

Clinical and Radiological Characteristics of Patients Diagnosed with Spontaneous Pneumothorax: Treatment Options and Clinical Outcomes. A Retrospective Analysis 2004 to 2017

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ABSTRACT **Background:** Primary spontaneous pneumothorax (PSP) tends to occur in young adults without underlying lung diseases and is usually followed by limited symptoms, while secondary spontaneous pneumothorax (SSP) is a complication of a pre-existing lung disease. Surprisingly, for such common conditions, there is a considerable inconsistency regarding management guidelines.

Objectives: To evaluate the risk factors for spontaneous pneumothoraxes and to summarize outcomes and complications based on our clinical experience.

Methods: This retrospective study group was comprised of 250 consecutive patients older than 18 years of age who were diagnosed with spontaneous pneumothorax and hospitalized at the Meir Medical Center (2004–2017). Data on demographic characteristics, indicating symptoms, chest X-rays, and chest computed tomography (CT) results were collected. Our experience and outcomes were then compared to a large multicenter study.

Results: Most of the patients were male (85%) and past or current smokers; 69% presented with PSP, while the rest were SSP. No occupational relation was noted. About 55% of the cases presented with a moderate or large pneumothorax (over 1/3 hemithorax). Most patients (56%) required chest tube drainage and 20% undergone surgery. Nearly 10% presented with a recurrent pneumothorax with the mean time to recurrence being 11 ± 20 days. Although the length of hospital stay of patients that underwent surgery was the longest $P < 0.001$ for both PSP and SSP, the recurrence rate was actually reduced, suggesting some benefit for the surgical treatment option.

Conclusions: Our experience showed that the traditional approach to the PSP treatment should be further considered, as previously suggested.

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Pneumothorax is a global health problem, with considerable associated morbidity, as without a prompt diagnosis and management, pneumothorax could be fatal. Primary spontaneous pneumothorax (PSP) occurs in patients without clinically apparent lung disease, while secondary spontaneous pneumothorax (SSP) is a complication of a pre-existing lung disease. SSP is associated with a considerably increased morbidity and mortality compared to PSP, because of the existing decrease in cardio-pulmonary reserve in patients with a pre-existing lung disease.

Based on previous reports, the incidence of PSP was estimated at 18–28 men/100,000 and 1.2–6 women/100,000 inhabitants [1]. The peak incidence is observed in the age range of 15–34 years [2]. The most substantial risk factor for this condition is tobacco addiction. Compared to non-smokers, the risk is 21 times higher in moderate smokers and 80 times higher in heavy smokers [3]. Surprisingly, in spite of it being a relatively common condition, there are considerable inconsistencies regarding its management [4,5]. The available options range from simple observation to aspiration or drainage (with or without chemical pleurodesis) to surgical intervention [6].

The chest drain insertion is a painful procedure, with up to 50% of patients experiencing pain levels of 9–10 on a scale of up to 10 [7]. In addition, it has several complications, such as organ injury, bleeding, infection, and even death [8]. Since hospital admission is required when chest drain is inserted, with an average length of stay (LOS) of about 4 days [8,9], in addition to air leaks that may occur and result in surgery [5,10], the necessity of any interventional approach for PSP has been challenged [10–12].

In this study, we aimed to determine clinical and epidemiological characteristics of patients diagnosed with primary or secondary spontaneous pneumothorax, in regard to initial interventions and their influence on the recurrence rate, LOS and other related outcomes. We retrospectively evaluated our choices of treatment to discover possible underlying factors that could affect future decision-making.

PATIENTS AND METHODS

STUDY POPULATION AND STUDY PARAMETERS

The initial retrospective study group consisted of 443 patients who were older than 18 years of age and diagnosed with pneumothorax between January 2004 and December 2017 at the Meir Medical Center. With the iatrogenic pneumothorax defined as exclusion criterion, the final study group included 250 patients. The demographic data collected included patient age, gender, prior history of pneumothorax, presence of a lung disease, occupation, and tobacco smoking status. All available clinical records were reviewed for other underlying causes.

Patients were defined as having PSP or SSP according to history (emphysema, lung bullae, interstitial lung disease, and space occupying lesions) and imaging (chest X-ray and computed tomography [CT] findings).

Pneumothorax was characterized according to imaging as right- or left-sided, small (less than 1/3 of hemithorax volume), moderate (between 1/3 and 1/2 of hemithorax volume), or large (larger than 1/2 hemithorax) or full hemithorax. Only patients with symptomatic pneumothorax underwent treatment (drainage or surgery). The procedure of choice in our center was chemical pleurodesis for cases in which there was no background pulmonary disease and partial pleurectomy otherwise.

LOS was examined for all treatment options, including recurrent hospitalization in case of treatment failure. Recurrence was defined as hospitalization with the same diagnosis. Time to recurrence was defined as the elapsed time from the previous hospitalization.

STATISTICAL ANALYSIS

Table 1. Patient characteristics

Parameter	PSP N=173	SSP N=77	P value
Sex, male	155 (89.6%)	58 (75.3%)	0.003
Age	28.7 ± 11.8	46.32 ± 22.2	< 0.001
Smoking	78 (45%)	39 (50.6%)	0.003
Observation	49 (28.3%)	13 (16.9%)	< 0.0001*
Drainage	103 (59.5%)	37 (48.1%)	
Surgery	21 (12.1%)	27 (35.1%)	
Previous pneumothorax	45 (26%)	28 (36.4%)	0.097
Large pneumothorax	70 (40.4%)	41 (53.6%)	0.26

*Pearson chi-square for treatment options vs. PSP/SSP
PSP = primary spontaneous pneumothorax, SSP = secondary spontaneous pneumothorax

Continuous variables are presented as mean or median ± standard deviation, or as numbers and percentage for nominal parameters. Comparison between the two study groups was determined by *t*-test, Mann-Whitney test, Fisher's exact test, or Pearson chi-square test according to the scale measured variables. The difference between the groups was considered statistically significant at the two-sided $P < 0.05$. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 23 (SPSS, IBM Corp, Armonk, NY, USA).

ETHICS APPROVAL

All procedures performed in studies involving human participants were completed in accordance with the ethics standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethics standards. For this type of study no formal consent was required.

RESULTS

PATIENT CHARACTERISTICS

The study population was comprised of 250 patients, most of them young males (85%), with the average age 34 ± 18 years. Of these patients, 173 were PSP (69%) and the rest SSP. As expected, the average age of the PSP patients was significantly lower than the SSP patients ($P < 0.0001$). The study group included a significant number of active smokers (47%) [Table 1]. The side (left/right) distribution of the pneumothorax was equal (49% each), where only three patients (1.2%) presented with a bilateral pneumothorax. Seventy-three (29%) patients had a previous event. The majority of subjects (55%) presented with a moderate or large pneumothorax (more than one-third hemithorax) established by chest CT at admission. Recurrence of pneumothorax was more evident in the SSP group (14.2% vs. 7.9%, $P = 0.095$), when analyzing recurrence rates according to treatments [Table 1].

As for the treatments, most patients (56%) underwent drainage, 29% underwent a surgical procedure, while only 62 patients (25%) stayed under observation only. When examining the PSP cases only ($n=173$), we found that 28.3% were under observation only ($n=49$), while 59.5% were treated with chest tube drainage [Table 1].

Although smoking and age are significant risk factors for PSP, we found that these factors had no effect on the decision whether to perform an intervention. The most significant factors were the finding of a moderate and large pneumothorax and whether it was PSP or SSP. When comparing procedure choices, we found that those who had a previous pneumothorax and those with SSP were more prompted for surgery ($P < 0.0001$).

PATIENT OUTCOME

The percentage of cases that progressed to surgery in the observation group and the interventional group was similar (9.7% vs. 8.2%, $P = 0.73$). In total, approximately 10% of patients had a recurrence, with the average time of 11 ± 20 days

and average LOS of 6 ± 5.3 days. Half of the recurrent patients were re-admitted during the first month after discharge. Six patients had three pneumothorax episodes. Three of them were PSP and three SSP. While on their second event, these patients were treated mostly by drainage and only one remained in observation. However, on their third event they mostly underwent surgery (5 of 6 patients).

Although the LOS of patients that underwent surgery was the longest for both PSP and SSP, $P < 0.001$ [Figure 1A], the recurrence rate was actually reduced [Figure 1B], suggesting some benefit for the surgical treatment option.

OUR EXPERIENCE

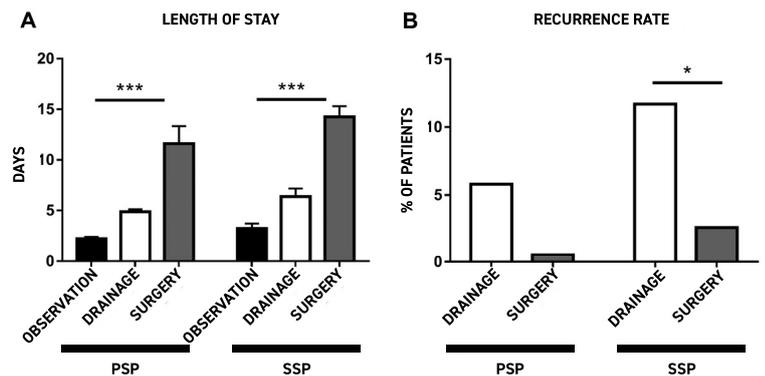
Although our study included a relatively large group of patients, we wanted to further validate the results by comparing them to recently published studies. We chose to focus on the work of Brown et al. [12] since it is a multicenter study, and therefore allowed for analysis with a similar number of patients. This comparison is shown in Table 2. The recurrence rates in the observation-only group, were similar between our study and theirs. The Brown group reported five (5.5%) events, while we had three (4.8%). However, in the intervention group, they reported 40 (17.2%) cases and we reported only 22 recurrent cases (11.7%, $P = 0.1$, chi-square analysis). These results support our results regarding the type of intervention, where the surgical option, which was used more by us, can in fact reduce the recurrence rate.

DISCUSSION

We summarized our experience with 250 spontaneous pneumothorax patients. Similar to previous studies [13-15], our cohort consisted of mainly young males, most of them smokers, with no correlation to their occupational status. Approximately one-third of our study population was diagnosed with SSP, and almost half presented with a moderate to large pneumothorax.

Figure 1. Hospital length of stay and recurrence rates differ according to the initial intervention [A] length of stay [B] recurrence rate

LOS = length of stay, PSP = primary spontaneous pneumothorax, SSP = secondary spontaneous pneumothorax



There is a wide range of treatment options for pneumothorax [16]. In this study, we examined the factors that affected the decision making regarding the treatment options, since current guidelines vary significantly. These characteristics include the smoking status, age, sex, occupation, previous pneumothorax, pneumothorax size, and SSP vs. PSP. We also evaluated the outcomes of the treatment options chosen, since the interventional approach for PSP has been recently challenged.

In total, 28% of the PSP cases were under observation only, and 59% were treated with chest tube drainage. These results are similar to the previous study by Brown et al. [12], described their experience with PSP patients that showed 33% to be under observation and 66% with drainage. Although our numbers are a bit lower, we did not find a significant difference.

We found that the decision whether to perform some kind of an intervention was mostly based on the size of the pneumothorax

Table 2. Comparison between patient characteristics in our study vs. Brown et al. [12]

	Parameter	Our data	Brown et al.	P value
PSP		N=173	N=225	
	Previous pneumothorax	45 (26%)	55 (24.4%)	0.720857
	Observation only	49 (28.3%)	75 (33.3%)	0.284739
	Drainage	103 (59.5%)	150 (66.6%)	0.142913
SSP		N=77	N=98	
	Previous pneumothorax	28 (36.4%)	27 (27.5%)	0.212562
	Observation only	13 (16.9%)	16 (16.3%)	0.9
	Drainage	37 (48%)	82 (83.7%)	0.000001

PSP = primary spontaneous pneumothorax, SSP = secondary spontaneous pneumothorax

and on whether it was primary or secondary. These findings correlate with previous publications [17] that stated that with a primary condition the recommendation is a traditional non-invasive treatment. In cases of a SSP or a treatment failure the recommendation is to proceed to the surgical option. Mendis et al. [18] also showed that SSP was an underlying consideration for an interventional procedure. Sahn and Heffner [14] showed that the size was a differentiating factor to determine the treatment choice. The smaller cases (under 15%) were treated more traditionally and the larger ones were treated with more invasive procedures. For SSP, current guidelines recommend chest drain insertion for moderate to large pneumothoraxes defined as larger than 30–50% of hemithorax volume, with a lower threshold for drainage insertion for smaller pneumothoraxes [4,5]. Generally, SSP management tends to involve a more interventional approach because of increased morbidity, symptoms, and cardiorespiratory compromise. Nevertheless, for PSP there is a debate whether the chest drain insertion is beneficial, as it was shown by Janssen et al. that an air leak is less likely to resolve spontaneously and the hospital stay is longer for those that undergone chest drain insertion [11]. Our results support these findings, as we found that the outcome of the drainage procedure is actually worse, with higher recurrence rates and a longer LOS compared to traditional observation.

In symptomatic cases where intervention is needed, official guidelines differ in the approach to PSP. The British Thoracic Society (BTS) advocates needle aspiration, while the American College of Chest Physicians (ACCP) advocates chest tube drainage. The recent prospective study comparing needle aspiration to chest tube insertion found that needle aspiration is effective as the initial approach, and may allow outpatient management for some pneumothorax cases [19,20]. In our cohort, needle aspiration was offered only for the younger patients with a minor PSP, which were discharged without hospitalization.

In our study, the recurrence rate was about 10%. This result corresponds to previous works that involved patients having either conservative management or drainage [21]. Brown and colleagues [12] showed recurrence rate of 5% for the traditional approach and 17% for those treated with a chest drain. One of the few randomized controlled trials performed, consisted of 66 patients with primary or secondary pneumothorax, allocated patients to either mini-thoracotomy or video-assisted thoracoscopic surgery (VATS), and showed equivalent recurrence rates [22].

Recently, two large open-label, randomized controlled trials were published regarding the treatment of patients with pneumothorax [23,24]. The first study assessed the role of conservative management versus interventional treatment for patients with unilateral moderate to large PSP [23]. They found that the conservative approach was non-inferior to interventional management, with a lower risk of serious adverse events. The second study assessed the role of ambulatory versus the standard guideline-based management of PSP [24]. In that study, Halifax and co-authors [24] found that ambulatory management reduced

the duration of hospitalization including re-admissions in the first 30 days, but at the expense of increased adverse events. Therefore, the outpatient based treatment should be considered for all patients with PSP, including the symptomatic cases.

Our study has several limitations. First, it is a retrospective cohort. However, our findings were similar to previous reports, therefore supporting published data. In addition, the randomized controlled trial option is extremely challenging. Second, our study population included only the hospitalized patients, therefore excluding the mild cases of minor pneumothorax. However, since the management of such cases is more consistent, we believe this did not affect our results.

CONCLUSIONS

Our experience showed that the traditional approach to the PSP treatment should be further considered, as previously suggested. However, although attempts have been made to discover additional underlying causes, such as risk-prone life style conduct [25], no clear guidelines exist. Further study is warranted to find the underlying causes and triggers to better define management guidelines in this relatively abundant situation.

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Capsule

Neuroprotective neutrophils?

The infiltration of activated immune cells into the central nervous system can contribute to the pathophysiology of conditions such as multiple sclerosis and traumatic brain injury. The roles that immune cells play in the resolution of inflammation and the regeneration of damaged tissue are less well understood. **Sas** et al. reported the existence of a distinct population of Ly6G^{lo} cells resembling immature neutrophils that were elicited in a mouse model of optic nerve injury. Intraocular injection of a fungal cell wall extract induced the migration of these cells into the eye,

where they promoted retinal ganglion cell survival and axonal regeneration, in part through a range of secreted nerve growth factors. These Ly6G^{lo} cells also spurred axonal regeneration in a mouse model of spinal cord injury. Similar regenerative capacity by an immature human neutrophil cell line suggests that immature granulocytes may be an attractive potential target for future neuroregenerative therapies.

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Capsule

An inflammatory cytokine signature predicts COVID-19 severity and survival

Several studies have revealed that the hyper-inflammatory response induced by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a major cause of disease severity and death. However, predictive biomarkers of pathogenic inflammation to help guide targetable immune pathways are critically lacking. **Del Valle** and colleagues implemented a rapid multiplex cytokine assay to measure serum interleukin (IL)-6, IL-8, tumor necrosis factor (TNF)- α , and IL-1 β in hospitalized patients with coronavirus disease-2019 (COVID-19) on admission to the Mount Sinai Health System in New York. Patients (n=1484) were followed up to 41 days after admission (median 8 days) and clinical information, laboratory test results, and patient outcomes were collected. The authors found that high serum IL-6, IL-8, and TNF- α levels at

the time of hospitalization were strong and independent predictors of patient survival ($P < 0.0001$, $P = 0.0205$, and $P = 0.0140$, respectively). Notably, when adjusting for disease severity, common laboratory inflammation markers, hypoxia and other vitals, demographics, and a range of co-morbidities, IL-6 and TNF- α serum levels remained independent and significant predictors of disease severity and death. These findings were validated in a second cohort of patients (n=231). They propose that serum IL-6 and TNF- α levels should be considered in the management and treatment of patients with COVID-19 to stratify prospective clinical trials, guide resource allocation and inform therapeutic options.

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