



Long-term clinical outcomes after initial secondary pneumothorax surgery

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Background: Given the heterogeneity of underlying lung disease and the higher morbidity and mortality associated with surgery for secondary pneumothorax (SP), treatment standardization and evidence-based early surgical management are challenging pursuits. Our aim was to document the clinical course of SP after initial surgical intervention and analyse related recurrence risk.

Methods: We conducted a retrospective review of 160 patients, each with SP, using clinical records housed in an institutional database. Clinical, imaging, and operative data were retrieved, and Cox proportional hazards (PH) analysis was undertaken to identify risk factors for recurrence.

Results: During a mean follow-up of 58.7 months, the overall recurrence rate in this cohort was 18.75% (ipsilateral, 14; contralateral, 16). A total of 24 patients had ≥ 3 ipsilateral episodes < 6 months prior to surgery, marked by initial index episodes. In multivariate Cox PH analysis, the strongest risk factor for recurrence was underlying lung pathology other than chronic obstructive pulmonary disease [COPD: hazard ratio (HR) = 5.3; $P < 0.001$].

Conclusions: In this setting, underlying lung disease of a non-COPD nature is a proven risk factor for postsurgical recurrence. There is also a tendency in some patients for multiple episodes of pneumothorax within short periods of time, especially in the absence of COPD. Underlying disease processes may thus merit consideration in treatment planning.

Keywords: Secondary pneumothorax (SP); recurrence; surgery; chronic obstructive pulmonary disease (COPD)

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Introduction

As a general rule, secondary pneumothorax (SP) is an event typically linked to underlying pulmonary disease or systemic conditions with lung involvement. The precise definition is apt to vary by source. Some may define SP more strictly, for example, British Thoracic Society (BTS) guidelines

stipulate that an older patient (> 50 years) with a heavy smoking history will more likely have related respiratory pathology, even if the chest X-ray is unremarkable (1). On the other hand, 2001 American College of Chest Physicians (ACCP) guidelines impose no age restriction but limit SP to the setting of underlying clinical lung disease (2).

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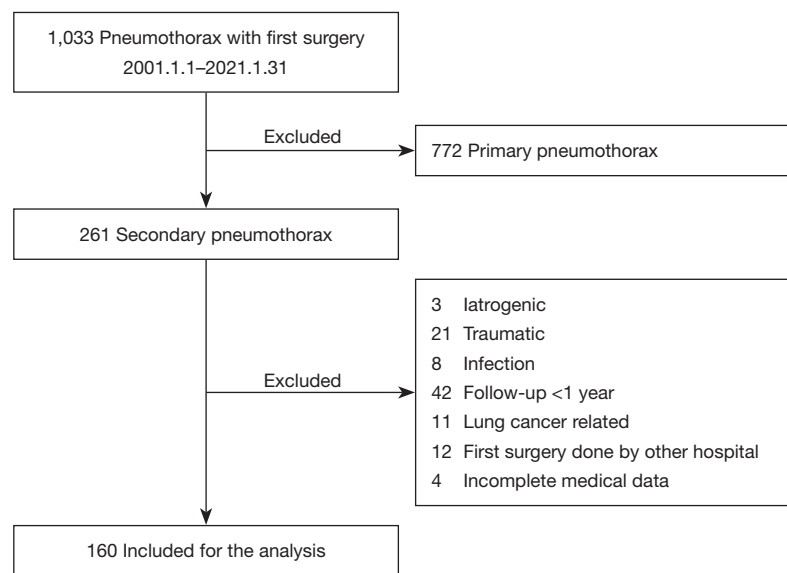


Figure 1 Flow diagram of the study.

While considered a common clinical problem, there are some aspects of pneumothorax that are not well understood, implicating a host of related clinical features and underscoring the challenge of patient management. Moreover, studies of SP often include instances of primary pneumothorax, thus clouding the interpretation of research findings and their relevance to clinical practice (3-5).

The age-adjusted incidence of SP in the United States is 3.8/100,000 population per year, whereas in France, the incidence is 9.8/100,000 population per year in men (4). A predisposition among older patients (50–60 years old),

mostly men in need of surgery, is generally acknowledged for SP; and the prognosis typically is poor, including longer postoperative hospital stays and morbidity (4).

Because the etiologies and clinical ramifications of SP are heterogenous, regardless of what various guidelines dictate, real-world patient management must be individualized, and generalizations are difficult. In addition, not much is known about the clinical course of SP after surgical treatment. Consequently, our objective was to document the clinical progress of patients with SP after initial surgical treatments, examining the potential for first postsurgical recurrences and the risk factors entailed. We present this article in accordance with the STROBE reporting checklist (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-867/rc>).

Highlight box

Key findings

- Type of lung disease impacts postsurgical recurrences of secondary pneumothorax (SP), which in some patients are clustered within relatively short time frames.

What is known and what is new?

- Unlike primary spontaneous pneumothorax, the heterogeneity of SP confers worse clinical outcomes (recurrences, morbidity).
- Type of underlying lung disease, especially if non-emphysematous, is the major determinant of recurrence risk after surgical treatment of SP.

What is the implication, and what should change now?

- Surgical intervention for SP may be beneficial in selected patients. Underlying disease aetiology should be considered when deciding treatment strategy.

Methods

Study population and variables

For the present investigation, we targeted adults undergoing initial surgical procedures for SP performed at the Seoul St. Mary's Hospital between January 1, 2001 and January 31, 2021 (Figure 1). By definition, SP was any pneumothorax tied to underlying pulmonary pathology, as demonstrated through computed tomography (CT) imaging or during ongoing care by a pulmonologist for disorders such as chronic obstructive pulmonary disease (COPD), interstitial

lung disease (ILD), combined pulmonary fibrosis and emphysema (CPFE), pneumoconiosis, or other rare forms of cystic lung disease. One or more of the following criteria were grounds for exclusion: (I) primary spontaneous pneumothorax; (II) iatrogenic, traumatic, malignancy-related, or infectious causes of SP; (III) performance of initial surgery elsewhere; (IV) <12 months of follow-up after initial surgical intervention; or (V) incomplete medical data. The latter may potentially affect study results and interpretation, and there were two reasons why infectious or malignant causes of SP were stipulated. If the cause of SP is due to malignant tumors, these are largely incurable; and the infections encountered, typically due to immune compromise (i.e., pneumocystis jiroveci pneumonia), are nearly incurable. Furthermore, none of such patients seem to survive for more than 6 months after surgery, which was mandatory for study inclusion.

Overall, 1,033 patients diagnosed with pneumothorax received surgical treatment at our hospital and were potential study candidates. However, those with primary spontaneous pneumothorax (n=772) or iatrogenic (n=3), traumatic (n=21), infectious (n=8), and lung-cancer related (n=11) causes of SP failed to meet stated inclusion criteria and were excluded. Others with short follow-up periods, initial surgeries performed elsewhere, and incomplete medical data were also ineligible (*Figure 1*).

At our institution, needle aspiration of SP is not routinely done. Depending on the severity of patient symptoms and X-ray findings, a chest tube is ordinarily inserted at initial presentation. The only exceptions are those patients proceeding directly to surgery on same or next days who tolerate not doing so. Once a chest tube is placed, the amount of air leaked and imaging features on chest X-rays and CT studies will determine the type of treatment undertaken. Surgery is usually pursued in the following instances: (I) persistent air leak for more than 5–7 days; (II) no or under re-expansion or lung collapse on follow-up radiographs for several days; (III) inadequate or no response to repeated bedside pleurodesis attempts; and (IV) large localised bullae or surgically resectable disease on chest CT. Surgical method and scope are usually matters of surgeon preference.

We defined a recurrence as any pneumothorax episode confirmed by chest X-ray after first surgery, whether ipsilateral or contralateral to the operative site, according to Venuta *et al.* (6). In terms of follow-up, censoring indicated institutional acquisition of last available chest X-ray or simply loss of follow-up.

All patient data were extracted in anonymized manner from the Catholic Medical Center clinical data warehouse (CMC nU-CDW) of Seoul St. Mary's Hospital, collecting the following information: (I) diagnoses and comorbidities based on International Classification of Disease (ICD)-10 codes; (II) medication use; (III) lab data; (IV) imaging data and readings of CT scans/chest X-rays; and (V) hospitalization summaries, operative records, and other outpatient electronic medical records (EMRs) enabling longitudinal follow-up. This provided us with basic demographics (age, sex) and other parameters, including comorbidities, body surface area (BSA) and body mass index (BMI), surgical events (i.e., operative date, natures of surgery, and materials used), admission and treatment details, and follow-up records of recurrence and survival.

This retrospective study was conducted in accordance with the Declaration of Helsinki (revised in 2013) and approved by the Institutional Review Board of the Catholic Medical Center (IRB No. KC22WISI0359). Written informed consent was waived, given that all extracted data had been anonymized.

Statistical analysis

The primary study outcome was trend in postoperative course following treatment of SP. As secondary outcomes, we analyzed risk factors for recurrence once initial surgical intervention had taken place.

For analytical convenience and clarity, some essential terms were defined as follows: (I) follow-up period was the interval from hospitalization for initial surgery to last outpatient visit, with final chest X-ray acquisition; (II) reference episode signified the pneumothorax event prompting initial surgery, at which time follow-up began; and (III) index episode referred to the first pneumothorax episode in instances where ≥ 3 additional ipsilateral pneumothoraces occurred within short periods (<6 months) after initial SP, regardless of past pneumothorax episodes or treatments.

The present study lacks some elements of the EMR, because all variables originated from an anonymised clinical data management (CDM) database. For example, the likelihood of a patient with one symptom only is low. However, so few records listed multiple symptoms that we were forced to extract and analyse main symptoms only among those described.

In an effort to consolidate the diversity of underlying pulmonary disease, only five working categories were

adopted. For COPD, qualifying patients were already diagnosed and under medical therapy or newly diagnosed at time of pneumothorax. The ILD category encompassed pneumoconioses and various types of ILD, including usual interstitial pneumonia (UIP) and idiopathic pulmonary fibrosis (IPF) (7). Patients with genetically linked conditions, such as Birt-Hogg-Dubé syndrome, or with radiographically and histologically confirmed lymphangiomyomatosis (LAM) were assigned to cystic lung disease (8). The immune-related category applied to those with existing connective tissue disorders or with graft-versus-host disease (GVHD) (9-11). Catamenial pneumothorax and assorted outliers were classified as others (12).

Study subjects were grouped by disease status after initial surgery (recurrence *vs.* non-recurrence), expressing patient characteristics as standardized statistical parameters, including mean \pm standard deviation (SD) or median values (continuous variables) and frequencies or percentages (categorical variables). Distributions of continuous variables were analyzed via Student's *t*-test or Mann-Whitney *U*-test, depending on results of Shapiro-Wilk normality test. Categorical variables were compared using chi-square or Fisher's exact test. To assess recurrence-free survival, Kaplan-Meier method was applied, and log-rank test served to compare survival curves by group.

We used Cox proportional hazards (PH) models to investigate factors associated with first recurrences after initial surgical interventions. Variables of significance ($P < 0.10$) by univariate analysis were tested in multivariate models. Several multivariate models were explored, basing model selection on Akaike information criterion (AIC) to choose the best fit for data. All analytics were driven by a conventional freeware (R v4.1.3; The R Project for Statistical Computing, Vienna, Austria), setting significance at $P < 0.05$.

Results

Baseline characteristics

Baseline characteristics of the two groups (with/without recurrences) are shown in *Table 1*. Ultimately, 160 patients with a mean follow-up of 58.7 months [interquartile range (IQR), 26.0–85.5 months] were selected for study. Distributions of baseline demographic data and clinical features (i.e., pertinent comorbidities, medication use, smoking history, and lab results) did not differ significantly

by group, whereas causes of SP showed significantly different group-wise distributions. The recurrence (*vs.* non-recurrence) group displayed a significantly lower incidence of COPD (46.7% *vs.* 76.9%; $P = 0.002$), with cystic lung disease found at significantly higher frequency (16.7% *vs.* 4.6%; $P = 0.034$). Smoking status did not differ significantly in the two groups, but amounts smoked (expressed in pack-years) were significantly greater for the recurrence (*vs.* non-recurrence) group. Group similarities in preoperative arterial blood gas analysis (not regularly obtained), albumin levels, and BMI status were also evident.

Clinical presentation of reference pneumothorax episode

Clinical attributes of reference pneumothorax episodes are summarized in *Table 2*. The most common symptom in both groups was dyspnea, followed by chest pain or discomfort; and duration of symptoms prior to hospital presentation was 2–3 days. Episodes of pneumothorax experienced before surgery ranged from 0–6, with means of 0.7 ± 1.1 and 0.6 ± 1.2 in non-recurrence and recurrence groups, respectively ($P = 0.42$). In both groups, initial surgery was performed on average 10 months after the first pneumothorax episode. The rate of surgery performed at first pneumothorax was 58.5% (non-recurrence group) and 66.7% (recurrence group) ($P = 0.170$).

Chest tubes were inserted at discretion of admitting surgeons, although 10 members (7.7%) of the non-recurrence group and 4 members (13.3%) of the recurrence group proceeded directly to surgery, without chest tubes ($P = 0.30$). Some surgical patients (non-recurrence: 26/130, 20.0%; recurrence: 5/30, 16.7%) were sent from outside hospitals with indwelling chest tubes, due to prolonged air leakage ($P = 0.80$). After chest tube placement, 55 (42.3%) and 11 (36.7%) patients in the respective groups opted for immediate surgery ($P = 0.682$), with mean times to surgery of 2.2 and 2.6 days, respectively. The others received conservative care, including bedside pleurodesis, with mean delays of 8.3 days (non-recurrence group) and 7.0 days (recurrence group) before surgery took place. Rates of pleurodesis for past pneumothorax events, prior to reference episodes, were 40.7% (22/54) in the non-recurrence group and 60.0% (6/10) in the recurrence group. Rates of preoperative pleurodesis for reference episodes of SP were also similar for these groups, performed in 27 (19.4%) and in 6 (19.4%) patients, respectively.

Table 1 Basic characteristics of the study population

Variables	No recurrence (n=130)	Recurrence (n=30)	P value
Age at the first operation (years)	63.2±13.29	61.9±15.15	0.654
Sex: male	116 (89.2)	24 (80.0)	0.284
BMI (kg/m ²)	22.01±3.32	22.24±4.49	0.554
Comorbidity			
Diabetes mellitus	13 (10.0)	2 (6.7)	0.739
Hypertension	54 (41.5)	11 (36.7)	0.777
Dyslipidemia	19 (14.6)	6 (20.0)	0.576
Tuberculosis	54 (41.5)	12 (40.0)	>0.99
Asthma	16 (12.3)	2 (6.7)	0.575
Rheumatologic disease	6 (4.6)	3 (10.0)	0.371
Underlying lung disease			
COPD	100 (76.9)	14 (46.7)	0.002
ILD	14 (10.8)	7 (23.3)	0.077
Pneumoconiosis	9 (6.9)	5 (16.7)	0.142
Cystic lung disease	6 (4.6)	5 (16.7)	0.034
Immune related	5 (3.8)	2 (6.7)	0.616
Others	7 (5.4)	2 (6.7)	0.677
Medication			
Inhalator	25 (19.2)	5 (16.7)	>0.99
Steroid	10 (7.7)	2 (6.7)	>0.99
Smoking history			
Current	26 (20.0)	9 (30.0)	0.114
Past	81 (62.3)	13 (43.3)	
Never	18 (13.8)	8 (26.7)	
Unknown	5 (3.8)	0 (0.0)	
Smoking pyrs (>0) [‡]	33.69±19.69	45.05±19.54	0.008
Hematocrit	42.00±4.84	41.36±4.46	0.362
Serum albumin	4.13±0.45	4.02±0.45	0.213
Arterial blood gas analysis [†]			
pH	7.398±0.079	7.430±0.042	0.046
PaCO ₂	45.64±49.41	36.79±5.81	0.186
PaO ₂	85.56±28.90	86.41±36.25	0.742

Continuous variables are presented as mean ± standard deviation and categorical variables as number (percentage). [†], arterial blood gas analysis was performed in 95 patients; [‡], missing values in 17 patients. BMI, body mass index; COPD, chronic obstructive lung disease; ILD, interstitial lung disease; pyrs, pack-years; PaCO₂, partial pressure of carbon dioxide; pH, potential of hydrogen; PaO₂, partial pressure of oxygen.

Table 2 Clinical characteristics of reference episode of pneumothorax and surgical treatment

Variables	No recurrence (n=130)	Recurrence (n=30)	P value
Symptoms [†]			0.869
Asymptomatic	5 (3.8)	1 (3.3)	
Chest pain/discomfort	34 (26.2)	10 (33.3)	
Cough	2 (1.5)	0 (0.0)	
Dyspnea	89 (68.5)	19 (63.3)	
Symptoms duration (days)	3.2±4.3	2.3±2.8	0.504
Sidedness compared to previous episode [‡]			0.371
Bilateral	1 (1.9)	1 (10.0)	
Contralateral	4 (7.4)	0 (0.0)	
Ipsilateral	49 (90.7)	9 (90.0)	
Side of pneumothorax			0.064
Left	45 (34.6)	16 (53.3)	
Right	85 (65.4)	14 (46.7)	
No. of previous pneumothorax			0.170
0	76 (58.5)	20 (66.7)	
1	28 (21.5)	7 (23.3)	
2	17 (13.1)	1 (3.3)	
3 or more	9 (6.9)	2 (6.6)	
Time from 1 st episode to 1 st surgery (months)	10.21±29.60	9.50±28.94	0.322
Planned surgery after chest tubes	55 (42.3)	11 (36.7)	0.682
Interval from tube to surgery (days)			
Straight to surgery	2.2±2.4	2.6±2.1	0.384
Delayed surgery	8.3±9.8	7.0±8.2	0.382
No. of pleurodesis before reference episode			0.847
0	108 (83.1)	24 (80.0)	
1	8 (6.2)	2 (6.7)	
2	11 (8.5)	3 (10.0)	
3	2 (1.5)	1 (3.3)	
6	1 (0.8)	0 (0.0)	
No. of preoperative pleurodesis at the reference episode	0.32±0.85	0.37±0.81	0.682
Index episode	15 (11.5)	9 (30.0)	0.023

Continuous variables are presented as mean ± standard deviation and categorical variables as number (percentage). [†], main symptoms only provided; [‡], cases with first episode are excluded from the calculation. No., numbers.

Table 3 Characteristics of index episodes

Variables	Index – (n=136)	Index + (n=24)	P value
Age	63.38±13.42	60.46±14.74	0.496
Sex: male	122 (89.7)	18 (75.0)	0.094
COPD	105 (77.2)	9 (37.5)	<0.001
Recurrence after surgery	21 (15.4)	9 (37.5)	0.023
Recur ipsi after 1 st op	6 (4.4)	7 (29.2)	<0.001
Recur contra after 1 st op	15 (11.0)	4 (16.7)	0.491
Chest tube to op (days)	5.91±8.35	4.29±4.60	0.395
Chest tube indwelling time after surgery (days)	5.05±6.03	4.04±2.31	0.904
Main procedure			0.012
Lung resection	127 (93.4)	18 (75.0)	
Non-resection	9 (6.6)	6 (25.0)	
Reinforcing method			0.125
None	9 (6.6)	3 (12.5)	
Single	13 (9.6)	1 (4.2)	
Double	70 (51.5)	12 (50.0)	
Triple	43 (31.6)	6 (25.0)	
Quadruple	1 (0.7)	2 (8.3)	
Additional procedure			0.035
None	118 (86.8)	16 (66.7)	
Diaphragm resection	2 (1.5)	2 (8.3)	
Pleurodesis	15 (11.0)	6 (25.0)	
Plication	1 (0.7)	0 (0.0)	
Time to recurrence (mo)	51.38±41.48	50.79±43.74	0.727
1 st PTX to surgery (mo)	8.74±28.78	17.62±32.22	<0.001

Continuous variables are presented as mean ± standard deviation and categorical variables as number (percentage). COPD, chronic obstructive lung disease; ipsi, ipsilateral; op, operation; contra, contralateral; PTX, pneumothorax; mo, months.

Index episodes

In reviewing our data, we noticed that some patients had recurrent ipsilateral episodes within relatively short periods of time for various reasons. As mentioned earlier in the text we defined the first of these as index episodes. There were ≥3 ipsilateral episodes less than 6 months apart in 15 members (11.5%) of the non-recurrence and in 9 members (30.0%) of the recurrence group (P=0.023) (Table 2).

Characteristics of index episodes are summarized in

Table 3 and in Table S1. Within the cohort overall, 24 patients (15.0%) registered index episodes. These particular cases did not differ from those without index episodes in comorbidities, smoking history, or preoperative blood chemistry, although the rate of COPD was significantly lower. In terms of surgical approach, pulmonary resection as the main procedure was done significantly fewer times in the index group, pleurodesis more often performed instead. Postoperative recurrences were higher, especially on operative sides.

Preoperative, intraoperative, and postoperative pleurodesis

A total of 36 patients (recurrent group, 5; non-recurrent group, 31) had undergone preoperative pleurodesis procedures when reference pneumothoraces developed, with 28 patients (17.5%) submitting to more than one pleurodesis for prior episodes of pneumothorax. Twelve of these 36 patients had received some form of pleurodesis prior to reference events. Single preoperative pleurodesis procedures took place in 15 patients, with two performed in 14 patients, three in six patients, and six in one patient. Agents utilised were subject to surgeon preference, but autologous blood, fibrin products, and doxycycline were favoured over talc and were often applied in combination. Preoperative pleurodesis was usually reserved for patients deemed medically unfit for surgery or was done as a presurgical trial to address persistent air leakage after chest tube insertion. The timing of such trials was often surgeon-dependent, but for the most part, 5 days or more has elapsed after tube placement.

Intraoperative pleurodesis was generally an adjunct to main procedures, especially if future operations might be risky or fraught with technical difficulties. Talc was the preferred agent (15 patients), with some use of fibrin products (3 patients) or betadine (3 patients). Postoperative pleurodesis was indicated for persistent air leakage, again the timing and agent at surgeon's discretion. The most commonly used agents were fibrin (4 patients), autologous blood (2 patients) and doxycycline (1 patient).

Surgical treatment and postoperative course

In most of our patients, bullae with air leaks were treated by wedge resection, although extended resections and additional procedures were variably undertaken as well (Table 4). Diaphragmatic resection was performed in four patients with catamenial pneumothoraces and defects (perforations) of the diaphragm. In one unusual case requiring lobectomy, the patient's upper lobe was severely emphysematous, leaving almost no residual healthy parenchyma. As surgical reinforcement, several types of fibrin glue, oxidized regenerated cellulose dressings [Surgicel; Ethicon (Johnson & Johnson), Raritan, NJ, USA], polyglycolic acid sheets (Neoveil; Gunze Medical, Osaka, Japan), or TachoSil patches (Corza Medical, Westwood, MA, USA) were applied (alone or in combination) at surgeon's discretion. The two groups did not differ significantly in this regard.

There was no operative mortality overall, and in the recurrence group, mean number of pneumothorax episodes after initial surgery was 1.5 ± 0.97 . Postoperative complications, including needed pleurodesis, reoperation (for prolonged air leakage), or other warranted procedures, were similar for the two groups.

During the median follow-up period of 48.00 months, there were 26 deaths (20.0%) in the non-recurrence group and 10 deaths (33.3%) in the recurrence group ($P=0.18$). Causes of death were identified in 18 patients. One suffered a recurrent pneumothorax, another died of coronavirus disease 2019 (COVID-19) pneumonia, and the majority succumbed to adult respiratory distress syndrome with aggravated underlying lung disease ($n=9$) or simply progression of malignancy ($n=7$). The two groups were similar in overall survival (non-recurrence, 66.39 ± 43.36 months; recurrence, 76.57 ± 55.20 months; $P=0.56$).

Among the 31 patients with recurrences, 14 recurrent events (46.7%) were on same sides as surgery, and 16 (53.3%) were not. Median time to first recurrence was 21.5 months (ipsilateral, 23.64 months; contralateral, 59.94 months). Patterns of recurrence are illustrated in Figure S1. Our graph depicting each pneumothorax episode and lateralities of surgical interventions is quite complex and inconsistent. However, it is apparent that pneumothorax may recur well after surgery is performed (Figure S1A,S1B), and that an index episode is present on some occasions (Figure S1C).

Univariate and multivariate Cox PH analyses were conducted to identify risk factors for recurrence, using variables of significance ($P<0.10$) in univariate analysis for the full Cox PH model (Table 5). Each variable in the multivariate model met the assumption of PH, with $P>0.05$ in Schoenfeld residuals testing. Inverse relations with recurrence were shown for right-sided surgery [hazard ratio (HR) =0.304, 95% confidence interval (CI): 0.136–0.676] and presence of COPD (HR =0.104, 95% CI: 0.016–0.665) in the full model. Model selection was based on AIC to determine best fit of data. In the final model, underlying disease (especially presence/absence of COPD) was strongly associated with postsurgical recurrence (HR =0.188; $P<0.001$). Kaplan-Meier plots indicated significantly greater risk of recurrence in the presence of non-COPD underlying pulmonary disease (*vs.* underlying COPD) (Figure 2).

Discussion

Unlike primary spontaneous pneumothorax, SP is a

Table 4 Surgical treatment and postoperative course

Variables	No recurrence (n=130)	Recurrence (n=30)	P value
Approach			0.036
VATS	110 (84.6)	20 (66.7)	
Thoracotomy	20 (15.4)	10 (33.3)	
Main procedure			0.280
Wedge resection	118 (90.8)	25 (83.3)	
Segmentectomy	1 (0.8)	0 (0.0)	
Lobectomy	0 (0.0)	1 (3.3)	
Plication	4 (3.1)	2 (6.7)	
Pleurodesis	6 (4.6)	2 (6.7)	
Diaphragm resection	1 (0.8)	0 (0.0)	
Additional procedure			0.121
None	112 (86.2)	22 (73.3)	
Diaphragm resection	2 (1.5)	2 (6.7)	
Pleurodesis	15 (11.5)	6 (20.0)	
Plication	1 (0.8)	0 (0.0)	
Reinforcing method			0.901
None	9 (6.9)	3 (10.0)	
Single	12 (9.2)	2 (6.7)	
Double	65 (50.0)	17 (56.7)	
Triple	41 (31.5)	8 (26.7)	
Quadruple	3 (2.3)	0 (0.0)	
Postop. chest tube indwelling time (days)	4.92±5.82	4.83±4.86	0.766
Postop. complication	17 (13.1)	3 (10.0)	0.769
Persistent air leakage (>5 days)	10 (7.7)	1 (3.3)	0.691
Chest tube reinsertion	5 (3.8)	1 (3.3)	>0.99
Empyema	1 (0.8)	0 (0.0)	>0.99
Pneumonia	4 (3.1)	0 (0.0)	>0.99
Reoperation due to PAL	4 (3.1)	0 (0.0)	>0.99
Wound infection	0 (0.0)	1 (3.3)	0.188
Postoperative pleurodesis	7 (5.4)	0 (0.0)	0.349
No of total PTX episode	1.7±1.13	3.1±1.52	<0.001

Continuous variables are presented as mean ± standard deviation and categorical variables as number (percentage). VATS, video-assisted thoracoscopic surgery; Postop., postoperative; PAL, persistent air leakage; PTX, pneumothorax.

Table 5 Cox pH analysis of risk factors of overall recurrence after surgery

Variables	Univariate			Multivariate					
	HR	95% CI	P	Full model			Best fit model [†]		
				HR	95% CI	P	HR	95% CI	P
Age	0.995	0.968–1.023	0.720	1.017	0.976–1.059	0.425	1.023	0.994–1.053	0.126
Sex: male	0.398	0.160–0.993	0.048	2.259	0.399–12.800	0.357			
COPD (Y)	0.191	0.090–0.406	<0.001	0.104	0.016–0.665	0.017	0.188	0.082–0.431	<0.001
Pneumoconiosis (Y)	2.878	1.170–7.076	0.021	1.246	0.291–5.343	0.767			
Rheuma (Y)	4.261	1.244–14.59	0.021	2.184	0.407–11.713	0.362			
Cystic (Y)	5.079	1.866–13.83	0.002	2.363	0.451–12.388	0.309	2.567	0.839–7.856	0.099
ILD (Y)	3.122	1.379–7.066	0.006	0.35	0.044–2.813	0.323			
Preop. inhalator	0.913	0.347–2.401	0.853						
Preop. steroid	1.201	0.282–5.121	0.804						
Exposure to smoking (Y)	0.604	0.267–1.363	0.225						
Index episode (Y)	2.828	1.281–6.246	0.010	1.517	0.604–3.807	0.323			
Surgery at 1 st pneumothorax	1.355	0.630–2.916	0.437						
Approach (VATS vs. thoracotomy)	1.214	0.505–2.919	0.665						
Main procedure (non-resection)	2.033	0.702–5.883	0.191						
Adjunctive procedure									
Diaphragm resection	5.396	1.245–23.40							
Pleurodesis/plication	1.41	0.525–3.787							
Intraoperative pleurodesis	0.339	0.116–0.988	0.048	0.304	0.136–0.676	0.399			
Reinforcing									
Single	0.253	0.046–1.392	0.114						
Double	0.329	0.107–1.015	0.053						
Triple	0.412	0.123–1.375	0.149						
No. PTX before surgery	0.887	0.626–1.257	0.501						
Side of surgery (Rt.)	0.369	0.176–0.775	0.008	0.304	0.136–0.676	0.004			
Early surgery after CTD	0.704	0.329–1.505	0.365						
Postop. morbidity	1.156	0.344–3.883	0.814						
PAL	0.753	0.103–5.599	0.782						
CTD reinsertion	1.211	0.163–8.983	0.852						

[†], final multivariate model incorporates only variables optimised by AIC while satisfying Cox proportional hazards assumption. HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive lung disease; Y, yes; Rheuma, rheumatologic lung disease (connective tissue disease related); Cystic, cystic lung disease; ILD, interstitial lung disease; Preop., preoperative; Postop., postoperative; VATS, video-assisted thoracoscopic surgery; No., number; PTX, pneumothorax; Rt., right; CTD, closed thoracostomy drainage; PAL, persistent air leakage; AIC, Akaike information criterion.

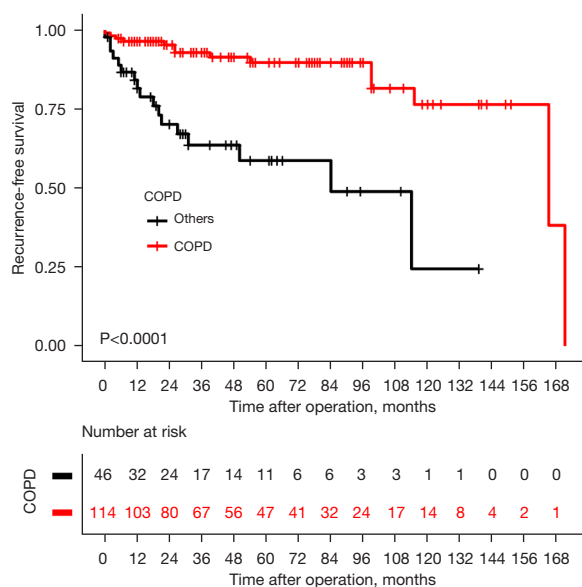


Figure 2 Kaplan-Meier plot for risk of recurrence in the patients with or without chronic obstructive lung disease. COPD, chronic obstructive pulmonary disease.

potentially life-threatening event, often refractory to treatment. Clinical management of SP is a challenging task on two fronts. First, the healing process is slow, and recurrences are more likely (with or without surgery) due to underlying lung disease. Second, susceptible patients are typically older, with multiple comorbidities and limited cardiopulmonary reserves, and frequently are given potentially problematic drugs, such as steroids, anticoagulants, or immunosuppressive agents, that may interfere with treatment (13,14). Hence, treatment of SP tends to be a case-by-case endeavor, rather than evidence-based proposition.

During our retrospective review of data, underlying lung disease emerged as the most important risk factor for recurrence after surgical treatment of SP. In univariate analysis, female sex, non-COPD disorders (i.e., pneumoconioses, cystic lung disease, or ILD), associated rheumatologic disease, and presence of index episodes were identified as risk factors for postoperative recurrence, whereas intraoperative pleurodesis showed a protective effect, preventing against recurrence. However, the only significant risk factor to surface from multivariate analysis proved to be underlying lung disease. The risk of postsurgical recurrence increases 5.3 times greater [inverse of HR (0.188) for COPD, Table 5]. Recurrence rates after surgical treatment of SP are reportedly in the range of

0–15.8% (14).

Previous investigations, although small-scale and sporadic, have shown that SP incidence and recurrence rates for various underlying lung disease differ in relation to treatment. In the context of SP, the underlying disease most often cited is COPD with emphysema, followed by cystic fibrosis, tuberculosis, lung cancer, interstitial pneumonitis, and others (3,4,13–15). Findings in our cohort were partly corroborative, COPD accounting for 71.3% (114/160), followed by ILD (13.1%), Birt-Hogg-Dubé syndrome or LAM, and GVHD-related pulmonary disease. The reported prevalence of SP among patients with COPD is 345/100,000 patients per year (16); and in documented instances of COPD, recurrent pneumothorax episodes are common, occurring in 20–60% of patients (17).

SP may develop as a complication of ILD, the reported incidence ranging from 12.9–20.2% (11,18). Because SP is ingrained in the clinical course of ILD, treatment options are usually limited, with unsatisfactory results. The known recurrence rate is high (up to 70%), and some cases are deemed intractable, necessitating lifelong closed thoracostomy drainage tubes (19). Birt-Hogg-Dubé syndrome is a rare autosomal dominant inherited condition where mutation of the *FLCN* gene leads to renal tumors and multiple pulmonary cysts (20,21). Such cysts are common manifestations, appearing in 70–89% of affected patients, with resultant spontaneous pneumothoraces in a fair percentage (24–38%). Thus, pneumothorax may be the first manifestation of this disease (22,23). The recurrence rate and clinical features after surgical intervention are not fully appreciated as yet. In our cohort, nine patients with this syndrome, and four of them developed recurrences.

During our exploratory data review, an interesting phenomenon was noted, namely the clustering of pneumothorax episodes on occasion. We have observed three or more consecutive ipsilateral SP recurrences, occurring within 6-month periods, arbitrarily referencing the first incident as index episode while seeking to characterise related clinical features. The proportion of our patients with these index episodes was 15%, and some experienced cluster episodes long after first SP events. Underlying diseases were more likely non-COPD conditions, such to ILD, cystic lung disease, connective tissue disorders, or GVHD-related lung changes; and procedures other than bullae resections were involved, which may explain the observed series of ipsilateral postsurgical recurrences. We therefore tentatively assert that pneumothorax events may be clustered in some

patients with non-COPD disease, calling for careful intervention (including surgery or other procedures) to reduce recurrences and necessitating longer follow-up monitoring. Of course, this requires large-scale studies to provide needed confirmation.

Concerns over postoperative morbidity (i.e., pneumonia, persistent air leakage) and mortality tend to make decisions on surgical treatment of SP more guarded (24). Chest tube placement is aimed at lung re-expansion, symptom relief, and perhaps healing of injured visceral pleura. It is not a means for mitigating recurrence. Considering the high propensity to recur, which varies by source (25–50%), and the medical emergencies attached, preventing recurrences is clearly worthwhile (5). Unfortunately, available guidelines are at odds on the timing of recurrence prevention. Although the BTS recommends prevention at second occurrence, the ACCP suggests earlier attempts at first SP episode (1,2). We cautiously support that judicious use of early surgical treatment in medically fit patients, knowing that some events will be index episodes that eventuate in clusters of SP.

Surgical interventions for SP ultimately have two objectives: treatment of current episodes, especially if air leakage persists, and recurrence prevention. BTS guidelines also advocate consultation with a thoracic surgeon within 48 hours of chest tube insertion if persistent air leakage is anticipated. Decisions to operate at our institution have largely been based on failure of conservative management, including bedside pleurodesis and chest tube monitoring during reference episodes, or recurrent SP with the need for definitive therapy. Surgery is pursued only after in-depth discussion of benefits and risks with patient and family.

Limitations of the present study include its retrospective design, which inherently introduces selective bias. Our particular database-dependent analysis also kept us from grading degrees of emphysematous change or COPD. In addition, detailed analysis of comorbidities was curtailed, and some incomplete data was discarded, possibly affecting subsequent results. There is a caveat as well for retrospective studies of this sort, spanning lengthy time periods. Such extended reviews may encourage temporal biases (such as attrition bias), rendering ultimate findings less precise.

Our aim was to observe the natural history of SP after surgery, so long-term follow-up was essential. However, patient populations are apt to vary, and trends in management, physician preference, or even surgical approach (for example, thoracoscopy *vs.* thoracotomy) will

invariably shift over time. We used year of surgery as a surrogate marker of time-related bias, owing to constraints of our CDM sourcing, but this showed no statistical significance in either univariate or multivariate analysis. Nonetheless, it is our contention that some bias would be unavoidable. This issue may otherwise be addressed by a well-designed, prospective observational study.

Finally, our focus in the present study was on postsurgical aftermath, as opposed to deciding which SPs merit surgery at first presentations. The latter pursuit was beyond our capacity but would still be most helpful for clinicians and clearly demands further investigation. The value of this current effort was our ability to monitor factors associated with postsurgical SP recurrence during long-term follow-up (median, 48 months) in a qualifying patient population. We also confirmed a tendency in some for serial pneumothorax episodes, clustered within short periods of time. As shown by our analysis, observed recurrences are often attributable to underlying diseases other than COPD and are not expressly linked to treatment choice.

Conclusions

During a median follow-up of 58.7 months, the postoperative recurrence rate in patients with SP was 18.75% (30/160), with an 8.7% (14/160) rate of ipsilateral recurrence. Underlying lung disease, especially in non-COPD categories (such as ILD, cystic lung disease, connective tissue disorders, or GVHD-related changes), proved to be the major risk factor for first recurrence after surgery. In addition, some of our patients experienced successive SP events, with index episodes. It is imperative to conduct in-depth discussions with patients and their families, tailoring surgical intervention to each patient's clinical parameters and underlying disease aetiology. Long-term clinical follow-up may be beneficial in this setting, given the proclivity for recurrence and the constellation of predisposing lung pathology.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-867/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in the ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This retrospective study was conducted in accordance with the Declaration of Helsinki (revised in 2013) and approved by the Institutional Review Board of the Catholic Medical Center (IRB No. KC22WISI0359). Written informed consent was waived, given that all extracted data had been anonymized.

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