Male Adolescents with Contralateral Blebs Undergoing Surgery for Primary Spontaneous Pneumothorax May Benefit from Simultaneous Contralateral Blebectomy

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Research article

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Abstract

Background: In adults with primary spontaneous pneumothorax (PSP), contralateral recurrence occurs in about 25-28% when there are asymptomatic blebs. How to treat contralateral recurrence of PSP in pediatric populations remains controversial. This study evaluated the outcomes of excising contralateral blebs to prevent recurrence in adolescents being operated on for PSP under the same anesthesia.

Methods: One hundred thirty-two male PSP patients under age 19 were surgically treated in a single institution between January 2008 and December 2016. Thoracoscopic blebectomies with pleurodesis were performed in all patients. For the purpose of this study, the patients were categorized into those with contralateral blebs receiving one-stage bilateral surgeries (32 patients), those with contralateral blebs only receiving unilateral surgery (40 patients), and those without contralateral blebs only receiving unilateral surgery (60 patients). Perioperative details and postoperative outcomes were retrospectively analyzed.

Results: Significant differences in contralateral recurrence were found among the three groups (0%, 30%, and 1%, respectively; $P < 0.001$). Multivariate analysis showed that being under 16.5 years old was a risk factor for overall recurrence (hazard ratio [HR]=2.81, $P = 0.034$). Moreover, patients had contralateral blebs who only received unilateral surgery were at greater risk of overall recurrence (HR=6.06, $P = 0.004$). Kaplan-Meier analysis showed that contralateral and overall recurrence-free survival differed among the three groups ($P < 0.0001$, $P = 0.0002$).

Conclusions: Although younger male PSP adolescents treated with surgery were more likely to have postoperative recurrences, the performance of simultaneous contralateral blebectomy in those receiving one-stage bilateral surgeries significantly reduced future contralateral recurrence without compromising patient safety.

Introduction

Primary spontaneous pneumothorax (PSP) most often affects healthy young males. While the reported annual incidence of PSP is approximately 21 cases per 100,000 adults [1], that incidence is 3.4 per 100,000 in pediatric populations, peaking between 14 and 17 years of age, mainly in late adolescents [2]. Recurrence has always been a serious problem associated with PSP, yet it remains unclear what factors predispose its recurrence in adolescents and how it can best be managed surgically. There are probably multiple factors that lead to the recurrence in PSP. One widely-accepted risk factor is the rupture of pulmonary blebs or bullae, and so the presence of these air-containing lesions on high-resolution computed tomography (HRCT) is regarded as a potential predictor and has been investigated extensively [3–5].

Currently, the management of PSP in children is largely based on adult data. A few studies using early video-assisted thoracic surgery (VATS) bullectomy and mechanical pleurodesis for pediatric PSP have reported that children undergoing this surgery have less ipsilateral recurrence than those not receiving

operative treatment [6–8]. However, it is not clear how to best manage contralateral recurrence in pediatric patients. Ciriaco et al. recommended that VATS be reserved only for the affected side [8]. According to Soccorso and colleagues, CT scans revealed that 20% (10/49) of the pediatric patients with PSP they studied had asymptomatic contralateral blebs/bullae. Among those with the blebs, 40% developed pneumothorax within six months [9]. Some studies of adult PSP report that asymptomatic contralateral blebs put them at 25–28% risk of future spontaneous pneumothorax [3, 10–12].

Surgery seems to be the most effective method of preventing recurrence. Previously, our excisions of contralateral blebs significantly lowered contralateral recurrence in adult patients receiving operations for ipsilateral PSP [13]. However, it is not known whether the performance of prophylactic blebectomy in pediatric patients with asymptomatic contralateral blebs would have similar benefits. Therefore, we performed a retrospective cohort study to analyze the relevant risk factors for ipsilateral, contralateral, and overall recurrences and outcomes in male adolescent patients surgically treated for PSP during a nine-year period at our medical center. We divided our patient population into those with contralateral blebs receiving one-stage bilateral surgeries (B + cb) and those with contralateral blebs only receiving unilateral surgery (U + cb) as well as those without contralateral blebs only receiving unilateral surgery (U-cb).

Material And Methods

Study design

This retrospective cohort study was conducted from January 2008 to December 2016 at a single medical center. The Institutional Review Board of Kaohsiung Medical University Hospital approved this study and waived the requirement for written informed consent (KMUHIRB-E(I)-20190158). We included data for 155 patients aged under 19 years who underwent surgery for PSP. We excluded female patients (n = 12), those with concurrent bilateral PSP (n = 5), and those who did not having preoperative chest HRCT on file (n = 6). The female patients were excluded to rule out the possibility of catamenial pneumothorax and to obtain a homogenous analysis, as the population most affected by PSP are male adolescents. After exclusion, patients were classified into three groups, those with contralateral blebs receiving one-stage bilateral surgeries (B + cb) and those with contralateral blebs only receiving unilateral surgery (U + cb) as well as those without contralateral blebs only receiving unilateral surgery (U-cb) (Fig. 1).

Based on professional guidelines and scientific studies on the management of adult PSP [10, 14–19], we held surgical indications that predominantly included recurrent ipsilateral PSP, persistent air leaks (> 3 days) after chest tube drainage, and PSP at the first attack exhibiting ipsilateral and/or contralateral blebs on HRCT. We collected patient characteristic data including age, height, weight, body mass index (BMI), smoking habit, perioperative data, and length of hospital stays as well as postoperative recurrence. HRCTs were conducted at the time the patients were hospitalized after the affected lung expansion and interpreted by the radiologist and thoracic surgeon together to determine whether or not the patients had blebs/bullae. As reported in our previous study [4, 13], if HRCTs indicated that the patients had

contralateral blebs, we fully explained their ailments to them and their guardians. In these cases, we bring up the possibility of performing contralateral VATS while carrying out the unilateral PSP operation without trying to persuade the guardians one way or another. Rejection or acceptance of the contralateral preventive surgery is decided solely by the patient and their guardians.

Operative procedure and postoperative follow-up

In the 132 patients in this study, all VATS blebectomies or bullectomies with mechanical pleurodesis are performed by board-certified thoracic surgeons using 2-port or uniportal method as previously described [13]. For patients without obvious ipsilateral blebs/bullae showing on preoperative HRCT, we empirically performed apical wedge resection followed by pleurodesis in these cases if no air leaks were detected intraoperatively. All patients were advised to seek help in the event of any discomfort or suspicious symptoms of recurrence in addition to regular outpatient clinic follow-up with a 3-month interval during the first two year. Chest x-rays or even HRCT were performed for diagnosis of recurrent pneumothorax if the aforementioned condition developed at any time during follow-up. The patients were also followed up via electronic medical records and telephone interviews in May 2020 to determine the cumulative incidence of recurrence.

Statistical Analysis

Descriptive variables were expressed as numbers with percentages and continuous variables were described by means with standard deviation or medians with interquartile range (IQR). Continuous variables were compared using analysis of variance (ANOVA) or Kruskal-Wallis test and descriptive variables were compared using the Chi-square test. Multivariate analyses involved a backward elimination method. Only variables with a P-value less than < 0.10 were used in the final model. In addition, we also used Cox proportional hazard model to identify multivariable risk factors for different recurrence patterns. Cumulative incidence of recurrence and follow-up times were calculated from the date of surgery to the first event of recurrence and analyzed by the Kaplan-Meier method. Log-rank test was used to examine the differences between treatment groups. All statistical operations were performed using the SAS® 9.4 software (SAS Institute Inc., Cary, NC, USA) for Windows. A P-value less than 0.05 was considered significant.

Results

In total, we enrolled 132 male adolescents with PSP who had received VATS blebectomies with mechanical pleurodesis, had complete preoperative HRCT examination on file, and were followed up postoperatively during the 9-year period (2008–2016). Thirty-two patients belonged to group B + cb, 40 to group U + cb, and 60 to group U-cb. There were no significant differences in age, height, weight, BMI, or smoking among the three groups (Table 1). Figure 2 shows the age distribution of the three groups stratified by 0.5 using box plot analysis. Group B + cb had significantly longer operative times and the higher postoperative pain scores (both $P < 0.001$) (Table 1). However, there was no significant difference in length of hospital stay and complications among the three groups (Table 1). Furthermore, the most

frequent complication was persistent air leakage (persisting for > 7 days postoperatively), followed by pneumonia and wound infection. There was no need to re-operate for any of these complications. The percentage of contralateral recurrence for groups B + cb, U + cb, and U-cb were 0%, 30%, and 1.6%, respectively (Table 1). Notably, the percentage for group U + cb was significantly higher than that of the other 2 groups ($P < 0.001$). Nineteen patients in total had ipsilateral recurrences, twelve of whom had reoperations (thoracoscopic wedge resection of the postoperative bullae neogenesis), two chest tube drainage, and five were left for further observation. Thirteen patients in total had contralateral recurrences, for which they all received VATS blebectomies and pleurodesis. There were significant differences in follow-up periods ($P = 0.002$), concordant with the overall recurrence ($P < 0.001$). Group U + cb had highest number of recurrences and the shortest follow-up periods.

Table 1
Patient characteristics with perioperative data

	B + cb (n = 32)	U + cb (n = 40)	U-cb (n = 60)	p value
Age (mean ± SD) (y)	17.4 ± 1.0	17.0 ± 1.0	16.9 ± 1.3	0.190
Height (mean ± SD) (cm)	175.3 ± 5.5	174.4 ± 6.2	174 ± 5.6	0.612
Weight (mean ± SD) (kg)	57.6 ± 9	56.8 ± 7.8	57.3 ± 8	0.917
BMI (mean ± SD) (kg/m ²)	18.7 ± 2.3	18.6 ± 2.1	18.9 ± 2.1	0.852
Smoking (yes), % (n)	19 (6)	8 (3)	10 (6)	0.296
Operative time (median with IQR) (min)	120 (110–120)	60 (50–65)	55 (50–65)	< 0.001
Blood loss (median with IQR) (ml)	25 (20-27.5)	10 (5–15)	10 (5–15)	0.835
Postoperative pain score (median with IQR)	5.5 (5-6.5)	5 (4–5)	4 (3.5-5)	< 0.001
Postoperative hospital stays (median with IQR) (d)	6 (5–7)	4 (4–6)	5 (4–6)	0.255
Follow-up (median with IQR) (mo)	92 (74–121)	51 (14–109)	80 (55–111)	0.002
Complication, % (n)	13 (4)	15 (6)	13 (8)	0.426
Overall recurrence, % (n)	9 (3)	45 (18)	18.3 (11)	< 0.001
Contralateral recurrence, % (n)	0 (0)	30 (12)	1.6 (1)	< 0.001
Ipsilateral recurrence, % (n)	9 (3)	15 (6)	16.7 (10)	
<i>SD</i> , standard deviation; <i>BMI</i> , Body Mass Index; <i>IQR</i> , interquartile range; <i>B + cb</i> , those with contralateral blebs receiving one-stage bilateral surgeries; <i>U + cb</i> , those with contralateral blebs only receiving unilateral surgery; <i>U-cb</i> , those without contralateral blebs only receiving unilateral surgery. Data are presented as % (n).				

As can be seen in Table 2, in both our univariable or multivariable analyses, only age and type of intervention were significant risk factors for overall recurrence. We could not assess risk for ipsilateral and contralateral recurrences due to the small number of sample sizes. In our multivariate analysis, the independent risk factors for overall recurrence were age < 16.5 years (Hazard ratio [HR]: 2.81, $P = 0.034$) and intervention group U + cb (HR: 6.06, $P = 0.004$). Figure 3 and Fig. 4 shows the contralateral and overall recurrence-free rate calculated using the Kaplan-Meier method and compared through the Log-rank test. Among patients with contralateral blebs, those treated with simultaneous excision of contralateral blebs (group B + cb) had significantly lower contralateral and overall recurrence than those only treated with

unilateral surgery (group U + cb) ($P < 0.0001$ and $P = 0.0002$, respectively). The ipsilateral recurrence-free rate was comparable among the three groups ($P = 0.498$) (Fig. 5).

Table 2
Risk of overall recurrence based on patient characteristics and types of intervention

	Overall recurrence, % (n)	Univariate analysis		Multivariable analysis	
		HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
Age (y)					
age < 16.5	34 (11/32)	2.86 [1.11–7.38]	0.030	2.81 [1.08–7.30]	0.034
16.5 ≤ age < 18	27 (14/52)	1.94 [0.78–4.82]	0.151	1.49 [0.60–3.74]	0.393
18 ≤ age < 19	15 (7/48)	Reference		Reference	
BMI (kg/m ²)					
≥ 18.5	30 (20/67)	Reference		Reference	
< 18.5	18 (12/65)	0.9 [0.45–1.81]	0.777	0.98 [0.49–1.97]	0.950
Smoking					
No	26 (31/117)	Reference		Reference	
Yes	7 (1/15)	0.22 [0.03–1.63]	0.139	0.35 [0.05–2.60]	0.303
Intervention					
B + cb	9 (3/32)	Reference		Reference	
U + cb	45 (18/40)	6.44 [1.89–21.93]	0.003	6.06 [1.77–20.75]	0.004
U-cb	18 (11/60)	2.11 [0.59–7.55]	0.253	1.81 [0.50–6.58]	0.365
<i>BMI</i> , Body Mass Index; <i>B + cb</i> , those with contralateral blebs receiving one-stage bilateral surgeries; <i>U + cb</i> , those with contralateral blebs only receiving unilateral surgery; <i>U-cb</i> , those without contralateral blebs only receiving unilateral surgery. Data are presented as % (n).					

Discussion

In this retrospective study of a nine-year period, 72 of 132 patients with unilateral PSP were found to have contralateral blebs by HRCT. The incidence (54.5%) in this study was comparable to the rate reported in the literature [3–5]. Studies disagree with regard to the predictability of a contralateral episode following

a first occurrence of PSP. Some have found an association between HRCT detection of blebs/bullae in the contralateral lung after ipsilateral PSP and higher risk of contralateral recurrence, three studies reporting 26%, 26.7%, and 25.8% [3, 10, 11]. According to one recent large retrospective cohort study of 1055 PSP patients reported by Jang and colleagues [12], the 5-year cumulative incidence of contralateral recurrence reached 28.2% for the contralateral asymptomatic blebs/bullae. In that study, the authors suggested that preemptive surgery be considered particularly in patients with multiple blebs/bullae.

We weighed the advantages and disadvantages of unilateral VATS and bilateral VATS in patients with and without contralateral blebs. Group B + cb had longer operative times and greater blood loss due to the need for sequential bilateral procedures performed under the same anesthesia as well as higher postoperative pain scores and longer hospital stays. Despite these differences, there was no significant differences in postoperative complications rates among the three groups. Consequently, we consider it is safe for physiologically fit male adolescents to receive one-stage bilateral operations. The patients and their guardians were satisfied with the outcomes in respect of the prevention of recurrence. In our patients in whom contralateral blebs were detected, group B + cb had significantly lower contralateral recurrence than group U + cb (0% vs. 30%, $P < 0.001$). Our results were comparable to those of the above-mentioned studies reporting recurrence rates of asymptomatic contralateral blebs/bullae ranging 25–28% [3, 10–12]. To the best of our knowledge, our study is the first to take evaluate risk of recurrence and long-term outcomes of simultaneous treatment of contralateral blebs with bilateral VATS for pediatric PSP, especially in a male adolescent population.

Although VATS blebectomies with pleurodesis for pediatric PSP has been found to produce similar treatment outcomes in young adult patients, ipsilateral recurrence seems to be more prevalent in adolescents than in young adults even after surgery [8, 20, 21]. Similarly, this study found the cumulative incidence of ipsilateral recurrence to be comparable among the three groups (9%, 15%, and 16.7%; respectively). The recurrence rate was, however, much higher than what we found in a previous study in young adults (7.1%, 8.1%, and 8.5%; respectively) [13].

Another controversial issue is the correlation between risk factors and pneumothorax recurrence. Factors such as younger age, gender, smoking, prolonged air leakage, low BMI, and HRCT detection of blebs/bullae have been associated with recurrence [22–25]. Cardillo et al. found smoking to be significantly associated with PSP recurrence [26]. Huang and colleagues found contralateral blebs/bullae and underweightness (BMI < 18.5) to be predictors of contralateral recurrence [3, 5]. Typically, PSP occurs in tall and thin young males with BMIs indicating underweightness [27]. In this series, we included only adolescents under 19 years old and excluded 12 female patients initially, making our findings more relevant to a homogenous population. In addition, we did not find smoking or lower BMI have any statistical difference with regard to recurrence risk. Only 11.3% (15/132 patients) of our male adolescent patients with PSP were smokers, which can be explained by the lower prevalence of smoking in pediatric population compared to adults [28]. Thus, although smoking might play a role in recurrence, it does not factor in as much in the development of recurrence in adolescent PSP.

In both our univariate and multivariate analyses, younger age (< 16.5 years) and intervention group U + cb were the independent risk factors for overall recurrence (Table 2), a result consistent with the finding of high incidence of recurrence in adolescents in a nationwide population-based study [29]. Physical development has been shown to differ in individuals of ages belonging to adolescent period. For individuals younger than 16 years, growth rates are higher than those in 17- or 18-years-olds and remain steady in individuals over the age of 19 years [20]. The rapid increase in the vertical dimension of the thorax compared with the horizontal dimension could produce an increase in negative intrathoracic pressure at the apex of lung, which may lead to formation of subpleural blebs/bullae that can induce PSP upon rupturing [30]. This may also contribute to higher recurrence rates after surgery in younger patients. Therefore, some authors even suggest that surgery for pediatric PSP might be delayed in younger groups (age < 16) [20].

One key strength of our study is its long-term follow-up period (median, 80 months; IQR, 50–113 months). The age distribution among the three groups was also similar (median age 17 years old) (Fig. 2). The result of our Kaplan-Meier analysis revealed that over the half of contralateral recurrences (9/13; 69%) and ipsilateral recurrences (11/19; 58%) tended to occur during the first 2-years after surgery (Fig. 3 and Fig. 5). Notably, all the overall recurrences occurred within 5 years, except for one patient in group B + cb and another patient in group U-cb, who had ipsilateral recurrences at 68 and 62 months, respectively (Fig. 4). Hence, we suggest vigilant postoperative follow-ups throughout adolescence because there is a close relationship between this age range and potential physical development and chest dimension growth.

The main limitation of this study is that it is a retrospective study design with no randomization of subjects. Therefore, some selection bias dose unavoidably exist, including absence of HRCT interpretation for blebs/bullae or patient's and/or their guardians' viewpoint toward the preemptive contralateral surgery. In addition, we did not include the female PSP patients due to the small sample size.

Conclusions

Although recurrence is high following surgery for PSP in younger adolescents, the performance of simultaneous contralateral blebectomy in those receiving bilateral surgeries may significantly decrease future contralateral recurrence. Our results suggest that one-stage bilateral VATS can be used for certain patients with contralateral blebs without compromising their safety.

Abbreviations

PSP
primary spontaneous pneumothorax
VATS
video-assisted thoracic surgery

B + cb

those with contralateral blebs receiving one-stage bilateral surgeries

U + cb

those with contralateral blebs only receiving unilateral surgery

U-cb

those without contralateral blebs only receiving unilateral surgery

HR

hazard ratio

CI

confidence interval

HRCT

high-resolution computed tomography

BMI

body mass index

IQR

interquartile range

Declarations

Ethics approval and consent to participate: The Institutional Review Board of Kaohsiung Medical University Hospital approved this study and waived the requirement for written informed consent (KMUHIRB-E(I)-20190158).

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: Liu YW and Chou SH designed the study. Kao CN, Chou SH, and Liu YW wrote the manuscript. Kao CN, Tsai MJ, Chang PC, and Liu YW did data acquisition. Tsai MJ and Liu YW analysed and interpreted the data. All authors read and approved the final manuscript.

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Figures

Figure 1

Flow diagram for patient recruitment. PSP, primary spontaneous pneumothorax; HRCT, high-resolution computed tomography

Figure 2

Age distribution of the three groups stratified by 0.5 using box plot analysis. B+cb, those with contralateral blebs receiving one-stage bilateral surgeries; U+cb, those with contralateral blebs only receiving unilateral surgery; U-cb, those without contralateral blebs only receiving unilateral surgery

Figure 3

Kaplan–Meier analysis showing contralateral recurrence-free rate of patients with PSP treated in different groups. PSP, primary spontaneous pneumothorax; B+cb, those with contralateral blebs receiving one-stage bilateral surgeries; U+cb, those with contralateral blebs only receiving unilateral surgery; U-cb, those without contralateral blebs only receiving unilateral surgery

Figure 4

Kaplan–Meier analysis showing overall recurrence-free rate of patients with PSP treated in different groups. PSP, primary spontaneous pneumothorax; B+cb, those with contralateral blebs receiving one-stage bilateral surgeries; U+cb, those with contralateral blebs only receiving unilateral surgery; U-cb, those without contralateral blebs only receiving unilateral surgery

Figure 5

Kaplan–Meier analysis showing ipsilateral recurrence-free rate of patients with PSP treated in different groups. PSP, primary spontaneous pneumothorax; B+cb, those with contralateral blebs receiving one-stage bilateral surgeries; U+cb, those with contralateral blebs only receiving unilateral surgery; U-cb, those without contralateral blebs only receiving unilateral surgery