Recurrence rates in primary spontaneous pneumothorax: a systematic review and meta-analysis

Abstract

Primary Spontaneous Pneumothorax (PSP) recurrence rates vary widely in the published literature, with limited data describing the factors that influence recurrence. The aims of this systematic review were to determine an estimation of PSP recurrence rates and describe risk factors for recurrence.

A systematic review was conducted of all studies reporting PSP recurrence. Electronic searches were performed to identify English language publications of randomised trials and observational studies. The population was adults with PSP, who underwent conservative management, pleural aspiration or chest drainage. The outcome of interest was recurrence. Articles were screened, and data extracted from eligible studies by two reviewers.

Of 3607 identified studies, 29 were eligible for inclusion, comprising 13,548 patients. Pooled 1-year and overall recurrence rates were 29.0%(95% CI 20.9% to 37.0%) and 32.1%(95% CI 27.0% to 37.2%) respectively. Female gender was associated with increased recurrence, OR 3.0(95% CI 1.24 to 7.41), whilst smoking cessation was associated with fourfold decrease in risk, OR 0.26(95% CI 0.10 to 0.63). I^2 for random effects meta-analysis was 94%(p<0.0001) reflecting high heterogeneity between studies.

This systematic review demonstrates a 32% PSP recurrence rate, with greatest risk in the first year. Female gender was associated with higher risk, suggesting possible gender-specific pathophysiology.

Introduction

Primary spontaneous pneumothorax (PSP) is a disease of young people, with an annual incidence of 7.4 per 100,000 in males and 1.2 per 100,000 in females[1]. Current BTS guidelines advise that pneumothorax recurrence is an indication for surgery (whether second ipsilateral or first contralateral),[2] however the incidence of recurrence is unknown. PSP recurrence rates are typically cited as between 16 and 52%, which makes counselling about future risk difficult and creates uncertainty regarding the optimal management[3].   If recurrence rates are genuinely as high as 50%, an argument could be made for definitive surgical repair at an earlier stage. If the true rate is closer to the lower estimate, however, waiting for a recurrent episode before considering surgery is appropriate.

Unfortunately, there are no established factors that predict recurrence and consequently no method for risk-stratifying patients. Female gender, low body weight, smoking and height in males have all been postulated as risk factors for recurrence (4-7). Certain radiographic features have also been suggested to confer additional risk, including bullae on CT and pleural thickening on chest radiograph(8-10). Importantly, there is no consensus on which treatment offers the greatest reduction in risk of recurrence(11-14).

This study aimed to systematically review, appraise and synthesise the existing literature to determine an accurate estimate of PSP recurrence rates and to describe risk factors associated with recurrence. The primary research question was "what is the rate of recurrence of PSP in adults who have undergone medical management and what factors are associated with increased risk of recurrence?". The secondary research question was "What patient factors increase recurrence risk?".

Materials and Methods

Search Strategy and selection criteria

A systematic review was conducted to identify English-language studies, including randomised trials, non-randomised trials, and observational studies of more than 10 participants. Review articles, editorials, conference abstracts and animal or in vitro studies were excluded. The population of interest was adults (≥18 year of age) with PSP, although studies including adolescents of 11 years and older were included if they comprised less than 25% of

the study population or if recurrence data for adults could be extracted separately. Studies that examined patients with first occurrence or subsequent occurrence were included. Secondary spontaneous pneumothorax, iatrogenic and traumatic pneumothoraces were excluded and mixed studies where PSP recurrence outcomes could not be differentiated from other types of pneumothorax (secondary spontaneous, iatrogenic, traumatic) were also excluded. Interventions and comparators included in the review were conservative management, needle aspiration (NA), intercostal drainage (ICD) and ambulatory management. Studies which only examined surgical, thoracoscopic or pleurodesis interventions were excluded, as were mixed studies where surgical and pleurodesis outcomes could not differentiated from non-surgical/pleurodesis outcomes. The outcome of interest was recurrence (either ipsilateral or contralateral) at any time point. Studies that only documented contralateral recurrence rates were not eligible.

The initial electronic search was performed on 18/1/18 within Medline (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Janaury 2018) and EMBASE (1950 to January 2018). The full search strategy is shown in Appendix A, and included MeSH headings and keyword searches of "pneumothorax", "recurrence" and "epidemiology". Two authors (SW and PH) independently screened abstracts for eligibility and excluded studies that did not meet the inclusion criteria. Discrepancies were resolved with discussion with third author (NAM). Eligible studies were obtained in full-text format and reviewed independently by two reviewers (SH and PH). The search was repeated on 22/2/18 to capture recently published studies.

Data-analysis

Data were extracted independently by two authors (SW and PH), using the data collection sheet shown in Appendix B. Name of study, type of study, sex, age, number of PSP cases, interventions, whether PSP cases were first or recurrent episode, 1-year; 2-year; and overall recurrence rates, and follow-up period were extracted from each study.

The principal summary measure was overall recurrence rate for all included studies, described using basic descriptors (mean, 95% confidence intervals (CI)). 1-year and 2-year recurrence rates pooled for all studies that reported these outcomes. Odd ratios for recurrence were calculated, where possible, for different interventions. Odds ratios were calculated for smokers vs non-smokers, males vs females, and BMI (greater/less than 20 kg/m^2). Hazard ratios were extracted for males versus females where available. In studies with mixed population (e.g. PSP and SSP, or adolescents and adults) only data pertaining to adults with PSP were extracted. If a study stated in its methodology that data relevant to the PICO criteria was collected but did not report it, the authors were contacted and asked to provide raw data.

Separate meta-analyses were conducted to examine overall recurrence rates, and 1-year and 2-year recurrence rates. All studies that reported the outcome of interest were included in the meta-analyses. Due to high anticipated heterogeneity between study populations and interventions, a random-effects model was used. Heterogeneity was calculated using estimates of I^2. Pooled recurrence rates were calculated separately for clinical cohorts and epidemiological studies reporting data from the general population. Separate meta-analyses were performed for studies that reported recurrence stratified by gender, intervention, weight and smoking status to provide estimates of recurrence based on patient characteristics. Random effects models were used for all these analyses due to high anticipated heterogeneity. Univariable meta-regression was used to assess whether study-level characteristics were associated with increased reported recurrence rates. Characteristics examined were type of study (RCT vs non-RCT), year of publication (before 2000, after 2000), PSP type (first or recurrent), sample size and follow-up period (greater or less than two years). All analyses were conducted in Stata MP Version 13.1.

Randomised studies that met the inclusion criteria were assessed using the Cochrane risk of bias tool. Bias was assessed over the following pre-specified domains: random sequence generation, concealment of allocation, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, selective reporting and other potential sources of bias. Non-randomised studies that met the inclusion criteria were assessed using the Newcastle-Ottawa assessment tool over the following pre-specified domains: selection, comparability and outcome (15). Risk of bias was assessed independently by two reviewers (SW and AB). Differences of opinion were resolved by discussion or by involvement of a third party (NAM).

The review was registered prospectively on the PROSPERO database, registration number CRD42018089409. Full methodological details are available at http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018089409).

Role of funding source

Results

The search identified 3,607 publications, of which 29 were eligible for inclusion (Figure 1). Overall pooled recurrence rate was 32.1% (95% CI 27.0% to 37.2%) (Figure 2). 12 studies documented 1-year recurrence, with a pooled recurrence rate of 29.0% (95% CI 20.9% to 37.0%).

A total of 13,548 patients were included in the studies, with a median sample size of 79(range 18 to 10,956). 85% were male. Study dates ranged from 1965 to 2017. Four randomised control trials (RCT) were included; one compared NA to ICD insertion, 2 compared pleurodesis with standard care and one compared conservative management to surgery. Twenty-five observational studies were included: 21 retrospective, 3 prospective and one population-based epidemiological study. Average follow-up time varied significantly between studies, with mean duration ranging from 3 to 96 months. A summary of included studies is provided in Table 1.

There was considerable variation in reported recurrence rates, ranging from 8% to 74% (8). I^2 for the random effects meta-analysis was 94% (p<0.0001). This is likely to reflect the wide variety of patient populations, methodologies and interventions studied in the included papers. Assessment of risk of bias showed a high risk of bias in at least one domain for all included studies (see Appendix C).

Table 1: Study Characteristics								
Name	Date	Type of study	N (PSP)	Interventions	Excluded patients (n)	1st episode	Follow-up (months)	Overall Recurrence rates
Al-Alawi (16)	2009	Retrospective	208	Cx, ICD,	Nil	Not stated	42MN	0.35
Al-Mourgi (17)	2015	RCT	22	Cx, S	Underwent surgery(19)	1st	32.4MN	0.41
Andersen (18)	1965	Retrospective	138	Cx, ICD	SSP (48)	1st	71MN	0.16
Casali (10)	2013	Retrospective	176	Cx, ICD,	Nil	1st	58 MN	0.46
Chan (12)	2006	Retrospective	89	NA	Nil	1st & recurrent	12	0.16
Chen (19)	2008	Retrospective	18	ICD, S	Underwent surgery (34)	1st	16MN	0.28
Chen (20)	2008	Retrospective	33	NA, P	Underwent pleurodesis (31)	1st	13 MN	0.33
Chen (21)	2013	RCT	108	ICD, P	Underwent pleurodesis (106)	1st	12	0.49
Ganesalingam (9)	2010	Retrospective	100	Cx, ICD	Nil	1st	57MN	0.54
Harvey (22)	1994	RCT	73	NA vs ICD	Nil	1st	12	0.21
Huang (23)	2017	Epidemiological	10956	Cx, ICD, S	Underwent surgery (8606)	1st	60 to 144	0.24
Karasaki (24)	2014	Retrospective	93	HVCD	Underwent surgery (6)	1st	12.5MD	0.34
Kim (25)	2014	Retrospective	55	Cx, ICD, S	Underwent surgery (1)	1st & recurrent	Unclear	0.16
Kuan (26)	2009	Retrospective	48	Cx, NA, ICD, S	Underwent surgery (13) Recurrent pneumotherax (21)	1st	3	0.08
Lichter (27)	1974	Retrospective	24	Cx, ICD, S	SSP (54)	1st	60-144	0.08

					Underwent surgery (18)			
Light (28)	1990	RCT	22	ICD, P	SSP (171) Underwent tetracycline pleurodesis (19)	1st & recurrent	29.1[MN]	0.32
Martinez-Ramos(29)	2007	Retrospective	55	Cx, ICD	Nil	1st	30.7[MN]	0.24
Mehta (30)	2016	Retrospective	216	ICD	Nil	Not stated	14[MD]	0.13
Nishiuma (31)	2012	Retrospective	66	NA	Failed NA (25)	1st & recurrent	12	0.36
Noh (32)	2015	Retrospective	109	Cx, ICD, S	≤19 age (328) + Underwent surgery (76)	Not stated	Unclear	0.48
Noh (33)	2015	Retrospective	79	Cx, ICD	Underwent surgery (183)	Not stated	Unclear	0.37
Olesen (6)	2016	Prospective cohort study	257	Cx, ICD	Nil	1st	43.2[MD]	0.56
Ouanes -Besbes (13)	2006	Prospective	63	Cx, NA, ICD, P, S	Underwent pleurodesis (16) Underwent surgery (1)	1st	34[MN]	0.23
Primavesi (8)	2016	Retrospective	23	Cx, ICD, S	Underwent surgery (33)	1st	67[MD]	0.74
Sadikot (4)	1997	Retrospective	153	Cx, NA, ICD	Nil	1st	54[MN]	0.54
Sayar (34)	2014	Prospective	154	ICD, S	Underwent surgery (27)	Not stated	30.6[MN]	0.14
Schramel (35)	1996	Retrospective case control	78	Cx, ICD, S	Underwent surgery (97) No follow up (34)	1st & recurrent	96[MN]	0.39
Tan (5)	2017	Retrospective	97	Cx, NA, ICD, S	Underwent surgery (176)	1st	39[MD]	0.56
Tulay (36)	2015	Retrospective	68	ICD, S	Underwent surgery (14)	1st	Unclear	0.27

Cx: Conservative; HVCD: Heimlich valve chest drain; ICD: intercostal drain; MN: mean; MD: Median; NA: needle aspiration; NS: not stated; RCT: randomised control trial; P: Pleurodesis; S: Surgery

Study types

All studies included participants drawn from clinical populations, apart from one epidemiological study that analysed population-level data, from a national health research database in Taiwan(23). This study of over 10,000 people, from a 13 year period, reported a slightly lower recurrence rate of 23.7% (95% CI 22.9 to 24.5), when surgically managed patients were excluded, compared with the pooled estimate for clinical studies (32.6%, 95% CI 26.1 to 39.2). Recurrence rates were similar for randomised and non-randomised studies (35.4%, 95% CI 18.7 to 52.1 vs 31.7%, 95% CI 26.3 to 37.1).

Factors associated with recurrence

Eleven observational studies examined the association between gender and PSP recurrence(4-6, 8-10, 13, 16, 30, 32, 33), with eight demonstrating increased recurrence rates in females (4-6, 9, 10, 13, 16, 32). Odd ratios could be determined from seven studies,(4, 5, 9, 13, 16, 30, 32) with random-effects meta-analysis demonstrating an OR of 3.0 (95% CI 1.24 to 7.41, p=0.015) for female gender (see Figure 3). 4 studies reported hazard ratios for gender and meta-analysis yielded an estimated HR of 1.2 (95% CI 0.83 to 1.67, p=0.35) associated with being female (6, 8-10). Two studies, which demonstrated no difference between genders, were not included as either OR/HR could not be calculated(23), or only contralateral recurrences were examined in the gender subgroup analysis(33).

Several different definitions and cut-offs were used to categorise smoking habits, weight and age, and therefore meta-analysis was not possible. Five observational studies examined the relationship between current smoking and recurrence (4-6, 9, 16) with only one demonstrating a convincing association(16). However, smoking cessation was

associated with reduced recurrence in 2 studies with OR of 0.22 (95% CI 0.05 to 0.97) and 0.28 (95% CI 0.10 to 0.89) respectively, with a pooled OR 0.26 (95% CI 0.10 to 0.63) (4, 16).

Eight observational studies examined BMI or weight(4-6, 8, 10, 16, 32, 33), with 2 demonstrating a significant association between low BMI/weight and recurrence (5, 6). Thirteen studies examined whether age correlated with recurrence, with ten studies finding no association (4-6, 9, 10, 13, 16, 25, 37, 38). Three studies demonstrated an increased risk with younger patients (23, 32, 33).

Four studies examined CT radiographic scoring systems, based on number, size and distribution of air-filled lesions. (8, 10, 13, 29) The scores were not comparable, and produced conflicting results, which were not suitable for meta-analysis. Two studies found an association between radiographic evidence of blebs and recurrence risk (8, 10) and two studies did not (13, 29). One study concluded that chest radiograph features such pleural thickening, blebs/bullae, pleural irregularities and pleural adhesions were associated with an increased likelihood of recurrence (9).

Only one study compared recurrence in patients treated with needle aspiration versus chest drain(22) therefor precluding meta-analysis. There were no RCTs comparing medical interventions with conservative management. Six non-randomised studies compared conservative management with either NA or ICD, with neither approach demonstrating a reduction in recurrence risk (OR 0.78, 95% CI 0.47 to 1.31, p 0.353 - see Figure 4) (4, 6, 9, 23, 25, 32).

Meta-regression

Univariable meta-regression did not demonstrate any significant association between PSP recurrence and study size, publication year, eligibility criteria, type of study, PSP type (first or recurrent) or follow up period (see Table 2). There was considerable unexplained residual heterogeneity even after adjusting for the different study characteristics.

Table 2: Univariable meta-regression of study characteristics

	N Studies	Pooled recurrence rate, % (95% CI)	P for difference	Residual I^2
Study sample size				
<100	18	28.8 (21.7, 36.0)	0.234	94.05%
>100	11	37.0 (28.4, 46.6)		
Publication year				
Before 2000	6	26.3 (11.5, 41.1)	0.324	94.05%
After 2000	23	33.6(27.8, 39.4)		
Pneumothorax type				
1st pneumothorax	18	35.7 (27.9, 43.5)	0.273	94.02%
1st & recurrent pneumothorax	6	23.4 (16.7, 30.1)		
Not stated	5	29.4 (17.0, 41.8)		
Follow-up period				
<24 months	10	26.5 (17.7, 35.2)	0.303	93.84%
>24months	15	35.9 (27.9, 43.9)		
Not stated	4	31.9 (18.4, 45.4)		
Type of study				
Non-randomised	25	31.7 (26.3, 37.1)	0.729	93.91%
Randomised	4	35.4 (18.7, 52.1)		

Discussion

This is the first study to systematically review the literature on recurrence rates in adults with PSP who have been medically managed. Meta-analysis of data from 29 studies, totalling over 13,000 patients showed that 32% of patients will experience PSP recurrence, with most occurring within the first year.

There was strong evidence that female gender was a risk factor for recurrence. This is consistent with an epidemiological study that found an increased rate of pneumothorax recurrence in female patients, particularly in the age group 31-50 years of age, with re-hospitalisation rates of 54% compared with 46% in males (39). It is recognised that a proportion of pneumothoraces in women are secondary to underlying gender-specific pathophysiology, including lymphangioleiomyomatosis (LAM) and catamenial (endometriosis and non-endometriosis related) pneumothoraces. Whilst catamenial pneumothoraces were historically thought to be a rare entity, with an early study attributing only characterising 1% of PSPs as such(40), a recent retrospective study demonstrated that up to 25% of women referred to surgery for recurrent pneumothoraces had evidence of thoracic endometriosis (41). The presence of these underlying conditions may explain the higher risk of recurrence seen in women.

Low BMI is an established risk factors for the initial development of PSP (42, 43). Whilst two studies (5, 6) demonstrated increased risk of recurrence with low weight and BMI respectively, differing classifications precluded meta-analysis. The hypothesis that PSP recurrence is linked with low body weight, either due to nutritional deficiencies affecting α_1-antitrypsin levels or due to unbalanced physical development was supported by two papers (5, 6, 44-46).

There is strong evidence supporting the link between smoking and developing a pneumothorax, with a clear dose-response relationship (42, 47). However, only one study in this review demonstrated an association between smoking and recurrence,(16) with several studies demonstrating a trend towards increased recurrence in non-smokers (4-6, 9, 16, 48). It has been suggested that there is a difference in aetiology between PSP in smokers and non-smokers, with 'never smokers' suffering from a genetic predisposition to pulmonary bullae, regardless of smoking habit. However, a more likely explanation is that the detrimental effect of smoking was obscured by the high base-line rates of cigarette smoking in the included studies and the heterogeneous classifications used to define smoking status. The fact that smoking cessation reduced the risk of PSP recurrence adds further weight to the relationship between smoking and PSP. Interestingly, this finding also suggests that smoking-related risk is reversible, at least in terms of early PSP recurrence (4, 16).

There were insufficient number of studies included to determine if the choice of medical interventions (NA vs ICD) for PSP influenced recurrence rates. A recent meta-analysis comparing RCTS of NA versus ICD insertion found no difference of recurrence at one year between the interventions (49). There was no randomised data comparing conservative management to NA or ICD, but non-randomised data demonstrated no difference in recurrence between conservative management and intervention. It has been hypothesised that conservative management decreases the risk of recurrence, as slow re-expansion of the lung enables healing of the pleural defect (50, 51). However, conversely, it has been postulated that chest drain insertion may inflame the pleural surfaces, promoting pleural symphysis and preventing long-term recurrence (16). An RCT comparing standard and conservative management is currently recruiting and may offer clarification(51).

The presence of bullae on imaging has been postulated as a predictor of recurrence, however, this theory was not supported by the findings of this review. The lack of standardised radiographic scoring system may explain the conflicting results, although the hypothesis that rupture of bullae causes PSP is also debated (13, 45). The modified dystrophic severity score (DSS), which assessed both blebs and bullae, appeared to be the most useful radiographic scoring system, however with a negative predictive value of over 90% but a positive predictive value of just 68%, it is of greatest value as a rule-out test (10). The DSS has been used in one small subsequent study, but further prospective validation is required(8).

The recurrence rates reported in the included studies varied widely, likely as a result of differences in study design and population, with no single identifiable study characteristics which explained the variation.

Strengths and weaknesses of study

This is the first systematic review of PSP recurrence rates, and it provides the most reliable estimate of overall recurrence to date, based on comprehensive evaluation of existing data. Having an accurate estimate for recurrence will enable clinicians to provide better counselling for patients who have experienced their first PSP.   Sub-group analysis identified factors associated with higher recurrence rates, including female gender and continued cigarette smoking. This finding will facilitate communication with patients and could be useful in guiding further treatment or investigations. For example, if a patient is thought to be at high risk of recurrence, early referral for surgery may be considered. Thus, this systematic review has clear clinical relevance and immediate potential for impact.

The methodology of this review was rigorous, with dual, independent screening of abstracts, review of papers, data extraction and assessment of study quality. Hence, we feel the result of this review is a reliable summation of the existing literature. Nonetheless, the review does have limitations. There was significant heterogeneity between the included studies, and although a random effects meta-analysis model was used, this heterogeneity may have reduced the precision of the final estimated recurrence rate. Some of this heterogeneity is likely to be a result of differing study populations, and it should be acknowledged that for specific populations their true recurrence rate might appreciably differ from the estimates given. The inclusion of studies with heterogeneous populations means the resultant estimate for recurrence rate can be considered representative of the population at large, at the expense, however, of more accurate estimates for specific populations. Whilst patients who were surgically managed or received pleurodesis were excluded from the meta-analysis on overall recurrence rates, this was not always possible in the subgroup analysis, which may confound these results. This review is also limited by the quality of the data in the included studies. RCT data was limited, and all included studies were at high risk of bias in at least one domain. Non-randomised observational studies are at risk of selection bias and confounding by indication, and since many of the studies were also retrospective, there was a high risk of reporting and ascertainment bias.

Conclusion

In conclusion, this is the first systemic review of factors associated with PSP recurrence, combining rates from a broad range of sources to provide a pooled overall risk. It demonstrates that 32% of patients will develop a recurrence, with most of the risk in the first year. Recurrence rates did not differ based on the initial intervention for PSP. Several factors were associated with a higher risk of recurrence, including female sex, lower BMI and radiological evidence of dystrophic lungs, whilst smoking cessation was associated with lower recurrence rates. There was insufficient data to consider development of a risk stratification system.

Word count: 2934

1.   Melton LJ, 3rd, Hepper NG, Offord KP. Incidence of spontaneous pneumothorax in Olmsted County, Minnesota: 1950 to 1974. Am Rev Respir Dis. 1979;120(6):1379-82.
2.   MacDuff A, Arnold A, Harvey J, Group BTSPDG. Management of spontaneous pneumothorax: British Thoracic Society Pleural Disease Guideline 2010. Thorax. 2010;65 Suppl 2(Suppl 2):ii18-31.
3.   Schramel FM, Postmus PE, Vanderschueren RG. Current aspects of spontaneous pneumothorax. Eur Respir J. 1997;10(6):1372-9.
4.   Sadikot R, Greene T, Meadows K, Arnold A. Recurrence of primary spontaneous pneumothorax. Thorax. 1997;52(9):805-9.
5.   Tan J, Yang Y, Zhong J, Zuo C, Tang H, Zhao H, et al. Association Between BMI and Recurrence of Primary Spontaneous Pneumothorax. World J Surg. 2017;41(5):1274-80.

6.   Olesen WH, Lindahl-Jacobsen R, Katballe N, Sindby JE, Titlestad IL, Andersen PE, et al. Recurrent Primary Spontaneous Pneumothorax is Common Following Chest Tube and Conservative Treatment. World Journal of Surgery. 2016:1-8.

7.   Guo Y, Xie C, Rodriguez RM, Light RW. Factors related to recurrence of spontaneous pneumothorax. Respirology. 2005;10(3):378-84.

8.   Primavesi F, Jager T, Meissnitzer T, Buchner S, Reich-Weinberger S, Ofner D, et al. First Episode of Spontaneous Pneumothorax: CT-based Scoring to Select Patients for Early Surgery. World J Surg. 2016;40(5):1112-20.

9.   Ganesalingam R, O'Neil RA, Shadbolt B, Tharion J. Radiological predictors of recurrent primary spontaneous pneumothorax following non-surgical management. Heart, Lung and Circulation. 2010;19(10):606-10.

10.   Casali C, Stefani A, Ligabue G, Natali P, Aramini B, Torricelli P, et al. Role of blebs and bullae detected by high-resolution computed tomography and recurrent spontaneous pneumothorax. The Annals of thoracic surgery. 2013;95(1):249-55.

11.   Brown SG, Ball EL, Macdonald SP, Wright C, Mc DTD. Spontaneous pneumothorax; a multicentre retrospective analysis of emergency treatment, complications and outcomes. Internal medicine journal. 2014;44(5):450-7.

12.   Chan SS, Rainer TH. Primary spontaneous pneumothorax: 1-year recurrence rate after simple aspiration. Eur J Emerg Med. 2006;13(2):88-91.

13.   Ouanes-Besbes L, Golli M, Knani J, Dachraoui F, Nciri N, El Atrous S, et al. Prediction of recurrent spontaneous pneumothorax: CT scan findings versus management features. Respir Med. 2007;101(2):230-6.

14.   Noppen M, Alexander P, Driesen P, Slabbynck H, Verstraeten A. Manual aspiration versus chest tube drainage in first episodes of primary spontaneous pneumothorax: a multicenter, prospective, randomized pilot study. American journal of respiratory and critical care medicine. 2002;165(9):1240-4.

15.   Wells G, Shea B, O'connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa (ON): Ottawa Hospital Research Institute; 2009. Available in March. 2016.

16.   Al-Alawi A, Ayed AK. Recurrence of primary spontaneous pneumothorax: Rate and risk factors. Kuwait Medical Journal. 2009;41(4):288-91.

17.   Al-Mourgi M, Alshehri F. Video-Assisted Thoracoscopic Surgery for the Treatment of First-Time Spontaneous Pneumothorax versus Conservative Treatment. International journal of health sciences. 2015;9(4):428-32.

18.   Andersen B, Nielsen J. Recurrence risk in spontaneous pneumothorax. A follow-up of 178 initial occurrences in a Danish county in a ten-year period. Acta chirurgica Scandinavica Supplementum. 1965;356:160.

19.   Chen JS, Hsu HH, Tsai KT, Yuan A, Chen WJ, Lee YC. Salvage for unsuccessful aspiration of primary pneumothorax: thoracoscopic surgery or chest tube drainage? The Annals of thoracic surgery. 2008;85(6):1908-13.

20.   Chen JS, Tsai KT, Hsu HH, Yuan A, Chen WJ, Lee YC. Intrapleural minocycline following simple aspiration for initial treatment of primary spontaneous pneumothorax. Respir Med. 2008;102(7):1004-10.

21.   Chen JS, Chan WK, Tsai KT, Hsu HH, Lin CY, Yuan A, et al. Simple aspiration and drainage and intrapleural minocycline pleurodesis versus simple aspiration and drainage for the initial treatment of primary spontaneous pneumothorax: an open-label, parallel-group, prospective, randomised, controlled trial. Lancet. 2013;381(9874):1277-82.

22.   Harvey J, Prescott RJ. Simple aspiration versus intercostal tube drainage for spontaneous pneumothorax in patients with normal lungs. Bmj. 1994;309(6965):1338-9.

23.   Huang YH, Chang PY, Wong KS, Chang CJ, Lai JY, Chen JC. An Age-Stratified Longitudinal Study of Primary Spontaneous Pneumothorax. The Journal of adolescent health : official publication of the Society for Adolescent Medicine. 2017;61(4):527-32.

24.   Karasaki T, Shintomi S, Nomura Y, Tanaka N, Saito H, Yoshida Y. Outcomes of outpatient treatment for primary spontaneous pneumothorax using a small-bore portable thoracic drainage device. Thorac Cardiovasc Surg. 2014;62(6):516-20.

25.   Kim JT, Oh TY, Chang WH, Kong JH, Baek KS, Lee WJ, et al. Natural course of spontaneous pneumothorax without bullae or blebs under high-resolution computed tomography. Thorac Cardiovasc Surg. 2014;62(6):505-8.

26.   Kuan WS, Lather KS, Mahadevan M. Primary spontaneous pneumothorax--the role of the emergency observation unit. The American journal of emergency medicine. 2011;29(3):293-8.

27.   Lichter I. Long-term follow-up of planned treatment of spontaneous pneumothorax. Thorax. 1974;29(1):32-7.

28.   Light RW, O'Hara VS, Moritz TE, McElhinney AJ, Butz R, Haakenson C, et al. Intrapleural tetracycline for the prevention of recurrent spontaneous pneumothorax. Results of a Department of Veterans Affairs Cooperative Study. Journal of the American Medical Association. 1990;264(17):2224-30.

29.   Martínez-Ramos D, Ángel-Yepes V, Escrig-Sos J, Miralles-Tena JM, Salvador-Sanchís JL. Usefulness of computed tomography in determining risk of recurrence after a first episode of primary spontaneous pneumothorax: therapeutic implications. Archivos de Bronconeumología ((English Edition)). 2007;43(6):304-8.

30.   Mehta CK, Stanifer BP, Fore-Kosterski S, Gillespie C, Yeldandi A, Meyerson S, et al. Primary Spontaneous Pneumothorax in Menstruating Women Has High Recurrence. The Annals of thoracic surgery. 2016;102(4):1125-30.

31.   Nishiuma T, Ohnishi H, Katsurada N, Yamamoto S, Yoshimura S, Kinami S. Evaluation of simple aspiration therapy in the initial treatment for primary spontaneous pneumothorax. Internal medicine. 2012;51(11):1329-33.

32.   Noh D, Lee S, Haam SJ, Paik HC, Lee DY. Recurrence of primary spontaneous pneumothorax in young adults and children. Interact Cardiovasc Thorac Surg. 2015;21(2):195-9.

33.   Noh D, Keum DY, Park CK. Outcomes of Contralateral Bullae in Primary Spontaneous Pneumothorax. The Korean journal of thoracic and cardiovascular surgery. 2015;48(6):393-7.

34.   Sayar A, Kok A, Citak N, Metin M, Buyukkale S, Gurses A. Size of pneumothorax can be a new indication for surgical treatment in primary spontaneous pneumothorax: a prospective study. Annals of thoracic and cardiovascular surgery : official journal of the Association of Thoracic and Cardiovascular Surgeons of Asia. 2014;20(3):192-7.

35.   Schramel FM, Sutedja TG, Braber JC, van Mourik JC, Postmus PE. Cost-effectiveness of video-assisted thoracoscopic surgery versus conservative treatment for first time or recurrent spontaneous pneumothorax. Eur Respir J. 1996;9(9):1821-5.

36.   Tulay CM, Ozsoy IE. Spontaneous Pneumothorax Recurrence and Surgery. The Indian journal of surgery. 2015;77(Suppl 2):463-5.

37.   Chan SSW, Rainer TH. Primary spontaneous pneumothorax: 1-Year recurrence rate after simple aspiration. European Journal of Emergency Medicine. 2006;13(2):88-91.

38.   Primavesi F, Aspalter M, Jager T, Buchner S, Ofner D, Hutter J. Early surgical treatment of primary spontaneous pneumothorax reduces recurrence-rates in patients with blebs and bullae detected by computed tomography. European Surgery - Acta Chirurgica Austriaca. 2013;2):S73.

39.   Bobbio A, Dechartres A, Bouam S, Damotte D, Rabbat A, Régnard J-F, et al. Epidemiology of spontaneous pneumothorax: gender-related differences. Thorax. 2015:thoraxjnl-2014-206577.

40.   Nakamura H, Konishiike J, Sugamura A, Takeno Y. Epidemiology of spontaneous pneumothorax in women. Chest. 1986;89(3):378-82.

41.   Alifano M, Jablonski C, Kadiri H, Falcoz P, Gompel A, Camilleri-Broet S, et al. Catamenial and noncatamenial, endometriosis-related or nonendometriosis-related pneumothorax referred for surgery. American journal of respiratory and critical care medicine. 2007;176(10):1048-53.

42.   Bense L, Eklund G, Wiman L-G. Smoking and the increased risk of contracting spontaneous pneumothorax. CHEST Journal. 1987;92(6):1009-12.

43.   Biffl WL, Narayanan V, Gaudiani JL, Mehler PS. The management of pneumothorax in patients with anorexia nervosa: A case report and review of the literature. Patient safety in surgery. 2010;4(1):1.

44.   Bar-El Y, Ross A, Kablawi A, Egenburg S. Potentially dangerous negative intrapleural pressures generated by ordinary pleural drainage systems. Chest. 2001;119(2):511-4.

45.   Noppen M, Baumann MH. Pathogenesis and treatment of primary spontaneous pneumothorax: an overview. Respiration; international review of thoracic diseases. 2003;70(4):431-8.

46.   Yu L, Li H, Hou S, Hu B, Zhao L, Miao J, et al. Abnormal bone mineral density and bone turnover marker expression profiles in patients with primary spontaneous pneumothorax. Journal of thoracic disease. 2016;8(6):1188.

47.   Cheng YL, Huang TW, Lin CK, Lee SC, Tzao C, Chen JC, et al. The impact of smoking in primary spontaneous pneumothorax. J Thorac Cardiovasc Surg. 2009;138(1):192-5.

48.   Lippert H, Lund O, Blegvad S, Larsen H. Independent risk factors for cumulative recurrence rate after first spontaneous pneumothorax. European Respiratory Journal. 1991;4(3):324-31.

49.   Carson-Chahhoud KV, Wakai A, van Agteren JE, Smith BJ, McCabe G, Brinn MP, et al. Simple aspiration versus intercostal tube drainage for primary spontaneous pneumothorax in adults. The Cochrane Library. 2017.

50.   Simpson G. Spontaneous pneumothorax: time for some fresh air. Internal medicine journal. 2010;40(3):231-4.

51.   Brown SG, Ball EL, Perrin K, Read CA, Asha SE, Beasley R, et al. Study protocol for a randomised controlled trial of invasive versus conservative management of primary spontaneous pneumothorax. BMJ open. 2016;6(9):e011826.