Effects of Different Treatment Regimens on Primary Spontaneous Pneumothorax: A Systematic Review and Network Meta-Analysis

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Research Article

Keywords: Primary spontaneous pneumothorax, Recurrence, Systematic review, Network meta-analysis

Posted Date: March 18th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1292619/v1

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Abstract

**Background** The best treatment strategy for primary spontaneous pneumothorax is controversial and varies widely in practice, so we conducted a systematic review and network meta-analysis to clarify which treatment is optimal.

**Methods** Literatures were searched from relevant databases till 24 August 2021. A Bayesian network meta-analysis was conducted to compare the outcomes of various treatment regimens with the following endpoints: recurrence rate; postoperative chest tube duration; postoperative air leakage duration; length of hospital stay and rate of complications. The surface under the cumulative ranking curve was used to rank the treatments.

**Results** 7210 patients of 20 randomized controlled trials and 17 cohort studies were included. In terms of recurrence reduction, there was no significant difference between any pairs of conservative treatment, manual aspiration and chest tube drainage. Surgical methods had a significantly lower recurrence rate compared to manual aspiration and chest tube drainage. Besides, bullectomy combined with additional procedures such as chemical pleurodesis, mechanical pleurodesis or staple line coverage can reduce the recurrence rate of PSP compared to bullectomy alone, but none of them were statistically significant. In terms of reducing postoperative chest tube duration, "bullectomy with tubular Neovail" outperformed "bullectomy + pleural abrasion" (MD, 95%CI: -2.5 [-4.63, -0.35]) and "bullectomy + apical pleurectomy" (MD, 95%CI: -2.72 [-5.16, -0.27]).

**Conclusions** Surgical methods were superior to manual aspiration, chest tube drainage and conservative treatment in terms of recurrence reduction. There was no significant difference between manual aspiration and chest tube drainage in reducing recurrence rate, but manual aspiration was linked to a shorter hospital stay and a lower rate of complications. Conservative treatment is an acceptable alternative to chest tube drainage or manual aspiration due to similar recurrence rates but lower incidence of complications. Among surgical methods, chemical pleurodesis is more effective than mechanical pleurodesis and staple line coverage among the additional procedures based on bullectomy. Moreover, bullectomy with tubular Neovail was superior to bullectomy alone. However, more randomized controlled trials are needed to confirm these findings and raise the level of evidence.

**Registration** The protocol was registered with PROSPERO (CRD42021236922).

Introduction

Pneumothorax is defined as the entry of air into the pleural cavity, increasing transmural pressure and causing collapse of the lung. It can be classified as spontaneous, traumatic and iatrogenic. Spontaneous pneumothorax is termed primary spontaneous pneumothorax (PSP) when there is no obvious precipitating factor, and secondary spontaneous pneumothorax (SSP) when there is an underlying pulmonary disease(1). The annual incident rate of PSP is 22.7 for every 100,000 people with a gender ratio of 3.3:1 (male: female) (2). PSP seriously affects the quality of life of patients due to its high recurrence rate. The recurrence rate of PSP varies widely with interventions and observation time. The reported rates were about 30% (ranging from 16-52%)(3).

In terms of the etiology of PSP, anatomic abnormalities have been revealed, even if there's no obvious underlying lung disease. Emphysema-like changes, subpleural blebs and bullae were found on thoracoscopy and on high-resolution computed tomography scanning in up to 90% of PSP patients (4). The rupture of subpleural blebs and bullae is thought to be a usual cause of PSP(5). This notion is outdated, although air leakage from bullae can occasionally cause PSP. Recent evidence suggests that the subpleural lung parenchyma undergoes a more diffuse histopathological and inflammatory process, resulting in an increase in diffuse porosity, which may contributed to the pneumothorax(6). Although the etiology of PSP is unclear, risk factors such as male sex, height, smoking and a family history of pneumothorax have been identified(7).

According to the guideline, PSP can be treated conservatively or with intervention. Conservative treatment (CT) entails observing the patient, giving patients appropriate analgesia and oxygen therapy. Interventional treatment (IT) options include manual aspiration (MA), chest tube drainage (CTD) and surgical methods (8,9). In patients of PSP, air can be withdrawn through percutaneous catheter aspiration (manual aspiration) or intercostal chest tube drainage. Besides, PSP can be treated surgically in a variety of ways. Bullectomy (BT) is a common procedure and can be done alone or in combination with additional procedure such as pleurodesis or staple line coverage (SLC). Pleurodesis is a procedure that involves mechanical pleurodesis (10) or chemical pleurodesis (CP) to cause adhesions between the two pleural layers to prevent recurrent pneumothorax(8,11). Mechanical pleurodesis includes pleural abrasion and apical pleurectomy. Furthermore, because of the high recurrence rate at the staple line, it can be covered with absorbable mesh to attempt to reduce recurrence rate (12,13).

However, the best management strategy is still debatable and varies greatly in practice due to a lack of high-quality evidence. Vuong et al. previously completed a network meta-analysis (NMA) on PSP which included a total of 4262 individuals, searching the database before the end of June 2016(14). However, many studies have been published since the last literature search, including the biggest randomized controlled trial (RCT) of conservative treatment and numerous studies about new surgical strategy in the last 5 years. Besides, the previous NMA included some literature on SSP, and the interventions included in the previous NMA were insufficient. Therefore, a systematic review and update of the network meta-analysis is required.

Materials And Methods

Our systematic review was completed in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) extension statement for network meta-analysis(15) and AMSTAR (Assessing the methodological quality of systematic reviews) guidelines. The PRISMA checklist is in Supplementary table 1. Besides, our research was registered with PROSPERO (International Prospective Register of Systematic Reviews, CRD42021236922).

Search strategy
A systematic literature search was conducted on PubMed, Web of Science, Embase, Ovid, Science Direct, Scopus, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, WHO-International Clinical Trials Registry Platform, ISRCTN registry, Open Grey, OSTI-GOV, CNKI, VIP, Sino Med and Wan Fang databases from inception to 24 August 2021. The detailed search strategy is in the Supplementary table 2. There were no restrictions on language, gender and race. The reference list of review articles was checked for additional articles that may not have been retrieved by our search strategy.

**Selection criteria**

The inclusion criteria were: studies compared the different treatment regimens for patients with PSP. The exclusion criteria were: 1. secondary spontaneous pneumothorax; 2. traumatic or iatrogenic pneumothorax; 3. follow-up duration was less than 6 months; 4. animal studies; 5. based on future unpublished trials; 6. review study; 7. conference literature; 8. data which cannot be extracted and studies not providing the full text; 9. duplicate and overlapping literature.

We included both RCTs and cohort studies. This is because including real-world data from non-randomized studies may improve the accuracy of NMA results(16). As cohort studies are more prone to bias, only those studies with similar baseline characteristics were included. Two researchers (M.M and K.P) first assessed eligibility independently by title and abstract. The shortlisted studies were then searched in full-text. In the event of disagreement, it was resolved through a third reviewer (Z.L).

**Data extraction**

Two reviewers (M.M and K.P) independently extracted and recorded all data and a third reviewer (S.Q) checked for correctness. The extracted information included the following: author, year, country, study design, follow-up duration, number of patients, treatment arms, outcomes, age, sex, body mass index (BMI), the proportion of smokers, PSP frequency, method of PSP diagnosis. If the reported details were insufficient, the authors were contacted for further information.

**Quality assessment**

The risk of bias for RCTs was independently assessed by two reviewers (M.M and K.P) by applying the Cochrane Collaboration Risk of Bias 2 Tool (RoB2) for RCTs (17). For cohort studies, the risk of bias in non-randomized studies of interventions assessment tool (ROBINS-I) was used (18). When the opinions were not unified, the third reviewer resolved the disagreements (J.X). Five sources of bias were evaluated with the RoB2: bias produced in the randomization process, deviations from intended interventions, missing result data, measurement of results and selection of reported results. With the ROBINS-I, we evaluated 7 domains: confounding, selection of patients, classification of treatments, deviations from the predefined interventions, missing data, measurement of results, and selection of reported outcomes. In addition, we assessed the quality of evidence contributing to network estimates of the main outcomes with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework(19).

**Statistical analysis**

We used a Bayesian network meta-analysis to compare multiple treatment options for PSP. By accounting for the association among multi-arm studies, the NMA model incorporates evidence about direct and indirect comparisons of regimens(20). We assumed that there was no difference between the direct and indirect evidence for a treatment comparison, a concept known as evidence consistency. Because most head-to-head comparisons only contained one trial providing direct evidence, the NMA was conducted in a Bayesian framework using a random-effect model. For dichotomous variables (recurrence rate, rate of complications), the effect was estimated using odds ratios (OR) and for continuous variables (postoperative chest tube duration, postoperative air leakage duration, length of hospital stay), the effect was estimated using mean difference (MD), both with 95% confidence intervals (CI). If the 95%CI of the MD intersects with 0 (null line), it is considered that there is no statistical significance between the two treatments; If the 95%CI of the OR intersected 1 (invalid line), no statistical significance was found between the two treatments.

We performed random-effects NMA using R software (http://cran.r-project.org/doc/faq/R-FAQ.html#Citing-R version x64 3.6.1)(21) with the gemtc package and used the Markov Chain Monte Carlo algorithm(22) for each qualified outcome based on 50,000 simulation iterations and 20,000 adaptation iterations. A thinning interval of 10 was applied, which collected 1 sample every 10 iterations. Consistency model and Monte Carlo Markov chain simulation without information prior distribution were used to analyze the results. We evaluated the ranking probabilities and calculated the surface under the cumulative ranking curves (SUCRA). Besides, we used STATA (http://www.stata.com/support/faqs/resources/citing-software-documentation-faqs/StataCorp, College Station, Texas, United States of America, version 16.1)(23) to draw a network evidence plot. The node-splitting method was used for the inconsistency test. If P<0.05 was achieved for each node, local inconsistency is considered to exist. The "anohe" function was used to estimate the deviation of the heterogeneity variance parameter $I^2$ and evaluate the overall heterogeneity of the model. We examined the distributions of baseline characteristics across trials and treatment comparisons to assess transitivity. Besides, subgroup and sensitivity analysis were completed to verify whether the results of NMA were influenced by the disease's progression, treatment strategy, or research design. Subgroup analysis was performed by dividing into first episode of PSP and recurrent PSP. Sensitivity analysis was performed by restricting analysis to only RCTs, and results were compared using randomized or fixed models. Besides, the visual inspection of funnel plots was used to investigate publication bias.

**Results**

**Study selection**

The initial search found 6,151 results. These studies were evaluated based on the inclusion and exclusion criteria outlined in the methods section. The titles and abstracts of 4,368 articles were evaluated, and 677 studies were found to be appropriate for full-text review. After excluding 640 studies, we were enabled to include 20 RCTs and 17 observational studies in our NMA. This process is presented in the PRISMA flowchart (Figure 1).

**Study characteristics and quality assessment**

The assumption of transitivity was accepted because no variability was found in the research and population baselines (Table 1). The sample size ranged from 19 to 757. The mean age of patients was 26.2(range 17-50) years, and the median proportion of men was 82.4%. The mean follow-up duration was 24(range 6-96) months. The mean BMI was 20.0kg/m² and the mean smoking rate was 46.5%. The characteristics of each study were summarized in Table 1. The risk of bias in the included studies was substantially low to moderate (Supplementary table 3 and Supplementary figure 1). The detailed risk of bias assessments and the certainty of evidence (GRADE) for each outcome was summarized in Supplementary table 4. No significant asymmetry was found in the funnel plots of primary and secondary outcomes (Supplementary figure 2).

**Network meta-analysis**

Network plots were used to visually compare the different treatments for each outcome (Figure 3). Each circle represented a treatment arm, and the thickness of the connecting lines represented the number of head-to-head comparisons between adjacent treatment arms.

**Primary outcomes**

**Recurrence rate**

There was no significant difference in recurrence reduction between any pairs of “conservative treatment”, “manual aspiration” and “chest tube drainage”. Patients who underwent surgical methods generally had superior outcomes in terms of recurrence reduction than those who underwent “conservative treatment”, “manual aspiration” or “chest tube drainage”. Among the surgical methods, "bullectomy + pleural abrasion + staple line coverage" was more effective than "bullectomy" (OR, 95%CI: 0.23[0.05, 0.89]) and "bullectomy + pleural abrasion" (OR, 95%CI: 0.28[0.08, 0.92]). Furthermore, "bullectomy + pleural abrasion + chemical pleurodesis with minocycline" outperformed "bullectomy" (OR, 95%CI: 0.2[0.05, 0.71]), "bullectomy + pleural abrasion" (OR, 95%CI: 0.25[0.09, 0.68]) and "bullectomy + staple line coverage" (OR, 95%CI: 0.27[0.09, 0.82]) (Figure 3A). There was no statistical difference in recurrence reduction between the other surgical procedures. Moreover, "manual aspiration + chemical pleurodesis with minocycline" was better than chest tube drainage (OR, 95%CI: 0.43[0.18, 0.95]) and manual aspiration (OR, 95%CI: 0.39[0.2, 0.75]) in reducing the recurrence rate. All of the comparisons are displayed in the Supplementary table 5. Additionally, in terms of reducing recurrence rate, the SUCRA values of all studies included showed that pleurectomy ranked first, followed by "bullectomy + chemical pleurodesis with achrornycin", "bullectomy + chemical pleurodesis with minocycline", "bullectomy + pleural abrasion + staple line coverage", "bullectomy with tubular Neovell", "bullectomy + chemical pleurodesis with talc", "bullectomy + chemical pleurodesis with dextrose solution", "bullectomy + chemical pleurodesis with talc-dextrose solution mixed", "bullectomy with polyglycolic acid sleeve + pleural abrasion + staple line coverage", "thoracoscopic chemical pleurodesis with talc", "bullectomy + chemical pleurodesis with minocycline", "bullectomy + apical pleurectomy", "bullectomy + staple line coverage", "bullectomy + pleural abrasion", "bullectomy", "manual aspiration + chemical pleurodesis with minocycline", "chest tube drainage", "conservative treatment" and "manual aspiration". The rank probability and specific SUCRA values are in the Supplementary figure 3 and Supplementary table 6.

**Secondary outcomes**

**Postoperative chest tube duration (days)**

In terms of reducing postoperative chest tube duration, "bullectomy with tubular Neovell" outperformed "bullectomy + pleural abrasion" (MD, 95%CI: -2.5[-4.63, -0.35]) and "bullectomy + apical pleurectomy" (MD, 95%CI: -2.72[-5.16, -0.27]), with no statistical difference between the remaining intervention groups. The postoperative chest tube duration was significantly shorter in surgical methods compared to "chest tube drainage" and "thoracoscopic chemical pleurodesis with talc", with no significant difference between "chest tube drainage" and "thoracoscopic chemical pleurodesis with talc" (MD, 95%CI: 0.09[2.46, 2.65]). All of the comparisons are displayed in the Supplementary table 7. Furthermore, in terms of reducing postoperative chest tube duration, the SUCRA values indicated that "bullectomy with tubular Neovell" ranked first, followed by "bullectomy + chemical pleurodesis with achrornycin", "bullectomy + staple line coverage", "bullectomy with polyglycolic acid sleeve + pleural abrasion + staple line coverage", "bullectomy + pleural abrasion + chemical pleurodesis with minocycline", "bullectomy + chemical pleurodesis with dextrose solution", "bullectomy + pleural abrasion + staple line coverage", "bullectomy + pleural abrasion", "pleurectomy", "bullectomy + apical pleurectomy", "chest tube drainage" and "thoracoscopic chemical pleurodesis with talc". The rank probability and specific SUCRA values are in the Supplementary figure 4 and Supplementary table 8.

**Postoperative air leakage duration (days)**

There was no significant difference in postoperative air leakage duration between any pairs of "bullectomy", "bullectomy + pleural abrasion", "bullectomy + chemical pleurodesis with minocycline", "bullectomy with tubular Neovell", "bullectomy with polyglycolic acid sleeve + pleural abrasion + staple line coverage", and "chest tube drainage" (Figure 3D). All of the comparisons are displayed in the Supplementary table 9. Furthermore, "bullectomy with tubular Neovell" placed highest in the ranking probability histogram of postoperative air leakage duration, followed by "bullectomy with polyglycolic acid sleeve + pleural...
to guide clinical practice, we conducted this Bayesian network meta-analysis to clarify which treatment is the most optimal strategy for PSP. Our analysis was included some literature on SSP, and the interventions included in the previous NMA were insufficient. So as an answer to the shortage of high-grade evidence randomized controlled trial (RCT) of conservative treatment and numerous studies about new surgical strategy in the last 5 years. Besides, the previous NMA searching the database before the end of June 2016(14). However, many studies have been published since the last literature search, including the biggest clinicians often choose the final treatment based on their previous experience or patient preference. Vuong et al. previously completed a NMA on PSP, conservative treatment, manual aspiration, chest tube drainage and surgical approaches. However, the best treatment option remains controversial and many treatment options for PSP, including “bullectomy + staple line coverage”, “bullectomy + pleural abrasion + staple line coverage”, “bullectomy + pleural abrasion”, “bullectomy + pleural abrasion + chemical pleurodesis with minocycline”. The rank probability are in the Supplementary figure 5.

**Length of hospital stay (days)**

There was no significant difference between surgical methods in reducing the length of hospital stay and most surgical procedures outperformed “manual aspiration” and “chest tube drainage” (Figure 3E). Furthermore, “manual aspiration” was more effective than “chest tube drainage” in decreasing the hospitalization time (MD, 95%CI: -2.27[-3.75, -0.8]). Moreover, “conservative treatment” demonstrated a shorter hospitalization time than “chest tube drainage” (MD, 95%CI: 5.69[8.99, -2.39]) and did not differ significantly from “manual aspiration” or surgical procedures. All of the comparisons are displayed in the Supplementary table 10. In addition, in terms of decreasing the hospitalization time, the SUCRA values revealed that “bullectomy + staple line coverage” ranked first, followed by “bullectomy + chemical pleurodesis with aminocycline”, “bullectomy + chemical pleurodesis with minocycline”, “bullectomy + pleural abrasion + chemical pleurodesis with minocycline”, “bullectomy + chemical pleurodesis with talc”, “bullectomy with tubular Neoveil”, “bullectomy with polyglycolic acid sleeve + pleural abrasion + staple line coverage”, “bullectomy + chemical pleurodesis with dextrose solution”, “bullectomy”, “bullectomy + pleural abrasion”, “bullectomy + pleural abrasion + staple line coverage”, “conservative treatment”, “bullectomy + apical pleurectomy”, “manual aspiration”, “manual aspiration + chemical pleurodesis with minocycline”, “chest tube drainage” and “thoracoscopic chemical pleurodesis with talc”. The rank probability and specific SUCRA values are in the Supplementary figure 6 and Supplementary table 11.

**Rate of the complications**

There was no significant difference between surgical methods in terms of reducing complications (Figure 3F), except that “bullectomy + pleural abrasion + chemical pleurodesis with minocycline” and “bullectomy + chemical pleurodesis with talc” were better than “pleurectomy” (OR, 95%CI: 0.09[0.01, 0.96]; 0.05[0, 0.67]). Besides, “bullectomy with polyglycolic acid sleeve + pleural abrasion + staple line coverage” showed less complications than “bullectomy + pleural abrasion + staple line coverage” (OR, 95%CI: 0.15[0.01, 0.96]). Furthermore, “manual aspiration” and “chest tube drainage” both had lower complication rates than most surgical methods. In addition, “manual aspiration” was superior to “chest tube drainage” (OR, 95%: 0.14[0.02, 0.77]). All of the comparisons are displayed in the Supplementary table 12. Additionally, in terms of reducing complications, the SUCRA values ranked “conservative treatment” first, followed by “manual aspiration”, “manual aspiration + chemical pleurodesis with minocycline”, “bullectomy + chemical pleurodesis with talc”, “bullectomy with polyglycolic acid sleeve + pleural abrasion + staple line coverage”, “chest tube drainage”, “bullectomy + pleural abrasion + chemical pleurodesis with minocycline”, “bullectomy + chemical pleurodesis with minocycline”, “bullectomy”, “bullectomy + pleural abrasion + staple line coverage”, “bullectomy + staple line coverage”, “bullectomy with tubular Neoveil”, “bullectomy + pleural abrasion”, “bullectomy + apical pleurectomy” and “pleurectomy”. The rank probability and specific SUCRA values are in the Supplementary figure 7 and Supplementary table 13.

**Consistency, transitivity, and heterogeneity analysis**

The consistency of direct and indirect comparisons were checked using Bayesian P values derived by the node splitting method. Supplementary figure 8 contains the results of inconsistency analysis. The p values of most direct and indirect comparisons were greater than 0.05, indicating good consistency. We analyzed the distribution of baseline variables between trials and treatment comparisons to assess transitivity (Table 1). Supplementary figure 9 contains the results of the heterogeneity analysis.

**Sensitivity and Subgroup analysis**

The sensitivity analysis found that recurrence rate results were generally consistent both when only RCTs were included and when all studies were included, with the exception of “bullectomy + pleural abrasion + chemical pleurodesis with minocycline”, which showed no statistically difference in reducing recurrence rate when compared to “bullectomy”, “bullectomy + pleural abrasion”, and “bullectomy + staple line coverage”. Furthermore, “manual aspiration” and “chest tube drainage” showed no difference when compared to “manual aspiration + chemical pleurodesis with minocycline”. Besides, the results of NMA were consistent with both the random model and the fixed model (Supplementary table 14).

We performed a subgroup analysis based on PSP frequency and divided them into two groups. In the subgroup of the first episode of PSP (FPSP), 13 articles containing 7 interventions were included in the analysis. According to results of FPSP-NMA, “bullectomy + apical pleurectomy” ranked the highest in prevention of recurrent pneumothorax, followed by “bullectomy + pleural abrasion”, “bullectomy”, “manual aspiration + chemical pleurodesis with minocycline”, “chest tube drainage”, “conservative treatment” and “manual aspiration” (Supplementary table 15). In the recurrent PSP (RPSP) subgroup, 11 studies with a total of 11 interventions were included for analysis. According to results of RPSP-NMA, “bullectomy + chemical pleurodesis with minocycline” ranked the highest in prevention of recurrent pneumothorax, followed by “bullectomy + pleural abrasion + staple line coverage”, “bullectomy + pleural abrasion + chemical pleurodesis with minocycline”, “bullectomy + chemical pleurodesis with talc”, “bullectomy with polyglycolic acid sleeve + pleural abrasion + staple line coverage”, “bullectomy + apical pleurectomy”, “bullectomy + chemical pleurodesis with aminocycline”, “bullectomy + staple line coverage”, “bullectomy + pleural abrasion” and “bullectomy + chemical pleurodesis with dextrose solution” and “bullectomy” (Supplementary table 15).

**Discussion**

PSP is a common disease and undermining patients’ quality of life due to high recurrence rates. There are many treatment options for PSP including conservative treatment, manual aspiration, chest tube drainage and surgical approaches. However, the best treatment option remains controversial and clinicians often choose the final treatment based on their previous experience or patient preference. Vuong et al. previously completed a NMA on PSP, searching the database before the end of June 2016(14). However, many studies have been published since the last literature search, including the biggest randomized controlled trial (RCT) of conservative treatment and numerous studies about new surgical strategy in the last 5 years. Besides, the previous NMA included some literature on SSP, and the interventions included in the previous NMA were insufficient. So as an answer to the shortage of high-grade evidence to guide clinical practice, we conducted this Bayesian network meta-analysis to clarify which treatment is the most optimal strategy for PSP. Our analysis was...
far more comprehensive because of the significantly larger evidence base, and we were able to investigate more therapeutic options for PSP patients, such as "conservative treatment", "manual aspiration + chemical pleurodesis", "bullectomy with tubular Neovell", "bullectomy + pleural abrasion + staple line coverage", "bullectomy + pleural abrasion + chemical pleurodesis", "pleurectomy" and "thoracoscopic chemical pleurodesis".

The principle of treatment for PSP is to re-expand the lung in the most minimally invasive way and to reduce the recurrence rate. According to the British Thoracic Society (BTS) pleural disease guideline in 2010(8), chest tube drainage and manual aspiration are the first-choice treatment methods among various treatment options for PSP treatment in clinical practice. These two treatments are equally effective and manual aspiration is related to decreased hospitalization time. Our study confirmed no statistically significant difference between these two procedures in terms of recurrence rate. Furthermore, our study found that manual aspiration was associated with a 2.27-day reduction in hospitalization time and a lower rate of complications when compared to chest tube drainage. These findings support the 2010 BTS guideline that aspiration should be the first choice, and tube drainage should become the backup procedure in the case of initial aspiration failure.

Our research showed that surgical methods had a significantly lower recurrence rate and were associated with a reduced hospitalization time compared to manual aspiration and chest tube drainage. On the other hand, manual aspiration and chest tube drainage had significantly lower complication rates. These findings are consistent with a paired meta-analysis published in 2019(24), which compared chest tube drainage to surgical procedures. The benefit of surgical procedures in reducing recurrence rates (OR, 95%CI: 0.15[0.07, 0.33]) and length of hospitalization (SMD, 95%CI: -2.19[-4.34, -0.04]) was validated in this meta-analysis, which included four studies with a total of 479 individuals.

There are a variety of surgical options for PSP. The most common surgical method is "bullectomy", which can be complemented with pleurodesis or staple line coverage. Pleurodesis is a procedure that involves mechanical pleurodesis (pleural abrasion/apical pleurectomy) and chemical pleurodesis. Besides, because of the high recurrence rate at the staple line, it can be covered with absorbable mesh to reduce recurrence rate. Our study discovered that bullectomy with tubular Neovell, "bullectomy + chemical pleurodesis", "bullectomy + pleural abrasion", "bullectomy + apical pleurectomy" and "bullectomy + staple line coverage" could reduce the recurrence rate of PSP when compared to "bullectomy", but none of these treatments reached statistical significance. Besides, the recurrence rate reduction must be balanced with complications corresponding to these treatments. So we completed a two-dimensional plot (figure 5) to balance efficiency and safety, which revealed that chemical pleurodesis were more effective than mechanical pleurodesis and staple line coverage. These findings were consistent with previous meta-analysis published in 2019(25), which compared chemical pleurodesis versus mechanical pleurodesis. According to this meta-analysis, chemical pleurodesis had a lower recurrence rate of pneumothorax (1.2%) than mechanical pleurodesis (4.0%) (OR, 95%CI: 3.00[1.59, 5.67]). In addition, the chemical pleurodesis group spent less time in the hospital (MD, 95%CI: 0.42[0.12, 0.72]). In terms of postoperative complications (OR, 95%CI: 1.18[0.40, 3.48]) or operative time (MD, 95%CI: 3.50[7.28, 14.28]), there was no statistically significant difference between these two groups (OR, 95%CI: 1.18[0.40, 3.48]). These findings could indicate that chemical pleurodesis is superior to mechanical pleurodesis. Furthermore, bullectomy with tubular Neovell appears to be superior to bullectomy alone, as "bullectomy with tubular Neovell" is better than bullectomy in reducing recurrence rate and lowering complication rates. As for pleurectomy, our study discovered that pleurectomy, even as highly effective in reducing recurrence rates, had a high complication rate. However, because only one study on pleurectomy was included, more research is needed to confirm the role of pleurectomy in the treatment of PSP.

Our study also demonstrated that conservative treatment is an acceptable alternative to chest tube drainage or manual aspiration due to similar PSP recurrence rates but lower incidence of complications. However, because our NMA only included one randomized controlled trial of conservative treatment, more research is needed to determine the accuracy of the conclusions.

Combining the available research findings, we believe that in patients with a first episode of primary spontaneous pneumothorax, treatment principles can be determined based on the presence of risk factors for recurrence and the patient's occupation. For patients who opt for surgery, "bullectomy with tubular Neovell" is a great option. For patients with recurrent primary spontaneous pneumothorax, to further reduce the recurrence rate, we recommend thoracoscopic bullectomy with chemical pleurodesis as the optimal surgical option of choice. However, more randomized controlled trials are needed to confirm these findings and raise the level of evidence.

The gradient of evidence levels examined in this review may aid physicians and policymakers in their decision-making. Although, numerous researches found consistent outcomes. To validate these findings and raise the level of evidence, RCTs on these therapy regimens are required.

There are several limitations to this study. First, cohort studies were included. Although such inclusions may add bias to the final analysis, we determined that the benefits outweighed the risks for the reasons stated in the methods section. In addition, we tried to reduce bias by only including observational studies that took into account potential confounders. Sensitivity analyses were also performed using only RCTs. Second, some of the NMA outcomes don’t have the support of pairwise meta-analysis. On the other hand, the methodological power of NMA is believable, because empirical evidence suggests that NMA are more likely to provide stronger evidence for invalid hypotheses than standard pairwise meta-analysis (26). As a result, our NMA can have practical consequences for directing PSP management until more research is conducted. Third, several treatment options comprised a small number of studies, resulting in reporting bias. At last, the CIs for many treatment regimens were too large, indicating that effect measurements were not precise.

**Conclusion**

Surgical methods were superior to manual aspiration, chest tube drainage and conservative treatment in terms of recurrence reduction. There was no significant difference between manual aspiration and chest tube drainage in reducing recurrence rate, but manual aspiration was linked to a shorter hospitalization time and a lower rate of complications. Moreover, conservative treatment is an acceptable alternative to chest tube drainage or manual aspiration due to similar PSP recurrence rates but lower incidence of complications. In addition, our study showed that bullectomy combined with additional procedures such as chemical pleurodesis, mechanical pleurodesis or staple line coverage can reduce the recurrence rate of PSP compared to bullectomy along, but none of them were statistically significant. Balancing efficiency and safety, chemical pleurodesis was more effective than mechanical pleurodesis.
and staple line coverage among the additional procedures based on bullectomy. Additionally, we found that bullectomy with tubular Neoveil was superior to bullectomy along. However, more RCTs are needed to confirm these findings and raise the level of evidence.

**Abbreviations**

PSP: Primary spontaneous pneumothorax; SSP: Secondary spontaneous pneumothorax; NMA: Network meta-analysis; SUCRA: Surface under the cumulative ranking; CT: Conservative treatment; IT: Interventional treatment; MA: Manual aspiration; CTD: Chest tube drainage; BT: Bullectomy; BT(TN): Bullectomy with tubular Neoveil; BT+PA: Bullectomy + pleural abrasion; BT+AP: Bullectomy + apical pleurectomy; BT+CP: Bullectomy + chemical pleurodesis; BT+CP(mc): Bullectomy + chemical pleurodesis with minocycline; BT+CP(talc): Bullectomy + chemical pleurodesis with talc; BT+CP(ac): Bullectomy + chemical pleurodesis with achromycin; BT+CP(dt): Bullectomy + chemical pleurodesis with dextrose solution; BT+CP(talc-dt): Bullectomy + chemical pleurodesis with talc-dextrose solution mixed; BT+SLC: Bullectomy + staple line coverage with absorbable mesh; BT+PA+SLC: Bullectomy + pleural abrasion + staple line coverage; BT+PA+CP(mc): Bullectomy + pleural abrasion + chemical pleurodesis with minocycline; BT(PGA)+PA+SLC: Bullectomy with polyglycolic acid sleeve + pleural abrasion + staple line coverage; PT: Pleurectomy; MA+CP(mc): Manual aspiration + chemical pleurodesis with minocycline; TSCP(Talc): Thoracoscopic chemical pleurodesis with talc.

**Declarations**

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Availability of data and materials**

The datasets supporting the conclusions of this article is included within the article and its supplementary material.

**Competing interests**

The authors have no conflicts of interest to declare.

**Funding**

None.

**Authors’ contributions**

(I) Conception and design: Muredili Muhetaer, Liwei Zhang; (II) Administrative support: Xiaoliang Jing; (III) Provision of study materials or patients: Liang Zong; (IV) Collection and assembly of data: Muredili Muhetaer, Keriman Paerhati, Haiping Zhang; (V) Data analysis and interpretation: Muredili Muhetaer, Keriman Paerhati, Qingchao Sun, Desheng Li; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

**Acknowledgments**

Not applicable.

**Footnote**

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at Supplementary Material.

**References**


Tables

Table 1: Characteristics of included studies
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Figures

Figure 1

PRISMA flow diagram showing the screening and selection process.
**Figure 2**

Network plots of comparisons for outcomes: (A) Recurrence rate; (B) Postoperative chest tube duration (days); (C) Postoperative air leakage duration (days); (D) Length of hospital stay (days); (E) Rate of the complications. CT: Conservative treatment; IT: Interventional treatment; MA: Manual aspiration; CTD: Chest tube drainage; BT: Bullectomy; BT(TN): Bullectomy with tubular Neovel; BT+PA: Bullectomy + pleural abrasion; BT+AP: Bullectomy + apical pleurectomy; BT+CP: Bullectomy + chemical pleurodesis; BT+CP(mc): Bullectomy + chemical pleurodesis with minocycline; BT+CP(talc): Bullectomy + chemical pleurodesis with talc; BT+CP(ac): Bullectomy + chemical pleurodesis with achroneycin; BT+CP(dt): Bullectomy + chemical pleurodesis with dextrose solution; BT+CP(talc-dt): Bullectomy + chemical pleurodesis with talc-dextrose solution mixed; BT+SCL: Bullectomy + staple line coverage with absorbable mesh; BT+PA+SCL: Bullectomy + pleural abrasion + staple line coverage; BT+PA+CP(mc): Bullectomy + pleural abrasion + chemical pleurodesis with minocycline; BT(PGA)+PA+SCL: Bullectomy with polyglycolic acid sleeve + pleural abrasion + staple line coverage; PT: Pleurectomy; MA+CP(mc): Manual aspiration + chemical pleurodesis with minocycline; TSCP(Talc): Thoracoscopic chemical pleurodesis with talc.
**Figure 3**

Network meta-analysis of different interventions compared with control (Bullectomy) for outcomes. (A) Recurrence rate-all studies; (B) Recurrence rate-RCTs only; (C) Postoperative chest tube duration (days)-all studies; (D) Postoperative air leakage duration (days)-all studies; (E) Length of hospital stay (days)-all studies; (F) Rate of the complications-all studies; CT: Conservative treatment; IT: Interventional treatment; MA: Manual aspiration; CTD: Chest tube drainage; BT: Bullectomy; BT(TN): Bullectomy with tubular Neoveil; BT+PA: Bullectomy + pleural abrasion; BT+AP: Bullectomy + apical pleurectomy; BT+CP: Bullectomy + chemical pleurodesis; BT+CP(mc): Bullectomy + chemical pleurodesis with minocycline; BT+CP(talc): Bullectomy + chemical pleurodesis with talc; BT+CP(ac): Bullectomy + chemical pleurodesis with achromycin; BT+CP(dt): Bullectomy + chemical pleurodesis with dextrose solution; BT+CP(talc-dt): Bullectomy + chemical pleurodesis with talc-dextrose solution mixed; BT+SLC: Bullectomy + staple line coverage with absorbable mesh; BT+PA+SLC: Bullectomy + pleural abrasion + staple line coverage; BT+PA+CP(mc): Bullectomy + pleural abrasion + chemical pleurodesis with minocycline; BT(PGA)+PA+SLC: Bullectomy with polyglycolic acid sleeve + pleural abrasion + staple line coverage; PT: Pleurectomy; MA+CP(mc): Manual aspiration + chemical pleurodesis with minocycline; TSCP(Talc): Thoracoscopic chemical pleurodesis with talc.
Figure 4

Two dimensional plot. CT: Conservative treatment; IT: Interventional treatment; MA: Manual aspiration; CTD: Chest tube drainage; BT: Bullectomy; BT(TN): Bullectomy with tubular Neovil; BT+PA: Bullectomy + pleural abrasion; BT+AP: Bullectomy + apical pleurectomy; BT+CP: Bullectomy + chemical pleurodesis; BT+CP(mc): Bullectomy + chemical pleurodesis with minocycline; BT+CP(talc): Bullectomy + chemical pleurodesis with talc; BT+CP(ac): Bullectomy + chemical pleurodesis with achromycin; BT+CP(dt): Bullectomy + chemical pleurodesis with dextrose solution; BT+CP(talc-dt): Bullectomy + chemical pleurodesis with talc-dextrose solution mixed; BT+PA+SLC: Bullectomy + pleural abrasion + staple line coverage; BT+PA+CP(mc): Bullectomy + pleural abrasion + chemical pleurodesis with minocycline; BT(PGA)+PA+SLC: Bullectomy with polyglycolic acid sleeve + pleural abrasion + staple line coverage; PT: Pleurectomy; MA+CP(mc): Manual aspiration + chemical pleurodesis with minocycline; TSCP(Talc): Thoracoscopic chemical pleurodesis with talc.

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