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Do Blebs or Bullae on High-Resolution Computed Tomography Predict Ipsilateral Recurrence in Young Patients at the First Episode of Primary Spontaneous Pneumothorax?

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Background: The relationship between the size of bullae and pneumothorax recurrence is controversial. The aim of this study was to retrospectively evaluate the role of blebs or bullae in predicting ipsilateral recurrence in young patients experiencing their first episode of primary spontaneous pneumothorax (PSP) who underwent conservative treatment. **Methods:** A total of 299 cases of first-episode PSP were analyzed. The status of blebs or bullae was reviewed on high-resolution computed tomography (HRCT). The dystrophic severity score (DSS; range, 0 to 6 points) was calculated based on HRCT. **Results:** The 5-year recurrence rate was 38.2%. In univariate analysis, age (<20 years), body mass index (<20 kg/m^2), a unilateral lesion, and intermediate risk (DSS 4 and 5) were associated with recurrence. Sex; smoking history; and the presence, number, and maximal size of blebs or bullae were not related to recurrence. In Cox regression, age and intermediate risk were independent risk factors for recurrence. High risk (DDS 6) was not an independent risk factor. **Conclusion:** The presence, number, and size of blebs or bullae did not affect ipsilateral recurrence. DSS failed to show a positive correlation between severity and recurrence. The decision to perform surgery in patients experiencing their first episode of PSP should not be determined by the severity of blebs and bullae.

Key words: 1. Pneumothorax
2. Recurrence
3. Computed tomography
4. Bullae

Introduction

Primary spontaneous pneumothorax (PSP) commonly occurs in young patients [1]. Its recurrence rate ranges from 22.8% to 42% in patients who receive conservative treatment after the first episode [2]. The recurrence rate of patients treated with video-assisted thoracoscopic surgery (VATS) was reported to range from 0% to 13% [2]. The British Thoracic Society (BTS) and American College of Chest Physicians (ACCP) guidelines recommend conservative treatment including observation, aspiration, and chest tube drainage as the first-line treatment of first-episode PSP [3,4]. Still, there is no glob-

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ally-accepted risk stratification system for PSP to determine high-risk patients who would benefit from VATS rather than conservative treatment at initial presentation [5]. Recently, a randomized controlled trial (RCT) showed a positive correlation between the risk of recurrence and the size of bullae based on high-resolution computed tomography (HRCT) [6]. However, the data remain insufficient. Moreover, another study showed no correlation between the presence of bullae and recurrence [7]. The aim of this study was to evaluate the role of blebs or bullae detected using HRCT in predicting ipsilateral recurrence in young patients experiencing their first episode of PSP who underwent conservative treatment.

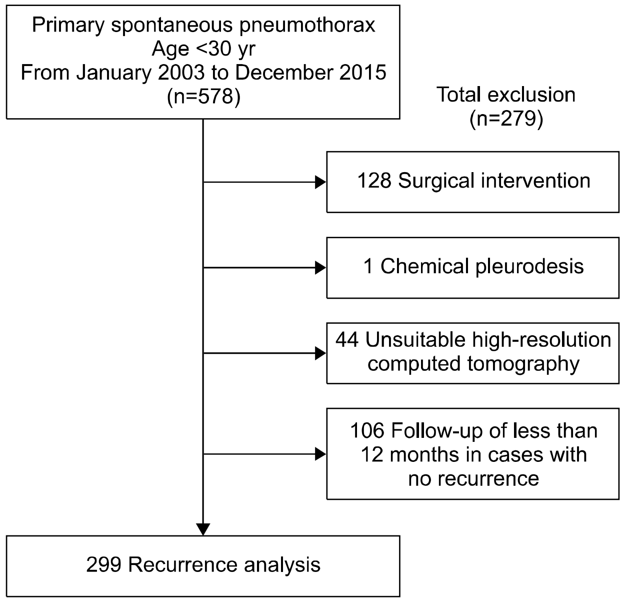

Fig. 1. Flow diagram of study design.

Methods

1) Patients

This study enrolled 524 patients younger than 30 years who visited the hospital for their first episode of PSP at a single institution from January 2003 to December 2015. PSP was defined as pneumothorax without underlying lung disease described in the medical record at the initial diagnosis. To exclude uncertain diagnoses of PSP in medical records, patients were limited to those younger than 30 years. This study was reviewed and approved by the Institutional Review Board and informed consent was waived (IRB approval no., 2019-02-018-001).

Fifty-four patients with simultaneous or sequential bilateral pneumothorax were counted as 2 cases for both thoraces. A total of 578 cases were extracted from outpatient and inpatient clinics, including the emergency department. Age, sex, body mass index (BMI), distribution of pneumothorax, smoking history, final management for first-episode PSP, and HRCT findings were collected from the patients' medical records. Of the 578 cases, 128 underwent VATS, and 1 underwent chemical pleurodesis. After excluding the cases of VATS and chemical pleurodesis, cases with unsuitable HRCT findings (n=44) and those with less than 12 months of follow-up without recurrence (n=106) were also excluded. Finally, 299 cases were enrolled to evaluate ipsilateral recurrence (Fig. 1).

2) High-resolution computed tomography examinations

HRCT without contrast media was generally conducted within 1–5 days after hospitalization. In our practice, if a patient had sequential bilateral pneumothorax and was evaluated using HRCT for pneumothorax on 1 side, HRCT was not conducted for the contralateral pneumothorax within 1 year. In this study design, HRCT used to assess pneumothorax on 1 side was assumed to be suitable to evaluate the status of blebs or bullae for a contralateral pneumothorax if it occurred within 1 month. If HRCT was assessed more than 1 month before the event, it was regarded as unsuitable for evaluation of the contralateral status. Such cases were excluded from the study.

HRCT scans were performed using a 64-channel multi-slice CT scanner (Philips Brilliance 64; Philips Medical Systems, Amsterdam, The Netherlands) with the following parameters: 120 kV, 250 mA (planned mA with D-Dom dose modulation), sharp filter, 5-mm slice thickness, 5-mm slice increment, and a pitch of 0674 units. Coronal reconstruction was applied with 2-mm slice thickness and 2-mm slice increments.

The presence, maximal size, and distribution of blebs or bullae were reviewed. Blebs were defined as gas-containing spaces smaller than 1 cm within the visceral pleura, and bullae were defined as gas-containing spaces 1 cm or more in diameter within the visceral pleura [8]. Some authors have defined blebs as being smaller than 2 cm [9-11], and a recent RCT showed that bullae larger than 2 cm were a risk factor for recurrence [6]. Therefore, bullae were divided into smaller (<2 cm) and larger bullae (≥2 cm). The dystrophic severity score (DSS) was proposed by Ouanes-Besbes et al. [7] and modified by Casali et al. [12]. The modified formula is the sum of scores for type (1 or 2 points for blebs or bullae), number (1 or 2 points for single or multiple), and distribution (1 or 2 points for unilateral or bilateral). If blebs or bullae were seen on HRCT, the DSS ranged from 3 to 6 points. If there were no blebs or bullae in HRCT, the DSS was recorded as 0 points. Cases were divided into 3 risk groups according to DSS: low risk (0 or 3 points), intermediate risk (4 or 5 points), and high risk (6 points). Two thoracic surgeons (SB and HJ) reviewed the HRCT scans. SB reviewed all HRCT scans, and HJ reviewed only the cases without blebs or bullae that were confirmed by SB.

3) Management

The indications for chest tube drainage were dyspnea, a distance of more than 1 cm between the lateral lung margin and chest wall, and gradually increasing size of the pneumothorax. Observation, including bed rest or outpatient clinic follow-up, was indicated in patients with no symptoms and a small pneumothorax, with less than 1 cm between the lateral lung margin and chest wall.

VATS was performed in 128 cases for persistent air leaks (>5 days, 53 cases), a history of contralateral pneumothorax (23 cases), complete lung collapse or tension pneumothorax (18 cases), simultaneous bilateral pneumothorax (8 cases), army service or studying abroad (8 cases), hemothorax (2 cases), and unknown reasons (16 cases). In a single case, chemical pleurodesis was performed in a patient who refused VATS for persistent air leaks.

4) Follow-up

Telephone interviews were performed in July 2018 by an investigator (JS). The incidence of recurrence was assessed through a telephone interview in 228 cases (39.5%), while the remaining 350 cases (60.5%) were reviewed (by JS) using medical records. The last outpatient clinic record of the thoracic department or the last inpatient admission record from other departments was accepted for review. The last outpatient clinic record from other departments was regarded as an incomplete record for evaluating the patient's history of pneumothorax. Cases with less than 12 months of follow-up and no recurrence were regarded as having been lost to follow-up and were excluded from the recurrence analysis, because most cases of recurrence develop during the first year [13]. The follow-up period was defined as extending from the date of diagnosis of the first PSP episode to the date of the last medical record or telephone interview. The recurrence-free period was defined as extending from the date of diagnosis of the first PSP episode to the date of ipsilateral recurrence in cases with ipsilateral recurrence and from the date of diagnosis of first PSP episode to the last follow-up date in cases without recurrence. The cumulative recurrence rate (cRR) was calculated as the rate of experiencing at least 1 recurrence.

5) Statistical analysis

All descriptive data were expressed as the frequency and mean with standard deviation. Frequency was compared using the chi-square and Fisher exact tests for dichotomous variables, and continuous variables were compared using the t-test and analysis of variance. The primary endpoint was ipsilateral cRR calculated by time to event using Kaplan-Meier analysis. The ipsilateral cRR according to each variable was calculated, and cRR curves were compared using the log-rank test. All p-values <0.05 were considered to indicate statistical significance. Cox regression was performed to identify variables independently associated with recurrence. All variables with p-values <0.05 were included in the analysis. Statistical analysis was performed using IBM SPSS ver. 24.0 (IBM Corp., Armonk, NY, USA).

Results

1) Characteristics of the patients

The characteristics of the enrolled and excluded groups were compared for each variable. Except for treatment modality, there was no difference between the groups (Table 1). A total of 299 cases were enrolled for the recurrence analysis. The mean age of the enrolled group was 20.5±3.98 years. Males were predominant (89.6%). The mean BMI was 19.4±2.23 kg/m^2. In 77 cases (25.8%), there were no visible

Table 1. Demographics and high-resolution computed tomography findings in enrolled and excluded patients

Variable	Enrolled patients (n=299)	Excluded patients (n=279)	p-value
Age (yr)	20.5±3.98	21.0±4.07	0.100
Sex			
Male	268 (89.6)	254 (48.7)	0.568
Female	31 (10.4)	25 (44.6)	
Distribution of pneumothorax			
Right	134 (44.8)	125 (44.8)	0.997
Left	165 (55.2)	154 (55.2)	
Smoking history			
No	210 (70.2)	192 (68.8)	0.711
Yes	89 (29.8)	87 (31.2)	
Body mass index (kg/m^2)	19.4±2.23	19.6±2.33	0.456
Presence of blebs or bullae[a)]			
No	77 (25.8)	57 (25.8)	0.758
Blebs (＜1 cm)	64 (21.4)	42 (19.0)	
Bullae (≥1 cm)	158 (52.8)	122 (55.2)	
Distribution of blebs or bullae[b)]			
Unilateral	92 (41.4)	70 (42.7)	0.807
Bilateral	130 (58.6)	94 (57.3)	
No. of blebs or bullae[b)]			
Single	29 (13.1)	24 (14.6)	0.658
Multiple	193 (86.9)	140 (85.4)	
Dystrophic severity score[a)]			
0	77 (25.8)	57 (25.8)	0.996
3	5 (1.7)	9 (4.1)	
4	51 (17.1)	25 (11.3)	
5	68 (22.7)	59 (26.7)	
6	98 (32.8)	71 (32.1)	
Treatment			
Observation	65 (21.7)	54 (19.4)	＜0.0001
Chest tube drainage	234 (78.3)	96 (34.4)	
Pleurodesis	-	1 (0.4)	
Surgery	-	128 (45.9)	

Values are presented as mean±standard deviation or number (%).
[a)]The data were limited to cases with suitable high-resolution computed tomography findings (221 cases were excluded). [b)]The data were limited to cases with the presence of bleb or bullae (enrolled group: n=222; excluded group: n=164).

blebs. Blebs were seen in 64 cases (21.4%) and bullae were seen in 158 cases (52.8%). More details are presented in Table 1.

2) Follow-up and recurrence

The median follow-up period was 76.3 months (range, 1.7–188.3 months). In 6 cases, the follow-up period was less than 12 months. However, these 6 cases experienced recurrence within a short-term follow-up period and were enrolled in the recurrence analysis. Another 293 cases had follow-up period longer than 12 months. During the follow-up period, 116 cases (38.8%) showed ipsilateral recurrence. A total of 86 cases (74.1%) recurred in the first year. The 1-year, 3-year, and 5-year cRRs of the enrolled group were 22.8%, 34.0%, and 38.2%, respectively (Fig. 2). There was no difference in the 5-year cRR between cases managed by observation and those managed by chest tube drainage (35.3% versus 39.3%, p=0.458).

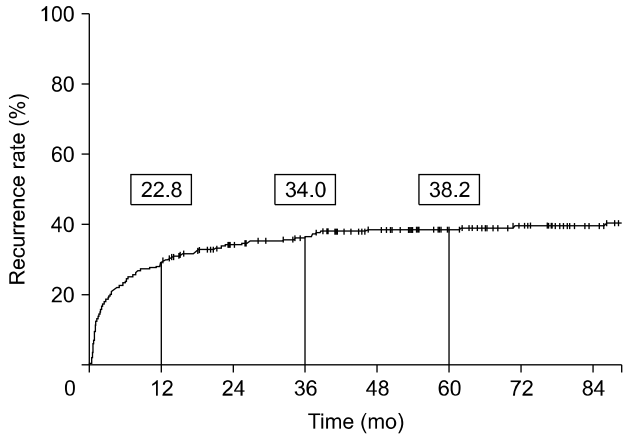

Fig. 2. Overall cumulative recurrence graph.

Table 2. Univariate analysis of the ipsilateral cumulative recurrence rate according to demographics

Variable	5-Year cumulative recurrence rate (%)	p-value
Age (yr)		0.001
<20	47.8	
≥20	26.3	
Sex		0.473
Male	39.2	
Female	30.2	
Distribution of pneumothorax		0.786
Right	38.7	
Left	37.8	
Smoking history		0.884
No	37.6	
Yes	39.6	
Body mass index (kg/m^2)		0.026
<20	42.9	
≥20	30.1	

3) *Univariate and multivariate analyses of demographic and high-resolution computed tomography findings*

Patients younger than 20 years of age showed a significantly higher 5-year cRR than those older than 20 years (Table 2). The 5-year cRR of patients with a BMI less than 20 kg/m^2 was significantly higher than those with a BMI over 20 kg/m^2 (Table 2). Sex, distribution of pneumothorax, and smoking history showed no statistically significant associations with the cRR (Table 2). The 5-year cRR did not differ to a statistically significant extent among those with no lesions and those with blebs and bullae (Table 3).

Table 3. Univariate analysis of the ipsilateral cumulative recurrence rate according to high-resolution computed tomography findings

Variable	5-Year cumulative recurrence rate (%)	p-value
Presence of blebs or bullae		0.429
No	32.3	
Blebs (<1 cm)	40.9	
Bullae (≥1 cm)	40.0	
Size of bullae		0.273
Smaller (≥1 cm, <2 cm)	43.9	
Larger (≥2 cm)	29.4	
Distribution of blebs or bullae		0.031
None	32.3	
Unilateral	48.6	
Bilateral	34.4	
No. of blebs or bullae		0.296
None	32.3	
Single	46.0	
Multiple	39.5	
Dystrophic severity score		0.021
Low risk (0, 3)	32.8	
Intermediate risk (4, 5)	46.8	
High risk (6)	32.3	

Table 4. Cox regression analysis of theipsilateral cumulative recurrence rate

Variable	Hazard ratio (95% confidence interval)	p-value
Age (yr)		
<20	1	
≥20	0.53 (0.36–0.79)	0.002
Body mass index (kg/m^2)		
<20	1	
≥20	0.70 (0.46–1.06)	0.095
Dystrophic severity score		
Low risk (0, 3)	1	
Intermediate risk (4, 5)	1.63 (1.03–2.58)	0.036
High risk (6)	1.02 (0.61–1.70)	0.935

When the bullae (≥1 cm) were divided into those with a maximal size less than 2 cm and those that were larger than 2 cm, there were 117 cases with bullae measuring 1–2 cm and 41 cases with bullae measuring ≥2 cm. Interestingly, the 5-year cRR of the group with larger bullae was lower than that of the group with smaller bullae (29.4% versus 43.9%). However, the difference did not reach statistical significance (p=0.273). The 5-year cRR of cases involv-

Table 5. Subgroup analysis according to high-resolution computed tomography findings

Group	Bleb (b) or bullae (B)	Single (S) or multiple (M)	Unilateral (U) or bilateral (B)	Dystrophic severity score	Cases	5-Year cumulative recurrence rate (%)
0	No	No	No	0	77	32.3
1	b	S	U	3	5	-
2	b	S	B	4	6	-
3	b	M	U	4	30	37.4
4	b	M	B	5	23	39.1
5	B	S	U	4	15	-
6	B	S	B	5	3	-
7	B	M	U	5	42	57.8
8	B	M	B	6	98	32.3

Group 3 versus 4: p=0.767; group 7 versus 8: p=0.002.

ing unilateral lesions was significantly higher than that of cases with no lesions or bilateral lesions (Table 3). Single lesions (blebs or bullae) had the highest 5-year cRR, but without statistical significance (Table 3). An intermediate-risk DSS was associated with a significantly higher 5-year cRR than a low- or high-risk DSS (Table 3). In Cox regression analysis, younger age (<20 years) and an intermediate-risk DSS were independent risk factors for ipsilateral recurrence (Table 4). However, a high-risk DSS did not affect the development of ipsilateral recurrence.

4) Subgroup analysis

In the HRCT findings, the presence, maximal size, and number of blebs or bullae were not risk factors for ipsilateral recurrence in the enrolled group. However, unilateral lesions were more strongly associated with the cRR than were bilateral lesions (Table 3). This may explain why an intermediate-risk DSS risk was an independent risk factor, while a high-risk DSS was not. Subgrouping was performed according to the number and distribution of blebs or bullae to investigate possible confounding factors (Table 5). The single-lesion group (1, 2, 5, and 6) was too small to analyze. Of the groups with blebs, group 3 (blebs, multiple and unilateral lesions) and group 4 (blebs, multiple and bilateral lesions) showed similar 5-year cRRs (37.4% versus 39.1%, p=0.767). However, in groups with bullae, group 7 (bullae, multiple and unilateral lesions) showed a significantly higher 5-year cRR than group 8 (bullae, multiple and bilateral lesions; 57.8% versus 32.3%, p=0.002).

A subgroup analysis of groups 7 and 8 was performed. Female sex (23.8% versus 7.1%, p=0.006) and lower BMI (18.8±2.06 kg/m^2 versus 19.7±2.12 kg/m^2, p=0.018) were significantly predominant in group 7. Mean age, distribution of pneumothorax, smoking history, the maximal size of bullae, and larger bullae (≥2 cm) did not show a significantly different distribution in groups 7 and 8 (data not reported). In the univariate analysis of groups 7 and 8, age less than 20 years (5-year cRR: 50% versus 28.4%, p=0.024) and unilateral lesions (57.8% versus 32.3%, p=0.001) were associated with recurrence. Sex, BMI, distribution of pneumothorax, smoking history, and larger bullae (≥2 cm) were not associated with recurrence. In the Cox regression analysis, age less than 20 years (hazard ratio [HR], 1.89; 95% confidence interval [CI], 1.09–3.27; p=0.023) and unilateral lesions (HR, 2.35; 95% CI, 1.39–3.98; p=0.002) were independent risk factors of recurrence. The presence of unilateral lesions was not influenced by female sex or lower BMI in the Cox regression analysis.

Discussion

This retrospective study was designed to evaluate the relationship between HRCT findings and ipsilateral recurrence after the first episode of PSP in patients receiving conservative treatment. The main positive finding of this study was that unilateral blebs or bullae had a higher recurrence rate than bilateral blebs or bullae, resulting in the intermediate-risk group (DSS 4 and 5) having a higher recurrence rate than the high-risk group (DSS 6). This finding has no practical utility in clinical settings. Bilateral disease is usually regarded as more severe than unilateral disease in general medicine. In a further investigation through a subgroup analysis, lesion distribution did not affect recurrence in patients with blebs (groups 3 and 4). However, in patients with bullae (groups 7 and 8), unilateral lesions were an independent risk factor for recurrence. This finding could not be explained by statistical trends. Other than distribution, all other parameters of HRCT findings, including the presence, size, and number of blebs or bullae, did not affect ipsilateral recurrence. Therefore, the relationship between recurrence and lesion distribution might have been pure coincidence, or it could be counterevidence against a dose-response relationship between the distribution of lesions and recurrence in cases of PSP.

By Laplace's law, surface tension is directly proportional to radius. According to this law, the largest bullae are theoretically the most prone to rupture. When VATS was performed in patients with pneumothorax, ruptured blebs or bullae could be found. However, it was not always the largest bleb or bulla that was ruptured. Sometimes, small blebs with thin walls in the superior segment of the lower lobe showed air leaks, instead of large bullae with thick walls in the apex of the upper lobe. Although such cases were not specifically investigated in our study, we suggest that this size-rupture mismatch could be responsible for our negative result regarding the relationship between maximal lesion size and recurrence.

Our findings are in disagreement with 3 recently published studies on HRCT findings and PSP recurrence [6,12,14]. The study populations of those 3 studies included patients with their first episode of PSP managed by conservative treatment, as in our study. In an RCT, patients with first-episode PSP were stratified by the presence of bullae (≥1 cm) and then randomized to VATS and chest tube management. In the 99 patients managed by chest tube drainage, those with bullae (≥2 cm) were at a higher risk for recurrence than those with no lesion on HRCT (HR, 4.4; 95% CI, 1.04–18.83; p=0.03) [6]. Interestingly, that RCT incorporated an analysis of ipsilateral DSS data, not full DSS data. Therefore, the maximal DSS was 5, not 6. Bilateral lesions may not have been a risk factor in their analysis, or asymptomatic contralateral lesions were not considered to have been responsible for ipsilateral recurrence. Unlike the size of the bullae, ipsilateral DSS was not found to be a risk factor for recurrence in that RCT. Although the sample size (n=23) was too small to draw a general conclusion, another small prospective study showed that high-grade patients (DSS 4, 5, and 6) had a 90% recurrence rate and that high-grade DSS was an independent risk factor (HR, 3.20; 95% CI, 1.11–9.22; p=0.03) compared to the low-grade group (DSS 0 and 3) [14]. Another retrospective study analyzed 176 patients, and the presence of blebs or bullae was significantly related to the development of ipsilateral recurrence [12]. The recurrence rate of patients with a DSS of 0 was remarkably lower than ours (6% versus 32.3%). This difference resulted in the presence of blebs or bullae being a risk factor. However, patients with a DSS of 3, 4, 5, or 6 showed no correlation with ipsilateral recurrence. Therefore, that retrospective study did not confirm the utility of risk stratification based on DSS.

On the contrary, other studies did not find any correlation between HRCT findings and recurrence [7,9,15]. Ouanes-Besbes et al. [7] originally proposed the DSS. The DSS was not statistically significantly associated with the risk of recurrence based on an analysis of 80 patients with first-episode PSP [7]. In other prospective studies (n=35), the number, size, and distribution of bullae showed no correlation with recurrence [9]. Similarly, another prospective study (n=55) demonstrated that the presence, size, or number of bullae had no influence on the recurrence rate [15]. However, these studies showing negative outcomes had sample sizes that were too small to draw conclusions.

In a recent meta-analysis, patients who received VATS showed a significantly lower recurrence rate than those who received conservative treatment [16]. Some groups have recommended VATS as the first treatment choice in patients with first-episode PSP regardless of risk stratification [2,17]. This recommendation is based only on the recurrence rate according to modality. However, overtreatment would occur if such recommendations were followed. The most recent German S3 guideline recommends VATS in selected cases of first-episode PSP [18], similar to the BTS and ACCP guidelines. In our study, sex, BMI, smoking history, and HRCT findings were not useful in the risk stratification of ipsilateral recurrence; only younger age was useful for this purpose. However, younger age has also been identified as a risk factor for recurrence after VATS [19], meaning that it is difficult to determine which age groups could benefit from VATS after the first episode of PSP.

The strengths of our study were as follows. First, the initial management strategy and surgical indications for first-episode PSP were consistent during the study period. Our policy was to observe the recommendations of guidelines. Second, chemical pleurodesis was performed in only 1 case. Therefore, the outcomes of conservative treatment were uniform. Third, HRCT was performed in 90% (520 of 578) of cases at the time of the first episode. Fourth, the excluded patients did not show statistically significant differences from the enrolled patients. The likelihood of selection bias was assessed as relatively low based on that comparison. Fifth, there were more cases than in previous studies, and the follow-up period was longer. This increases the reliability of our negative findings.

The primary limitation of this study is its retrospective design. Selection bias could not be completely eliminated by nature. In addition, 40% of cases were confirmed to have experienced recurrence by telephone interview, which could involve recall bias. Some patients might have been confused regarding ipsilateral versus contralateral recurrence. However, the investigator asked about recurrence in each thorax separately to reduce recall bias. Furthermore, only 12.7% (29 of 228) of interviewed cases reported having experienced recurrence. The timing of the HRCT examination might have influenced the size of the bullae. Optimal HRCT examinations occur when the lung is fully expanded. In our practice, HRCT was performed 1 to 5 days after pneumothorax, and generally showed minimal or moderate pneumothorax. This might have falsely decreased the size of the blebs or bullae. However, the proportion of cases with no lesion (25.8%; 77 of 299 cases) in our study was not higher than in another study (44%; 30 of 68 cases) designed to examine full lung expansion at 1 to 6 weeks after the event [10] or in the previous report (37%; 66 of 176 cases) with the largest number of patients [12]. Another possible weakness regarding HRCT in our study was that only thoracic surgeons performed the evaluations. However, the authors suggest that an evaluation of the size, number, and distribution of blebs or bullae does not require extensive radiologic training.

In conclusion, the ipsilateral recurrence rate was high in young patients with first-episode PSP who underwent conservative treatment. HRCT findings, including the presence, number, size, and bilaterality of blebs and bullae, were not predictors of ipsilateral recurrence in this study. In other words, the severity of blebs or bullae on HRCT was not useful for stratifying patients with a high risk of recurrence. Surgery based on HRCT findings in young patients (<30 years) with first-episode PSP could not be justified. To confirm the exact role of blebs or bullae on HRCT, a further well-designed, large-scale, prospective cohort study will be needed. Until then, the management of patients with first-episode PSP should follow international guidelines.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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