Hsu HH, Huang PM, Kuo SW, Lin MW, Chang CC, et al. Thoracoscopic pleurodesis for primary spontaneous pneumothorax with high recurrence risk: a prospective randomized trial. *Ann Surg* 2012;**255**:440–5.
17. Moreno-Merino S, Congregado M, Gallardo G, Jimenez-Merchan R, Trivino A, Cozar F, et al. Comparative study of talc poudrage versus pleural abrasion for the treatment of primary spontaneous pneumothorax. *Interact Cardiovasc Thorac Surg* 2012;**15**:81–5.
18. Chen JS, Chan WK, Tsai KT, Hsu HH, Lin CY, Yuan A, et al. Simple aspiration and drainage and intrapleural minocycline pleurodesis versus simple aspiration and drainage for the initial treatment of primary spontaneous pneumothorax: an open-label, parallel-group, prospective, randomised, controlled trial. *Lancet* 2013;**381**:1277–82.
19. Sepehripour AH, Nasir A, Shah R. Does mechanical pleurodesis result in better outcomes than chemical pleurodesis for recurrent primary spontaneous pneumothorax? *Interact Cardiovasc Thorac Surg* 2012;**14**:307–11.
20. Bialas RC, Weiner TM, Phillips JD. Video-assisted thoracic surgery for primary spontaneous pneumothorax in children: is there an optimal technique? *J Pediatr Surg* 2008;**43**:2151–5.
21. Chang LY, Chang IS, Lu CY, Chiang BL, Lee CY, Chen PJ, et al. Epidemiologic features of Kawasaki disease in Taiwan, 1996–2002. *Pediatrics* 2004;**114**:e678–82.
22. Chen CY, Liu CY, Su WC, Huang SL, Lin KM. Factors associated with the diagnosis of neurodevelopmental disorders: a population-based longitudinal study. *Pediatrics* 2007;**119**:e435–43.
23. Liao P, Ku M, Lue K, Sun H. Respiratory tract infection is the major cause of the ambulatory visits in children. *Ital J Pediatr* 2011;**37**:43.
24. Jeng MJ, Lee YS, Tsao PC, Yang CF, Luo YC, Soong WJ. A 10-year population-based nationwide descriptive analysis of pediatric emergency care. *BMC Pediatrics* 2014;**14**:100–8
25. Chen JS, Chan WK, Yang PC. Pleurodesis for primary spontaneous pneumothorax – Authors' reply. *Lancet* 2013;**382**:203–4.
26. Dotson K, Johnson LH. Pediatric spontaneous pneumothorax. *Pediatr Emerg Care* 2012;**28**:715–20.
27. Robinson PD, Cooper P, Ranganathan SC. Evidence-based management of paediatric primary spontaneous pneumothorax. *Paediatr Respir Rev* 2009;**10**:110–7.
28. Bobbio A, Dechartres A, Bouam S, Damotte D, Rabbat A, Regnard JF, et al. Epidemiology of spontaneous pneumothorax: gender-related differences. *Thorax* 2015;**70**:653–8.
29. Chen JS, Chan WK, Yang PC. Intrapleural minocycline pleurodesis for the treatment of primary spontaneous pneumothorax. *Curr Opin Pulm Med* 2014;**20**:371–6.
30. MacDuff A, Arnold A, Harvey J, BTS Pleural Disease Guideline Group. Management of spontaneous pneumothorax: British Thoracic Society Pleural Disease Guideline 2010. *Thorax*. 2010;**65**(Suppl 2):ii18–31.
31. Baumann MH, Strange C, Heffner JE, Light R, Kirby TJ, Klein J, et al. Management of spontaneous pneumothorax: An American College of Chest Physicians Delphi Consensus Statement. *Chest* 2001; **119**:590–602.
32. Barker A, Maratos EC, Edmonds L, Lim E. Recurrence rates of video-assisted thoracoscopic versus open surgery in the prevention of recurrent pneumothoraces: a systematic review of randomised and non-randomised trials. *Lancet* 2007;**370**:329–35.
33. Vohra HA, Adamson L, Weeden DF. Does video-assisted thoracoscopic pleurectomy result in better outcomes than open pleurectomy for primary spontaneous pneumothorax? *Interact Cardiovasc Thorac Surg* 2008;**7**:673–7.
34. Jordan KG, Kwong JS, Flint J, Muller NL. Surgically treated pneumothorax. Radiologic and pathologic findings. *Chest* 1997;**111**:280–5.
35. Casali C, Stefani A, Ligabue G, Natali P, Aramini B, Torricelli P, et al. Role of blebs and bullae detected by high-resolution computed tomography and recurrent spontaneous pneumothorax. *Ann Thorac Surg* 2013;**95**:249–55.
36. Ganesalingam R, O'Neil RA, Shadbolt B, Tharion J. Radiological predictors of recurrent primary spontaneous pneumothorax following nonsurgical management. *Heart Lung Circ* 2010;**19**:606–10.