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

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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 20.9–37.0%) and 32.1% (95% CI 27.0–37.2%), respectively. Female sex was associated with increased recurrence (OR 3.03, 95% CI 1.24–7.41), while smoking cessation was associated with a four-fold decrease in risk (OR 0.26, 95% CI 0.10–0.63). 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 sex was associated with higher risk, suggesting possible sex-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 British Thoracic Society 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 sex, 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 computed tomography (CT) and pleural thickening on chest radiography [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?". 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, nonrandomised 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 years of age) with PSP, although studies including adolescents aged ⩾11 years were included if they comprised <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, 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 or traumatic) were also excluded. Interventions and comparators included in the review were conservative management, needle aspiration, intercostal drainage (ICD) and ambulatory management. Studies that only examined surgical, thoracoscopic or pleurodesis interventions were excluded, as were mixed studies where surgical and pleurodesis outcomes could not be differentiated from nonsurgical/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 January 18, 2018 within MEDLINE (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE 1950 to January 2018) and Embase (1950 to January 2018). The full search strategy is shown in the supplementary material, and included MeSH (Medical Subject Headings) headings and key word searches of "pneumothorax", "recurrence" and "epidemiology". Two authors (S.W. and P.H.) independently screened abstracts for eligibility and excluded studies that did not meet the inclusion criteria. Discrepancies were resolved with discussion with a third author (N.A.M.). Eligible studies were obtained in full-text format and reviewed independently by two reviewers (S.P.W. and P.H.). The search was repeated on February 22, 2018 to capture recently published studies.

Data analysis

Data were extracted independently by two authors (S.P.W. and P.H.), using the data collection sheet shown in the supplementary material. 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 interval)). The 1-year and 2-year recurrence rates were 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 *versus* nonsmokers, males *versus* females and body mass index (BMI) >20 *versus* <20 kg·m^{-2}. Hazard ratios were extracted for males *versus* females where available. In studies with mixed population (*e.g.* PSP and secondary spontaneous pneumothorax 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 (population, intervention, control and outcomes) criteria were collected but did not report them, 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 sex, 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. Univariate meta-regression was used to assess whether study-level characteristics were associated with increased reported recurrence rates. Characteristics examined were type of study (randomised control trial (RCT) versus non-RCT), year of publication (before 2000 versus after 2000), PSP type (first versus recurrent), sample size and follow-up period (>24 versus <24 months). All analyses were conducted in Stata MP version 13.1 (StataCorp, College Station, TX, USA).

Randomised studies that met the inclusion criteria were assessed using the Cochrane risk of bias tool [15]. 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. Nonrandomised studies that met the inclusion criteria were assessed using the Newcastle–Ottawa assessment tool over the following pre-specified domains: selection, comparability and outcome [16]. Risk of bias was assessed independently by two reviewers (S.P.W. and A.C.B.). Differences of opinion were resolved by discussion or by involvement of a third party (N.A.M.).

The review was registered prospectively on the PROSPERO database with registration number CRD42018089409.

Results

The search identified 3607 publications, of which 29 were eligible for inclusion (table 1 and figure 1). Overall pooled recurrence rate was 32.1% (95% CI 27.0–37.2%) (figure 2). 12 studies documented 1-year recurrence, with a pooled recurrence rate of 29.0% (95% CI 20.9–37.0%).

In total, 13 548 patients were included in the studies, with a median (range) sample size of 79 (18–10 956). 85% were male. Study dates ranged from 1965 to 2017. Four RCTs were included: one compared needle aspiration with ICD insertion, two compared pleurodesis with standard care and one compared conservative management with surgery. 25 observational studies were included: 21 retrospective, three 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%. 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 (supplementary material).

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 [24]. This study of over 10 000 people, from a 13-year period, reported a slightly lower recurrence rate of 23.7% (95% CI 22.9–24.5%), when surgically managed patients were excluded, compared with the pooled estimate for clinical studies (32.6%, 95% CI 26.1–39.2%). Recurrence rates were similar for randomised and nonrandomised studies (35.4%, 95% CI 18.7–52.1% versus 31.7%, 95% CI 26.3–37.1%).

Factors associated with recurrence

12 observational studies examined the association between sex and PSP recurrence [4–6, 8–10, 13, 17, 24, 31, 33, 34], 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, 17, 31, 33], with random effects meta-analysis demonstrating OR 3.03 (95% CI 1.24–7.41; p=0.015) for female sex (figure 3). Four studies reported hazard ratios for sex and meta-analysis yielded an estimated HR 1.2 (95% CI 0.83–1.67; p=0.35) associated with being female [6, 8–10]. Two studies, which demonstrated no difference between sexes, were not included as either the odds ratio/hazard ratio could not be calculated [24] or only contralateral recurrences were examined in the sex subgroup analysis [34].

TABLE 1 Study characteristics

First author [ref.]	Year	Type of study	Primary spontaneous pneumothorax n	Interventions	Excluded patients (n)	First episode	Follow-up months	Overall recurrence rate
AL-ALAWI [17]	2009	Retrospective	208	Conservative, ICD	None	Not stated	42#	0.35
AL-MOURGI [18]	2015	RCT	22	Conservative, surgery	Underwent surgery (19)	First	32.4#	0.41
ANDERSEN [19]	1965	Retrospective	138	Conservative, ICD	Secondary spontaneous pneumothorax (48)	First	71#	0.16
CASALI [10]	2013	Retrospective	176	Conservative, ICD,	None	First	58#	0.46
CHAN [12]	2006	Retrospective	89	Needle aspiration	None	First and recurrent	12	0.16
CHEN [20]	2008	Retrospective	18	ICD, surgery	Underwent surgery (34)	First	16#	0.28
CHEN [21]	2008	Retrospective	33	Needle aspiration, pleurodesis	Underwent pleurodesis (31)	First	13#	0.33
CHEN [22]	2013	RCT	108	ICD, pleurodesis	Underwent pleurodesis (106)	First	12	0.49
GANESALINGAM [9]	2010	Retrospective	100	Conservative, ICD	None	First	57#	0.54
HARVEY [23]	1994	RCT	73	Needle aspiration versus ICD	None	First	12	0.21
HUANG [24]	2017	Epidemiological	10956	Conservative, ICD, surgery	Underwent surgery (8606)	First	60–144	0.24
KARASAKI [25]	2014	Retrospective	93	HVCD	Underwent surgery (6)	First	12.5¶	0.34
KIM [26]	2014	Retrospective	55	Conservative, ICD, surgery	Underwent surgery (1)	First and recurrent	Unclear	0.16
KUAN [27]	2009	Retrospective	48	Conservative, needle aspiration, ICD, surgery	Underwent surgery (13); recurrent pneumothorax (21)	First	3	0.08
LICHTER [28]	1974	Retrospective	24	Conservative, ICD, surgery	Secondary spontaneous pneumothorax (54); underwent surgery (18)	First	60–144	0.08
LIGHT [29]	1990	RCT	22	ICD, pleurodesis	Secondary spontaneous pneumothorax (171); underwent tetracycline pleurodesis (19)	First and recurrent	29.1#	0.32
MARTÍNEZ-RAMOS [30]	2007	Retrospective	55	Conservative, ICD	None	First	30.7#	0.24
MEHTA [31]	2016	Retrospective	216	ICD	None	Not stated	14¶	0.13
NISHIUMA [32]	2012	Retrospective	66	Needle aspiration	Failed needle aspiration (25)	First and recurrent	12	0.36
NOH [33]	2015	Retrospective	109	Conservative, ICD, surgery	≤19 years of age (328) and underwent surgery (76)	Not stated	Unclear	0.48
NOH [34]	2015	Retrospective	79	Conservative, ICD	Underwent surgery (183)	Not stated	Unclear	0.37
OLESEN [6]	2016	Prospective cohort	257	Conservative, ICD	None	First	43.2¶	0.56
OUANES-BESBES [13]	2006	Prospective	63	Conservative, needle aspiration, ICD, pleurodesis, surgery	Underwent pleurodesis (16); underwent surgery (1)	First	34#	0.23
PRIMAVESI [8]	2016	Retrospective	23	Conservative, ICD, surgery	Underwent surgery (33)	First	67¶	0.74
SADIKOT [4]	1997	Retrospective	153	Conservative, needle aspiration, ICD	None	First	54#	0.54
SAYAR [35]	2014	Prospective	154	ICD, surgery	Underwent surgery (27)	Not stated	30.6#	0.14
SCHRAMEL [36]	1996	Retrospective case–control	78	Conservative, ICD, surgery	Underwent surgery (97); no follow-up (34)	First and recurrent	96#	0.39
TAN [5]	2017	Retrospective	97	Conservative, needle aspiration, ICD, surgery	Underwent surgery (176)	First	39¶	0.56
TULAY [37]	2015	Retrospective	68	ICD, surgery	Underwent surgery (14)	First	Unclear	0.27

RCT: randomised controlled trial; ICD: intercostal drain; HVCD: Heimlich valve chest drain. #: mean; ¶: median.
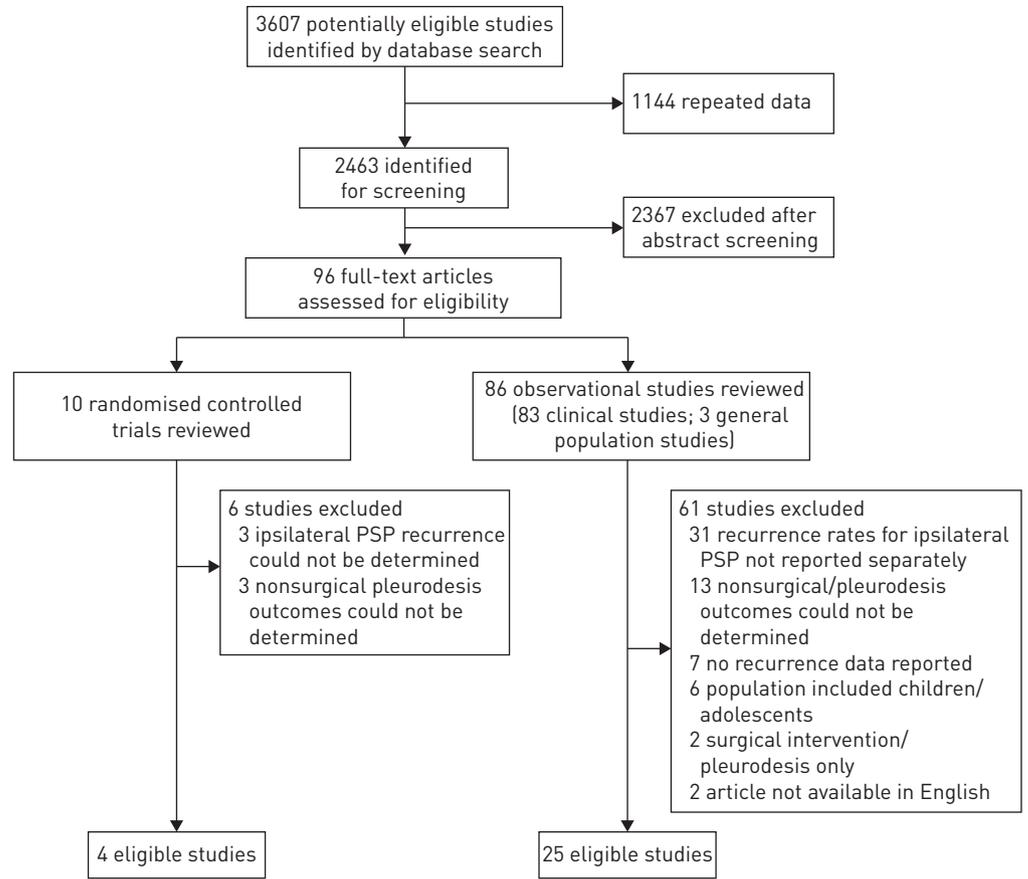
FIGURE 1 PRISMA flow diagram of study selection. PSP: primary spontaneous pneumothorax.

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, 17], with only one demonstrating a convincing association [17]. However, smoking cessation was associated with reduced recurrence in two studies with OR 0.22 (95% CI 0.05–0.97) and OR 0.28 (95% CI 0.10–0.89), with a pooled OR 0.26 (95% CI 0.10–0.63) [4, 17].

Eight observational studies examined BMI or weight [4–6, 8, 10, 17, 33, 34], with two demonstrating a significant association between low BMI/weight and recurrence [5, 6]. 13 studies examined whether age correlated with recurrence, with 10 studies finding no association [4–6, 8–10, 12, 13, 17, 26, 38]. Three studies demonstrated an increased risk with younger patients [24, 33, 34].

Four studies examined CT radiographic scoring systems, based on number, size and distribution of air-filled lesions [8, 10, 13, 30]. 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, 30]. One study concluded that chest radiographic features such as 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 [23] therefore precluding meta-analysis. There were no RCTs comparing medical interventions with conservative management. Six nonrandomised studies compared conservative management with either needle aspiration or ICD, with neither approach demonstrating a reduction in recurrence risk (OR 0.78, 95% CI 0.47–1.31; p=0.353) (figure 4) [4, 6, 9, 24, 26, 33].

Meta-regression
Univariate 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 (table 2).
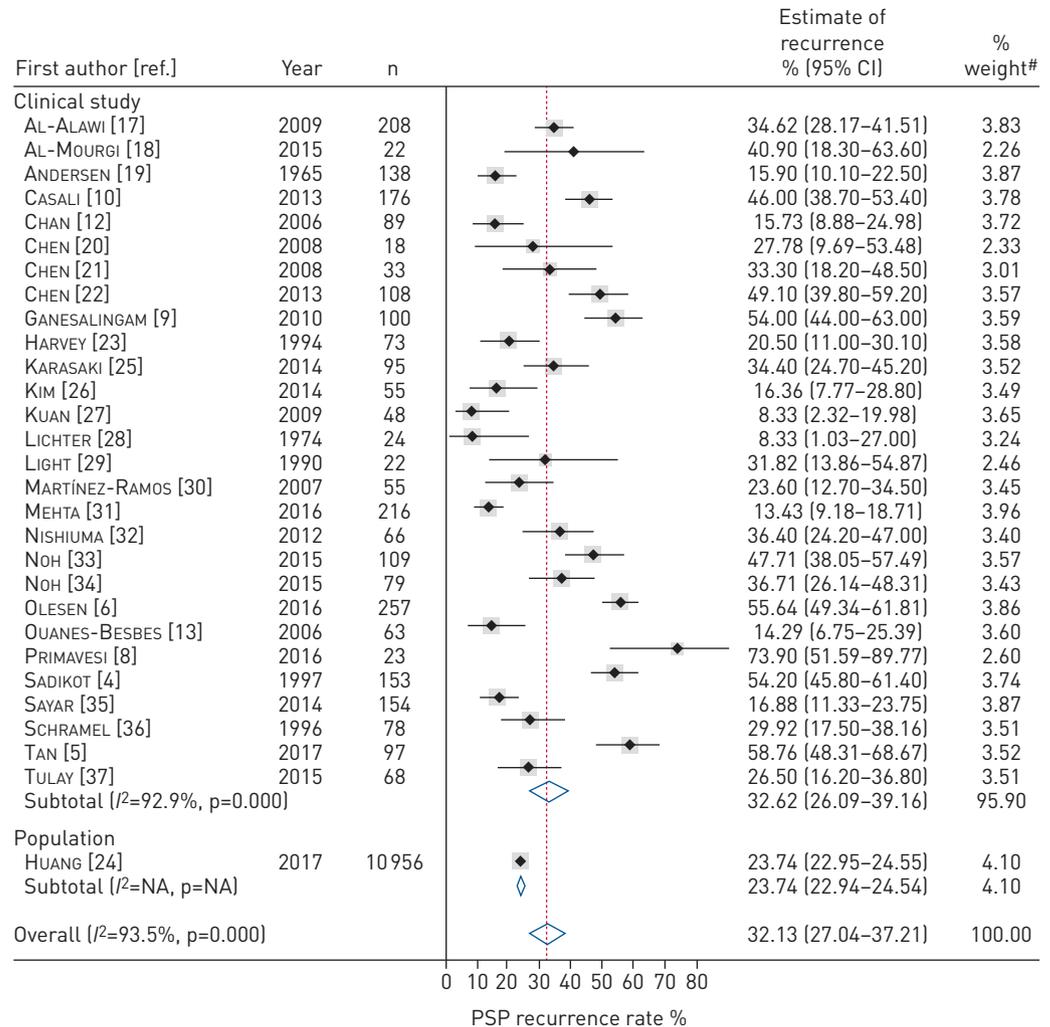
FIGURE 2 Estimate of recurrence of primary spontaneous pneumothorax (PSP) in clinical and population studies. NA: not applicable. #: weights are from random effects analysis.

There was considerable unexplained residual heterogeneity even after adjusting for the different study characteristics.

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 sex 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, with re-hospitalisation rates of 54% compared with 46% in males [39]. It is recognised that a proportion of pneumothoraces in females are secondary to underlying sex-specific pathophysiology, including lymphangioleiomyomatosis and catamenial (endometriosis and nonendometriosis related) pneumothoraces. While catamenial pneumothoraces were historically thought to be a rare entity, with one early study only attributing 1% of its pneumothoraces to this condition [40], a recent retrospective study demonstrated that up to 25% of females 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 females.

Low BMI is an established risk factors for the initial development of PSP [42, 43]. While two studies demonstrated increased risk of recurrence with low weight and BMI, respectively, differing classifications precluded meta-analysis [5, 6]. The hypothesis that PSP recurrence is linked with low body weight, either
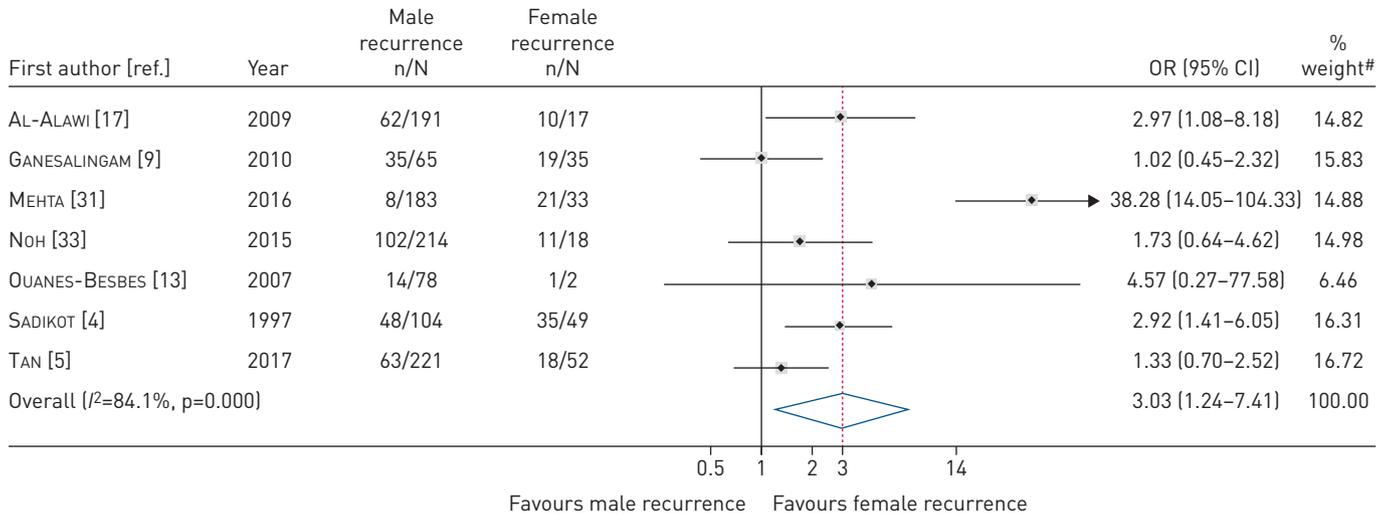
FIGURE 3 Meta-analysis of odds ratios for primary spontaneous pneumothorax recurrence in males *versus* females from seven observational studies. [#]: weights are from random effects analysis.

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 [17], with several studies demonstrating a trend towards increased recurrence in nonsmokers [4–6, 9, 17, 48]. It has been suggested that there is a difference in aetiology between PSP in smokers and nonsmokers, 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 baseline 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, 17].

There were insufficient numbers of studies included to determine if the choice of medical interventions (needle aspiration *versus* ICD) for PSP influenced recurrence rates. A recent meta-analysis comparing RCTs of needle aspiration *versus* ICD insertion found no difference of recurrence at 1 year between the interventions [49]. There were no randomised data comparing conservative management to needle
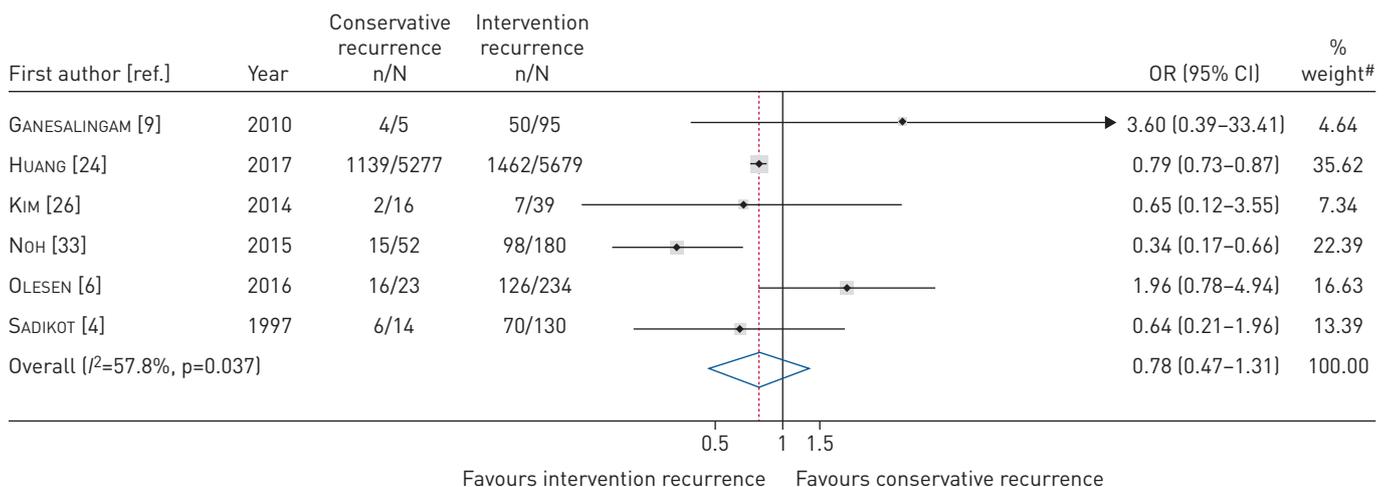
FIGURE 4 Odds ratios for recurrent pneumothorax following conservative management or intervention (needle aspiration or intercostal drainage) from six observational studies. [#]: weights are from random effects analysis.

TABLE 2 Univariate meta-regression of study characteristics

	Studies n	Pooled recurrence rate % (95% CI)	p-value for difference	Residual I^2 %
Study sample size n				
<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				
First	18	35.7 (27.9–43.5)	0.273	94.02
First and recurrent	6	23.4 (16.7–30.1)		
Not stated	5	29.4 (17.0–41.8)		
Follow-up period months				
<24	10	26.5 (17.7–35.2)	0.303	93.84
>24	15	35.9 (27.9–43.9)		
Not stated	4	31.9 (18.4–45.4)		
Type of study				
Nonrandomised	25	31.7 (26.3–37.1)	0.729	93.91
Randomised	4	35.4 (18.7–52.1)		

aspiration or ICD, but nonrandomised 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 [17]. 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, 44]. The modified dystrophic severity score, which assessed both blebs and bullae, appeared to be the most useful radiographic scoring system; however, with a negative predictive value of >90% but a positive predictive value of just 68%, it is of greatest value as a rule-out test [10]. The dystrophic severity score 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 that explained the variation.

Strengths and weaknesses of this 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. Subgroup analysis identified factors associated with higher recurrence rates, including female sex 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. While 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. Nonrandomised 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.

Conclusions

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, while smoking cessation was associated with lower recurrence rates. There was insufficient data to consider development of a risk stratification system.

Conflict of interest: None declared.

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