Original Article

Postoperative predictors of ipsilateral and contralateral recurrence in patients with primary spontaneous pneumothorax

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Background: Preventive surgery for contralateral recurrence of primary spontaneous pneumothorax (PSP) remains controversial and few studies discussed both ipsilateral and contralateral recurrences simultaneously. Thus, we aimed to identify the predictors of ipsilateral and contralateral PSP recurrence and to review literatures on the association of blebs/bullae on HRCT with PSP recurrence.

Methods: We retrospectively reviewed consecutive patients who were treated at our hospital for first recurrence of PSP between January 2001 and December 2005.

Results: This study included 553 patients who were followed-up for a mean period of 124 months. Ipsilateral and contralateral recurrence of PSP developed in 19.35% and 15.19% of patients, respectively. In the Cox regression analysis, the only significant predictors were no video-assisted thoracoscopic surgery (VATS) bullectomy (OR: 16.629, P<0.001) for ipsilateral recurrence, and the presence of blebs/bullae on HRCT (OR: 3.215, P=0.024) and low BMI (<18.5 kg/m^2) (OR: 1.560, P=0.045) for contralateral recurrence.

Conclusions: VATS bullectomy was a strong independent predictor for prevention of ipsilateral PSP recurrence. Patients with contralateral blebs or bullae on chest HRCT or those with low BMI may be candidates for preventive VATS bullectomy to avoid recurrences and possible complications.

Keywords: Blebs; computed tomography (CT); pneumothorax; recurrence; predictors

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Introduction

Primary spontaneous pneumothorax (PSP) usually occurs in young, tall, and lean men, especially smokers with no obvious underlying lung disease. It arguably results from rupture of subpleural blebs or bullae. The most frequent complication of PSP is recurrence, which is estimated to occur in 20% to 60% after conservative treatment (1,2). More than 50% of patients with PSP have contralateral blebs/bullae and about a quarter will develop contralateral pneumothorax (3). The British Thoracic Society (BTS) guidelines include first recurrence of contralateral pneumothorax and synchronous bilateral PSP as the only indications for surgery of the contralateral lung (4). However, surgery of the contralateral lung to prevent possible complications remains controversial (5-7). To date, only few studies on small populations have discussed both ipsilateral and contralateral recurrences of PSP. The purpose of our study was to identify the predictors of ipsilateral and contralateral recurrences of PSP and to review literatures on the association of blebs/bullae on high resolution computed tomography (HRCT) of the chest with PSP recurrence. Knowing the risk factors for PSP recurrence may enable us to optimize patient selection to avoid further recurrence and complications.

Methods

PSP patients

From January 2001 to December 2005, 878 patients were treated for pneumothorax at our hospital. Patients who were lost to follow-up or those who had secondary, traumatic, bilateral, or iatrogenic pneumothorax were excluded. Most patients who developed postoperative recurrence were referred back to our institution. For patients who did not develop recurrence or those who were referred to another hospital for recurrence, follow-up information was obtained from the outpatient clinic medical reports. All patients who were included in our study gave informed consent for medical research. This study has been approved by the Institutional Review Board/Ethics Committee of Tri-Service General Hospital (1-105-05-009).

Parameters

The medical records and operative notes of these patients were retrospectively reviewed. Data collected included detailed history, number of pneumothorax episodes and treatment modalities, age, sex, body mass index (BMI) in kg/m^2, and smoking habits. According to the suggestion of the World Health Organization, BMI is a simple and widely used method for estimating body fat mass, and underweight was defined as <18.5 kg/m^2. Pneumothorax was diagnosed by medical history and chest radiograph; HRCT of the chest was performed in all patients.

Managements for pneumothorax

Depending on the symptoms and radiologic findings, management included high-flow oxygen inhalation therapy, closed tube thoracostomy, and wedge resection by video-assisted thoracoscopic surgery (VATS) with mechanical pleurodesis. We used the Light index, which calculates the volume in cubes of the average lung diameter and the average hemithorax diameter, to quantify the size of the pneumothorax on chest radiographs. A pneumothorax <20% was treated with oxygen inhalation therapy, whereas a pneumothorax >20% was initially managed by closed tube thoracostomy. Indications for wedge resection by VATS included persistent (>4 days) air leak, tension pneumothorax at first presentation, hemopneumothorax, the occupation of the patient (diver, pilot, etc.), and recurrent pneumothorax. Wedge resection was performed using staplers, combined with mechanical pleurodesis with gauze. After surgery, a chest tube (18–20 F) was connected to an underwater seal drainage bottle. Suction (–10 to –20 cm of H_2O) was initially applied to the chest drain and was disconnected when air leak has resolved on coughing or Valsalva maneuver. The chest tube was removed after the air leak had stopped for at least 24–48 hours.

Statistical analysis

Descriptive data were expressed as mean ± standard deviation, unless otherwise specified. Student's *t*-test was used to analyze continuous variables, whereas chi-square test was used for comparison of categorical variables between groups of ipsilateral recurrence and contralateral recurrence. Probability for recurrent PSP was analyzed by the Kaplan-Meier method. A P value of less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 20.0 software (SPSS, Inc., Chicago, IL, USA).

Results

The study group comprised 504 men and 49 women. Among 553 patients with PSP who met the inclusion criteria, the 425 patients who underwent VATS bullectomy were reviewed retrospectively. Of these, 167 patients (43.26%) had recurrent spontaneous pneumothoraces. The patients were followed-up until December 2015; the average follow-up period was 124 months. All blebs/bullae identified on HRCT were localized to the apical segment of the lungs. No other lung anomalies were observed. The clinical demographics of the patients are shown in *Table 1*. Compared with the non-recurrent group, the recurrent group had similar gender distribution, but significantly differed in patients with smoking history (P=0.011), VATS bullectomy (P<0.001), younger age (P=0.002), and low BMI (P=0.033).

Univariate analysis of the clinical features affecting PSP recurrence is presented in *Table 2*. There were 107 (19.35%) patients with ipsilateral recurrence and 84 (15.19%) patients with contralateral recurrence. Compared with the non-recurrent group, the ipsilateral recurrent group had significantly higher proportion of patients with smoking history (P=0.034), VATS bullectomy (P<0.001), and low BMI (P=0.033), but similar gender distribution (P=0.183), HRCT findings of blebs/bullae (P=0.869), and age (P=0.106). Compared with the non-recurrent group, the contralateral recurrent group had significantly higher

Table 1 Comparison of clinical features between recurrent and non-recurrent primary spontaneous pneumothorax

Variable	Recurrent (n=167)	Non-recurrent (n=386)	P value†
Gender			0.297
Male	149	355	
Female	18	31	
Smoking			0.011†
Yes	106	200	
No	61	186	
VATS bullectomy			<0.001†
Yes	72	353	
No	95	33	
Age (y)	20.44±5.08	21.95±5.26	0.002†
BMI (kg/m^2)	19.15±2.05	19.56±2.08	0.033†

†, Significance level: P<0.05. VATS, video-assisted thoracoscopic surgery; BMI, body mass index.

proportion of patients with no VATS bullectomy (P<0.001), with HRCT findings of blebs/bullae (P<0.001), in younger age (P<0.001), and low BMI (P=0.004), but similar gender distribution (P=0.816) and smoking history (P=0.188). There were 24 patients with bilateral PSP recurrence.

Table 3 shows the results of Cox regression analysis of the factors affecting ipsilateral/contralateral PSP recurrence. Statistically significant predictors were no VATS with bullectomy (OR: 16.629, P<0.001; *Figure 1*) for ipsilateral PSP recurrence, and presence of blebs/bullae on HRCT (OR: 3.215, P=0.024; *Figure 2*) and low BMI (OR: 1.560, P=0.045, *Figure 3*) for contralateral PSP recurrence. Gender and smoking habit were not independent predictors of ipsilateral or contralateral PSP recurrence.

Discussion

Although not fatal, recurrent pneumothorax is the most common complication after an initial episode of PSP. Moreover, recurrent attacks require readmission to the hospital and additional medical costs. Therefore,

Table 2 Comparison of clinical features among patients with primary spontaneous pneumothorax

Variable	Ipsilateral			Contralateral		
	Recurrent (n=107)	Non-recurrent (n=446)	P value†	Recurrent (n=84)	Non-recurrent (n=469)	P value†
Gender			0.183			0.816
Male	94	410		76	428	
Female	13	36		8	41	
Smoking			0.034†			0.188
Yes	69	237		52	254	
No	38	209		32	215	
VATS bullectomy			<0.001†			<0.001†
Yes	25	400		32	393	
No	82	46		52	76	
Blebs on CT			0.869			<0.001†
Yes	82	362		68	264	
No	5	24		6	135	
No CT	20	60		10	70	
Age (yrs)	20.76±5.47	21.67±5.19	0.106	19.39±3.37	21.87±5.44	<0.001†
BMI (kg/m^2)	19.27±2.03	19.48±2.09	0.033†	18.83±2.19	19.55±2.04	0.004†

†, Significance level: P<0.05. VATS, video-assisted thoracoscopic surgery; BMI, body mass index; CT, computed tomography.

Table 3 Cox regression analysis of factors affecting recurrence of primary spontaneous pneumothorax

Factor	Ipsilateral		Contralateral	
	OR (95% CI)	P value	OR (95% CI)	P value
Gender				
Male	1	0.888	1	0.365
Female	1.044 (0.574–1.897)		1.414 (0.668–2.994)	
Smoking				
No	1	0.110	1	0.80
Yes	2.545 (0.810–8.001)		1.498 (0.953–2.355)	
Blebs on CT				
No	1	0.995	1	0.024†
Yes	0.999 (0.676–1.476)		3.215 (1.165–8.928)	
BMI (kg/m^2)				
>18.5	1	0.940	1	
≤18.5	1.016 (0.679–1.519)		1.560 (1.011–2.409)	0.045†
VATS with bullectomy				
Yes	1	<0.001†	1	0.365
No	16.629 (10.500–26.335)		1.414 (0.668–2.994)	

†Significance level: P<0.05. OR, odds ratio; CT, computed tomography; BMI, body mass index; VATS, video-assisted thoracoscopic surgery.

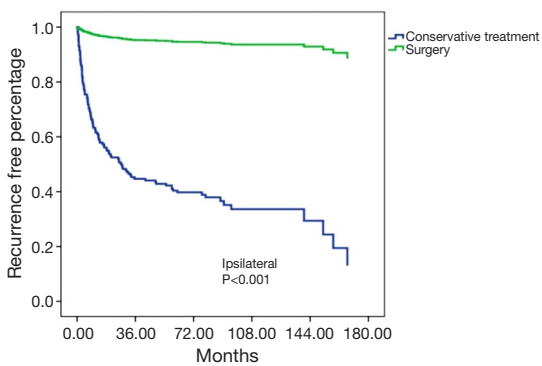

Figure 1 Probabilities of recurrent PSP increased up to 64.06% in the nonsurgical group and 5.88% in the surgical group. The statistically significant predictor was no VATS bullectomy (OR: 16.629, P<0.001) for ipsilateral PSP recurrence. PSP, primary spontaneous pneumothorax.

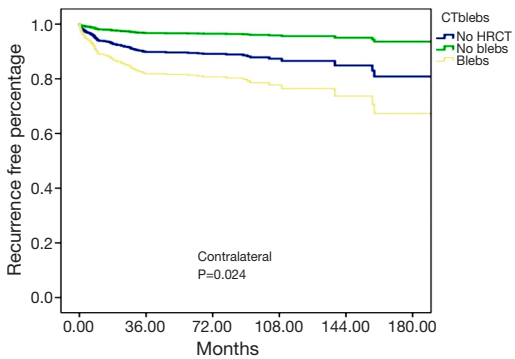

Figure 2 Probabilities of recurrent PSP increased up to 20.48% in the group with blebs/bullae on HRCT and up to 4.26% in the other group without blebs/bullae on HRCT. The statistically significant predictor was the presence of blebs/bullae on HRCT (OR: 3.215, P=0.024) for contralateral PSP recurrence. PSP, primary spontaneous pneumothorax; HRCT, high-resolution computed tomography.

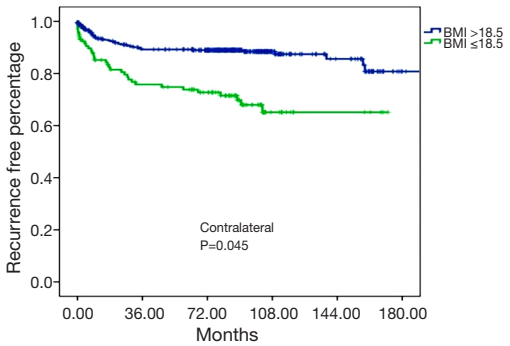

Figure 3 The statistically significant predictor was low BMI (OR: 1.560, P=0.045) for contralateral PSP recurrence. PSP, primary spontaneous pneumothorax; BMI, body mass index.

identification and documentation of risk factors for recurrence may reduce these additional burdens. Although younger age, male sex, and low BMI were reported as risk factors for recurrence after the first attack of PSP in previous studies (1,5), independent predictors for ipsilateral or contralateral recurrence of PSP are still unclear. There has been no definite agreement on the strategies for prevention of recurrence after the first episode, and preventive surgery for the contralateral lung remains controversial. We hypothesized that the predisposing conditions for ipsilateral or contralateral recurrence might be related to different risk factors because of variant conditions in bilateral lungs. In our study, ipsilateral recurrence was independently associated with no surgical intervention (thoracoscopic bullectomy with mechanical pleurodesis); the key result was that preventive VATS bullectomy for the contralateral lung is suitable only for patients with bullae or blebs on HRCT scan and those who are underweight (BMI <18.5).

A literature review on patients with recurrent PSP revealed that the incidence of blebs/bullae on HRCT scan was 44.83% to 56% in the pediatric population and 47.27% to 78.57% in the adult population (*Table 4*) (5,6,8-13). Among the pediatric population studies, only the report by Young Choi *et al.* showed that blebs or bullae on HRCT were significantly related with development of ipsilateral recurrence. In the adult population studies, there were three reports with significance in contralateral PSP recurrence and only one study with significance in both PSP recurrences. After review of existing literature, this study was the only report that divided a PSP recurrence population into ipsilateral (93.87%) and contralateral (70.19%) groups, which were compared in terms of incidence of blebs/bullae on HRCT scan. Our results may be more reliable because of the large number and analysis of the same patient population for predictors of ipsilateral and contralateral recurrence.

The role of blebs/bullae as a preexistent lesion for development of PSP has been questioned; in fact, some studies observed no correlation between its presence and the risk for PSP recurrence (6,8,9,11,12,14-17). However, there is some evidence on the lack of association between blebs and different recurrent patterns of PSP (ipsilateral or contralateral). In the previous studies (*Table 4*), 44.83% to 78.57% of patients with PSP had blebs on HRCT scan; our data showed a distinct distribution between ipsilateral (93.87%) and contralateral (70.19%) blebs. It is important to note that the quality of the CT scan should be assured first prior to considering surgery for prevention of PSP recurrence, especially contralateral recurrence. This will translate to shorter length of hospitalization and reduced need for chest tube drainage.

Prediction of contralateral recurrence is another controversial issue. Some authors suggested that presence of air-containing lesions on the contralateral lung was an independent predictive factor for contralateral pneumothorax and suggested single-stage bilateral VATS for PSP (5,11). On the other hand, Martinez-Ramos *et al.* showed that there is no association between the presence of bullae on CT scan and recurrence of PSP; therefore, they did not recommend surgery for PSP patients with bullae on CT scan (6). Sahn *et al.* proposed that the presence of bullae should not guide decision-making on prevention of PSP recurrence (7). Use of low radiation dose CT scan may mitigate the risks of radiation exposure, and lead to benefits outweighing risks (18).

Although somewhat unclear, the pathogenesis of PSP may be due to an imbalance in the development of the lungs and the body (19). Recurrence of PSP is more common at a younger age, because imbalanced development of the lungs and body cannot be corrected by surgery (20). According to the American College of Chest Physicians (21) and BTS guidelines (4), the preferred approach for prevention of recurrent pneumothorax is still surgical because of lower recurrence rates compared with instillation of sclerosing agents through a chest tube. However, the recurrence rate is still high at 5.9% to 24.5%, even after thoracoscopic stapled bullectomy (*Table 5*) (18,22-27). Therefore, Lee at al. proposed that visceral pleural coverage by cellulose mesh and fibrin glue after thoracoscopic bullectomy was not inferior to mechanical pleurodesis (28). Muramatsu *et al.* demonstrated a significantly reduced recurrence rate after

Table 4 Comparison of CT findings and recurrence rate in adults and children with primary spontaneous pneumothorax

Authors [year]	Total No. of patients	Blebs/bullae rate (%)	Follow-up (months)	Ipsilateral recurrence (%)				Contralateral recurrence (%)			
				HRCT+	HRCT−	P value	OR	HRCT+	HRCT−	P value	OR
Nathan (8) [2010]	25	56 (14/25)	72	21.43 (3/14)	27.27 (3/11)	0.734	0.727	NA	NA	NA	NA
Seguier-Lipszyc (9) [2011]	29	44.83 (13/29)	66	38.46 (5/13)	50 (8/16)	0.534	0.625	NA	NA	NA	NA
Young Choi (10) [2014]	114	55.26 (63/114)	43.1	60.32 (38/63)	31.37 (16/51)	0.003	3.33	15.9 (10/63)	11.8 (6/51)	0.596	1.42
Sihoe (11) [2000]	28	78.57 (22/28)	59	NR	NR	NR	NA	26.67 (4/15)	0	0.001	NA
Huang (5) [2007]	231	55.41 (128/231)	91.2	NR	NR	NR	NA	25.78 (33/128)	0	<0.001	NA
Ouanes-Besbes (12) [2007]	80	72.5 (58/80)	34	15.51 (9/58)	27.27 (6/22)	0.23	0.49	NA	NA	NA	NA
Martínez-Ramos (6) [2007]	55	47.27 (26/55)	30.7	23.08 (6/26)	24.14 (7/29)	0.92	0.94	NR	NR	NR	NA
Casali (13) [2013]	176	62.5 (110/176)	58	68.18 (75/110)	6.06 (4/66)	<0.001	33.21	19.09 (21/110)	0	0.001	NA
Current study [2016]	473	Ipsilateral: 93.87 (444/473); contralateral: 70.19 (332/473)	124	18.9 (82/444)	17.2 (5/29)	0.869	1.09	20.5 (68/332)	4.3 (6/141)	<0.001	5.80

†Significance level: P<0.05. OR, odds ratio; HRCT, high-resolution computed tomography; NR, not reported; NA, not available.

Table 5 Recurrence rates of spontaneous pneumothorax after thoracoscopic stapled bullectomy

Author (ref.)	Patient number	Year	Recurrence (%)	Follow-up (months)
Horio (22)	50	2002	16	38
Sakamoto (23)	126	2004	9.5	ND
Muramatsu (24)	310	2007	10	13.4
Nakanishi (25)	45	2009	24.5	43.5
Chiu (26)	171	2014	21	24
Chang (27)	149	2015	11.4	11.2
Noh (18)	285	2015	17.9	100
Our study	425	2016	5.9 (ipsilateral); 12.9 (contralateral)	124

ND, not described or discernible in the study.

thoracoscopic bullectomy with fleece-coated fibrin glue (TachoComb) (24).

Smoking is thought to be important in the pathogenesis of PSP (29). However, its role for the recurrence of PSP is controversial (1,30,31). In our study, smoking was not an independent predictor for ipsilateral or contralateral recurrence of PSP. Interestingly, smoking habit seemed to be significant and only in the ipsilateral recurrence group (*Table 2*). This might be due to a statistical bias because of the smaller population of smokers.

This study had several limitations, including the retrospective, single-center design. Although the number of patient in this study was the largest to date, there were only 107 cases of ipsilateral PSP recurrence and 84 cases of contralateral PSP recurrence. Therefore, there may have been selection bias, which limited the power of multivariate analysis.

The independent predictor for preventing ipsilateral PSP recurrence was VATS bullectomy. The presence of blebs or bullae in the contralateral lung on HRCT scan and low BMI after an initial episode of PSP may enable us to optimize patient selection for VATS bullectomy to prevent further recurrence and complications.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by the Institutional Review Board/Ethics Committee of Tri-Service General Hospital (No. 1-105-05-009).

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