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Original Article

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

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Purpose: The best treatment strategy for primary spontaneous pneumothorax is controversial and varies widely in practice.

Methods: Literatures were searched from databases till 24 August 2021. A Bayesian network meta-analysis was conducted to compare the outcomes of various treatments with the following endpoints: recurrence rate, postoperative chest tube duration, postoperative air leakage duration, length of hospital stay, and complications rate.

Results: In all, 7210 patients of 20 randomized controlled trials and 17 cohort studies were included. Surgery had a significantly lower recurrence rate compared to other treatments. Besides, bullectomy (BT) combined with chemical pleurodesis (CP), mechanical pleurodesis, or staple line coverage (SLC) can reduce the recurrence rate compared to BT alone, but none of them were statistically significant. In terms of reducing chest tube duration, BT with tubular Neoveil outperformed BT + pleural abrasion (mean difference [MD], 95% confidence interval [CI]: –2.5 [–4.63, –0.35]) and BT + apical pleurectomy (MD, 95% CI: –2.72 [–5.16, –0.27]).

Conclusions: Surgical methods were superior to manual aspiration (MA), chest tube drainage (CTD), and conservative treatment in terms of recurrence reduction. There was no significant difference between MA and CTD in reducing the recurrence rate. Among surgical methods, CP is more effective than mechanical pleurodesis and SLC among the additional procedures based on BT.

Keywords: primary spontaneous pneumothorax, recurrence, systematic review, network meta-analysis

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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

PT = pleurectomy

BT + AP = bullectomy + apical pleurectomy

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

MA + CP(mc) = manual aspiration + chemical pleurodesis with minocycline

TSCP(Talc) = thoracoscopic chemical pleurodesis with talc

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 underlying pulmonary disease.[1] The annual incident rate of PSP is 22.7 for every 100000 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% to 52%).[3]

In terms of the etiology of PSP, anatomic abnormalities have been revealed, even if there is 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 contribute to 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, and giving patients appropriate analgesia and oxygen therapy. Interventional treatment 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 (MA) or intercostal CTD. Besides, PSP can be treated surgically in a variety of ways. Bullectomy (BT) is a common procedure that can be performed alone or in combination with additional procedures to reduce recurrent rates. Pleurodesis or staple line coverage (SLC) or a combination of both are common additional procedures. 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 (PA) and apical pleurectomy (AP). In addition, because of the high recurrence rate at the staple line, it can be covered with absorbable mesh to attempt to reduce the recurrence rate.[12,13]

However, it remains controversial whether surgery on addition to BT can reduce the recurrence rate, and if it is effective, which additional surgery is the best remains more controversial. The optimal management strategy of PSP 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 CT 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 NMA is required.

Materials and Methods

Our systematic review was completed in line with Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) extension statement for NMA.[15] The PRISMA checklist is given in **Supplementary Table 1** (The supplementary file is available online.). 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 given in **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 comparing the different treatment regimens for patients with PSP. The exclusion criteria were 1) SSP, 2) traumatic or iatrogenic pneumothorax, 3) follow-up duration less than 6 months, 4) animal studies, 5) studies based on future unpublished trials, 6) review study, 7) conference literature, 8) data that cannot be extracted and studies not providing the full text, and 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 (L.Z.).

Data extraction

Two reviewers (M.M. and K.P.) independently extracted and recorded all data and a third reviewer (Q.S.) 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, and 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 (H.Z.). Five sources of bias were evaluated with the RoB2: bias produced in the randomization process, deviations from intended interventions, missing result data, measurement of the results, and selection of reported results. With the ROBINS-1, 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 Evaluations (GRADE) framework.[19]

Statistical analysis

We used a Bayesian NMA 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 the 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-effects model. For dichotomous variables (recurrence rate, rate of complications), the effect was estimated using odds ratios (ORs) 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 (CIs). If the 95% CI of the MD intersected 0 (null line), it was considered that there was 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 50000 simulation iterations and 20000 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 curve (SUCRA). Besides, we used STATA (version 16.1; StataCorp, College Station, TX, USA; http://www.stata.com/support/faqs/resources/citing-software-documentation-faqs)[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 was 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 analyses 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 primary spontaneous pneumothorax (FPSP) and recurrent PSP. Sensitivity analysis was performed by restricting analysis to only RCTs, and the 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 6151 results. These studies were evaluated based on the inclusion and exclusion criteria outlined in the Materials and Methods section. The titles and abstracts of 4368 articles were evaluated, and 677 studies were found to be appropriate for full-text review. After excluding 640 studies, we were enable to include 20 RCTs and 17 observational studies in our NMA. This process is presented in the PRISMA flowchart (**Fig. 1**). Details of the included study are provided in **Supplementary Table 3**.

Study characteristics and quality assessment

A total of 20 RCTs and 17 cohort studies with 7210 participants met our inclusion criteria for evaluating various treatment options for PSP patients. Numerous treatment options for PSP were identified: 1) CT, 2) MA, 3) CTD, and 4) surgery. Among them, MA included simple aspiration and MA + CP. As for surgery, there were many ways, including BT, BT + mechanical pleurodesis, BT + CP, BT + SLC, BT + mechanical pleurodesis + CP, BT + mechanical pleurodesis + SLC, pleurectomy, and TSCP(Talc). There were two types of BT: simple BT and BT with tubular Neoveil (BT(TN)). Mechanical pleurodesis included PA and AP. CP was achieved with minocycline, talc, Achromycin, dextrose solution, and talc–dextrose mixed.

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 years (range 17–50 years), and the median proportion of men was 82.4%. The mean follow-up duration was 24 months (range 6–96 months). The mean BMI was 20.0 kg/m^2 and the mean smoking rate was 46.5%. The characteristics of each study are summarized in **Table 1**. The risk of bias in the included studies was substantially low to moderate (**Supplementary Table 4** and **Supplementary Fig. 1**). The detailed risk of bias assessments and the certainty of evidence (GRADE) for each outcome are summarized in **Supplementary Table 5**. No significant asymmetry was found in the funnel plots of primary and secondary outcomes (**Supplementary Fig. 2**).

NMA

Network plots were used to visually compare the different treatments for each outcome (**Fig. 2**). 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 CT, MA, and CTD. Patients who underwent surgical methods generally had superior outcomes. Among the surgical methods, BT + PA + SLC was more effective than BT (OR, 95% CI: 0.23 [0.05, 0.89]) and BT + PA (OR, 95% CI: 0.28 [0.08, 0.92]). Furthermore, BT + PA + CP outperformed BT (OR, 95% CI: 0.2 [0.05, 0.71]), BT + PA (OR, 95%

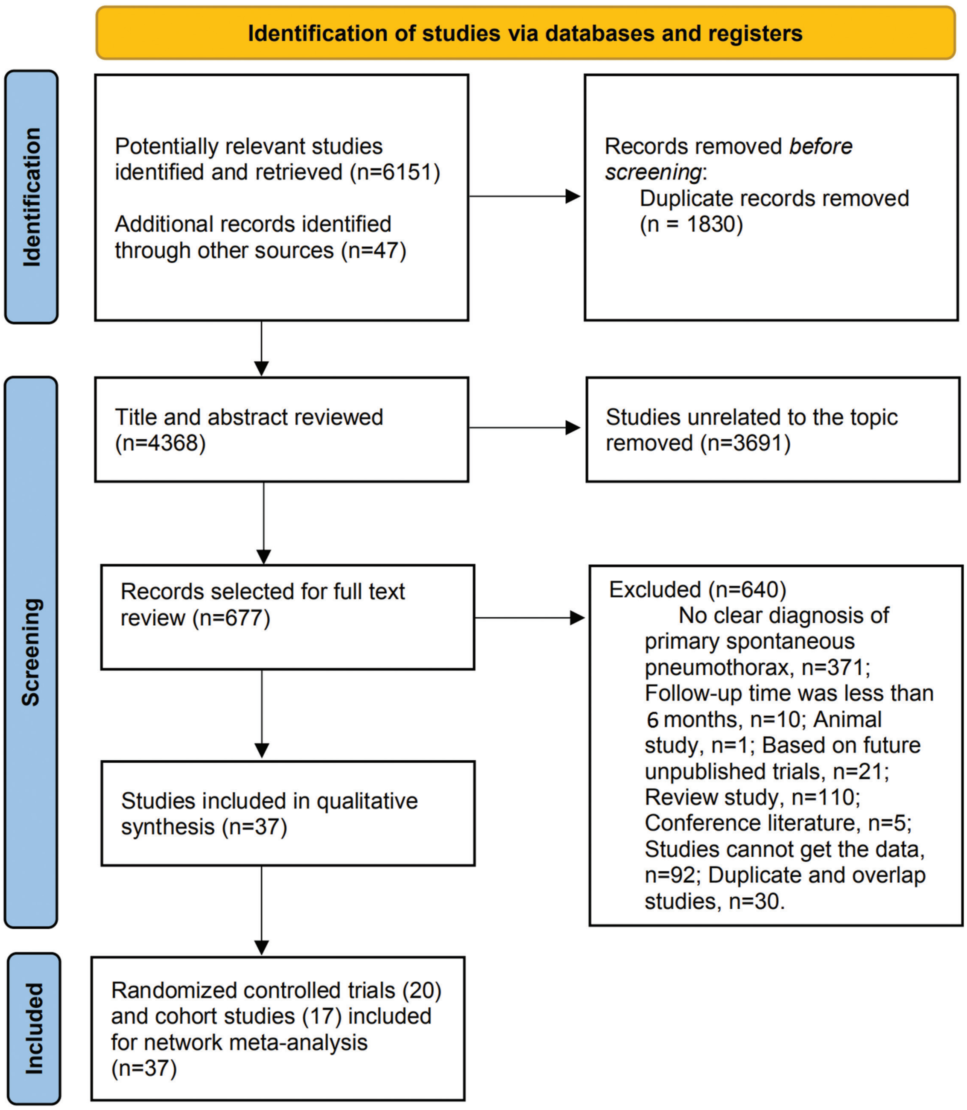

Fig. 1 PRISMA flow diagram showing the screening and selection process. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analysis

CI: 0.25 [0.09, 0.68]), and BT + SLC (OR, 95% CI: 0.27 [0.09, 0.82]) (**Fig. 3A**). There was no statistical difference in recurrence reduction between the other surgical procedures. Moreover, MA + CP was better than CTD (OR, 95% CI: 0.43 [0.18, 0.95]) and MA (OR, 95% CI: 0.39[0.2, 0.75]) in reducing the recurrent rate. All the comparisons are displayed in **Supplementary Table 6**. The rank probability and SUCRA values are given in **Supplementary Fig. 3 and Supplementary Table 7**.

Secondary outcomes

Postoperative chest tube duration (days)

In terms of reducing postoperative chest tube duration, BT(TN) outperformed BT + PA (MD, 95% CI: –2.5 [–4.63, –0.35]) and BT + AP (MD, 95% CI: –2.72 [–5.16, –0.27]), with no statistical difference between the remaining intervention groups (**Fig. 3C**). The postoperative chest tube duration was significantly shorter in surgical methods compared to CTD and thoracoscopic chemical pleurodesis with talc (TSCP(Talc)), with no significant difference between CTD and TSCP(Talc) (MD, 95% CI: 0.09 [–2.46, 2.65]). All the comparisons are displayed in **Supplementary Table 8**. The rank probability and SUCRA values are given in **Supplementary Fig. 4** and **Supplementary Table 9**.

Postoperative air leakage duration (days)

There was no significant difference in postoperative air leakage duration between any pairs of BT, BT + PA,

Table 1 Characteristics of included studies

Author, year	Country	Study design	Number of patients	Treatment arms	Age, mean (years)	Male (%)	BMI, mean (kg/m^2)	Smokers (%)	Follow-up duration (months)	PSP frequency	Left side (%)	Methods of PSP diagnosis
Harvey et al., 1994	England	RCT	35/38	MA/CTD	35/35	80/76	20/21	97/100	12	First episode and recurrence	43/38	NR/NR
Noppen et al., 2006	Belgium	RCT	27/33	MA/CTD	28/29	74/85	21/21	59/82	12	First episode	39/36	NR/NR
Ayed et al., 2006	Kuwait	RCT	65/72	MA/CTD	24/24	90/96	19/20	82/76	24	First episode	31/42	CXR
Ramouz et al., 2018	Iran	RCT	35/35	MA/CTD	49/50	44/41	21/22	23/16	12	First episode	19/24	CXR
Kim et al., 2019	Korea	RCT	21/19	MA/CTD	24/25	95/89	20/21	24/16	12	First episode	48/47	CXR
Shi, Ke et al., 2014	China	RCT	43/41	BT/BT + PA	21/22	91/90	NR/NR	NR/NR	6	First episode	NR/NR	CXR
Min et al., 2014	China	RCT	144/145	BT/BT + PA	22/22	90/90	19/20	15/23	24	First episode	57/48	CXR
Huo, Yuankui et al., 2017	China	RCT	87/90	BT/BT + PA	33/33	54/56	NR/NR	NR/NR	24	First episode and recurrence	56/59	HRCT
Ayed et al., 2000	Kuwait	Cohort study	39/33	BT + PA/ BT + AP	25	93	NR/NR	NR/NR	42	Recurrence	31	CXR
Chang et al., 2006	China	Cohort study	35/30	BT + PA/ BT + AP	24/28	94/90	NR/NR	37/37	24	First episode and recurrence	63/43	NR/NR
Rena et al., 2008	Italy	RCT	112/108	BT + PA/ BT + AP	25/25	79/83	22/20	43/50	24	Recurrence	45/42	NR/NR
Ocakcioglu et al., 2018	Turkey	Cohort study	48/40	BT + PA/ BT + AP	23/24	79/82	NR/NR	29/38	24	First episode and recurrence	52/53	CXR or HRCT
Chen et al., 2012	China	RCT	80/80	BT + PA + CP/ BT + AP	23/24	90/86	19/19	16/19	12	Recurrence	51/60	CXR
Alayouty et al., 2011	Egypt	Cohort study	42/42	BT + PA/ BT + CP	29/27	70/71	NR/NR	68/67	24	Recurrence	NR/NR	NR/NR
Merino et al., 2012	Spain	Cohort study	399/388	BT + PA/ BT + CP	25/29	98/99	22/24	54/60	96	First episode and recurrence	49/47	NR/NR
Chen et al., 2004	China	Cohort study	51/313	BT + PA/ BT + PA + CP	26/25	75/78	NR/NR	20/25	96	First episode and recurrence	39/52	NR/NR

(Coninued)

Table 1 (Continued)

Author, year	Country	Study design	Number of patients	Treatment arms	Age, mean (years)	Male (%)	BMI, mean (kg/m^2)	Smokers (%)	Follow-up duration (months)	PSP frequency	Left side (%)	Methods of PSP diagnosis
Chen et al., 2006	China	RCT	99/103	BT + PA/ BT + PA + CP	26/24	90/86	19/19	32/24	12	Recurrence	50/54	NR/NR
Wu Yu-bing et al., 2017	China	RCT	60/60	BT(TN)/ BT + PA	17/17	NR/NR	NR/NR	NR/NR	6	First episode and recurrence	NR/NR	NR/NR
Zhang et al., 2017	China	RCT	60/74	BT(PGA) + PA + SLC/ BT + PA + SLC	27/26	77/72	20/20	20/24	12	Recurrence	53/45	HRCT
Sakamoto et al., 2004	Japan	Cohort study	114/126	BT + SLC/BT	29/30	91/87	NR/NR	65/54	24	First episode and recurrence	51/48	NR/NR
Nakanishi et al., 2009	Japan	Cohort study	111/46	BT + SLC/BT	27/30	86/96	NR/NR	NR/NR	24	First episode and recurrence	54/46	NR/NR
Sun et al., 2011	China	Cohort study	96/43	BT + SLC/BT	NR/NR	88	NR/NR	NR/NR	24	First episode and recurrence	NR/NR	NR/NR
Hong, Ki Pyo et al., 2016	Korea	Cohort study	58/58	BT + SLC/BT	22/21	90/86	19/20	NR/NR	33	First episode and recurrence	49/36	CXR or HRCT
Hirai et al., 2015	Korea	Cohort study	181/98	BT + SLC/BT	31/26	80/89	19/19	50/57	30	First episode and recurrence	NR/NR	NR/NR
Lee et al., 2014	Korea	RCT	757/657	BT + SLC/ BT + PA	21/21	92/91	19/19	29/31	12	Recurrence	55/52	CXR or HRCT
Lee et al., 2013	Korea	Cohort study	129/128	BT + PA + SLC/ BT + PA	22/24	88/88	19/19	80/86	12	First episode and recurrence	59/53	CXR
Loubani et al., 2000	Ireland	Cohort study	26/26	BT/BT + CP	32/29	66/77	NR/NR	NR/NR	38	Recurrence	27/35	NR/NR
Chung et al., 2008	Korea	RCT	50/49	BT/BT + CP	22/23	92/94/100	NR/NR	NR/NR	12	Recurrence	52/53/57	NR/NR
Dżeljilji et al., 2019	Poland	Cohort study	33/40	BT + PT/PT	26/27	76/78	NR/NR	40/0	22	First episode and recurrence	NR/NR	NR/NR

(Coninued)

Table 1 (Continued)

Author, year	Country	Study design	Number of patients	Treatment arms	Age, mean (years)	Male (%)	BMI, mean (kg/m^2)	Smokers (%)	Follow-up duration (months)	PSP frequency	Left side (%)	Methods of PSP diagnosis
Divisi et al., 2015	Italy	Cohort study	61/61	BT + PA/CTD	20/22	NR/NR	NR/NR	NR/NR	60	First episode	56/32	CXR and HRCT
Olesen et al., 2018	Denmark	RCT	88/93	BT + PA/CTD	26/26	78/54	21/21	85/91	12	First episode	43/45	CXR and HRCT
Al-Mourgi et al., 2015	Saudi Arabia	RCT	19/22	BT + AP/CTD	24/23	95/91	19/19	NR/NR	24	First episode	NR/NR	CXR and HRCT
Tschopp et al., 2002	Switzer-land	RCT	61/47	TSCP/CTD	28/27	70/68	NR/NR	72/55	18	First episode and recur-rence	NR/NR	NR/NR
Chen et al., 2008	China	Cohort study	31/33	MA + CP/MA	23/24	90/76	19/19	48/30	12	First episode	55/61	CXR
Chen et al., 2013	China	RCT	106/108	MA + CP/MA	22/22	88/89	19/19	28/31	12	First episode	53/54	CXR
Chew et al., 2014	Australia	Cohort study	52/58	CT/CTD	37	75	NR/NR	NR/NR	24	First episode	NR/NR	NR/NR
Brown et al., 2020	Australia and New Zea-land	RCT	162/154	CT/IT	26/26	88/84	21/21	53/62	12	First episode	45/43	NR/NR

CXR: chest X-ray; HRCT: high-resolution computed tomography; NR: not reported; PSP: primary spontaneous pneumothorax; BMI: body mass index; CT: conservative treatment; RCT: randomized controlled trial; MA/CTD: manual aspiration vs chest tube drainage; BT/BT + PA: bullectomy vs bullectomy + pleural abrasion; BT + PA/BT + AP: bullectomy + pleural abrasion vs bullectomy + apical pleurectomy; BT + PA + CP/BT + AP: bullectomy + pleural abrasion + chemical pleurodesis vs bullectomy + apical pleurectomy; BT + PA/BT + CP: bullectomy + pleural abrasion vs bullectomy + chemical pleurodesis; BT + PA/BT + PA + CP: bullectomy + pleural abrasion vs bullectomy + pleural abrasion + chemical pleurodesis; BT(TN)/BT + PA: bullectomy with tubular Neoveil vs bullectomy + pleural abrasion; BT(PGA) + PA + SLC/BT + PA + SLC: bullectomy with PGA sleeve + pleural abrasion + staple line coverage vs bullectomy + pleural abrasion + staple line coverage; BT + SLC/BT: bullectomy + staple line coverage with absorbable mesh vs bullectomy; BT + SLC/BT + PA: bullectomy + staple line coverage with absorbable mesh vs bullectomy + pleural abrasion; BT + PA + SLC/BT + PA: bullectomy + pleural abrasion + staple line coverage with absorbable mesh vs bullectomy + pleural abrasion; BT/BT + CP: bullectomy vs bullectomy + chemical pleurodesis; BT + PT/PT: bullectomy + pleurectomy vs pleurectomy; BT + PA/CTD: bullectomy + pleural abrasion vs chest tube drainage; BT + AP/CTD: bullectomy + apical pleurectomy vs chest tube drainage; TSCP/CTD: simple thoracoscopic chemical pleurodesis with talc vs chest tube drainage; MA + CP/ MA: manual aspiration + chemical pleurodesis vs manual aspiration; CT/CTD: conservative treatment vs chest tube drainage; CT/IT: conservative treatment vs interventional treatment

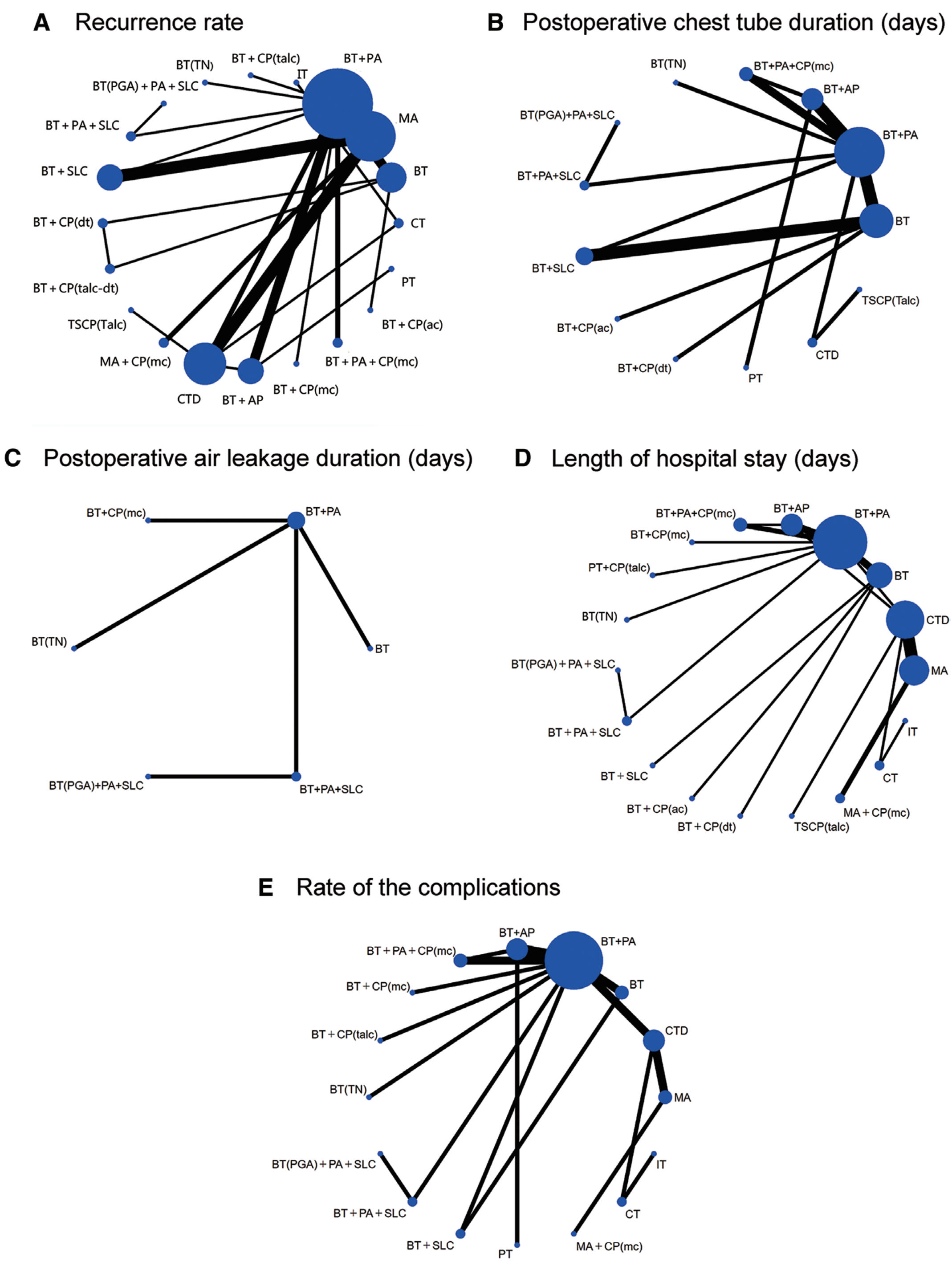

Fig. 2 Network plots of comparisons for outcomes: (**A**) recurrence rate, (**B**) postoperative chest tube duration (days), (**C**) postoperative air leakage duration (days), (**D**) length of hospital stay (days), and (**E**) rate of the complications. CT: conservative treatment; IT: interventional treatment; MA: manual aspiration, CTD: chest tube drainage; BT: bullectomy; BT(TN): bullectomy with tubular 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; 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

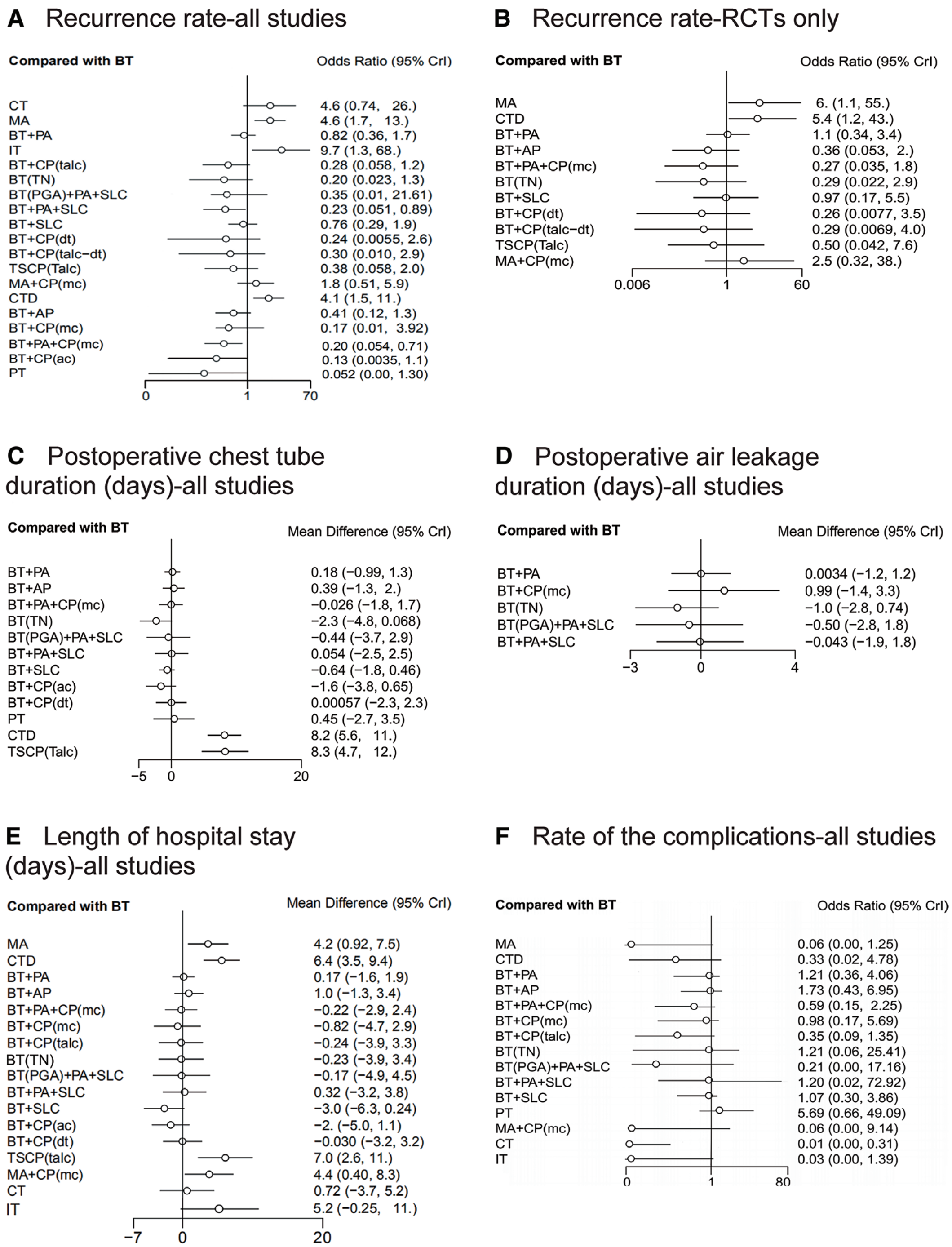

Fig. 3 NMA of different interventions compared with control (BT) for outcomes. (**A**) Recurrence rate – all studies, (B) recurrence rate – RCTs only, (**C**) postoperative chest tube duration (days) – all studies, (**D**) postoperative air leakage duration (days) – all studies, (**E**) length of hospital stay (days) – all studies, and (**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; 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

BT + CP, BT(TN), bullectomy with polyglycolic acid sleeve (BT(PGA)) + PA + SLC, and CTD (**Fig. 3D**). All the comparisons are displayed in **Supplementary Table 10**. Furthermore, BT(TN) was placed highest in the ranking probability histogram of postoperative air leakage duration. The rank probabilities are given in **Supplementary Fig. 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 MA and CTD (**Fig. 3E**). Furthermore, MA was more effective than CTD in decreasing the hospitalization time (MD, 95% CI: −2.27 [−3.75, −0.8]). Moreover, CT demonstrated a shorter hospitalization time than CTD (MD, 95% CI: 5.69 [−8.99, −2.39]) and did not differ significantly from MA or surgical procedures. All the comparisons are displayed in **Supplementary Table 11**. The rank probability and SUCRA values are given in **Supplementary Fig. 6** and **Supplementary Table 12**.

Rate of the complications

There was no significant difference between surgical methods in terms of reducing complications (**Fig. 3F**), except that BT + PA + CP and BT + CP were better than pleurectomy (OR, 95% CI: 0.09 [0.01, 0.96]; 0.05[0, 0.67]). Besides, BT(PGA) + PA + SLC showed less complications than BT + PA + SLC (OR, 95% CI: 0.15 [0.01, 0.96]). Furthermore, MA and CTD both had lower complication rates than most surgical methods. In addition, MA was superior to CTD (OR, 95%: 0.14 [0.02, 0.77]). All the comparisons are displayed in **Supplementary Table 13**. The rank probability and SUCRA values are given in **Supplementary Fig. 7** and **Supplementary Table 14**.

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 the heterogeneity analysis. **Supplementary Figure 9** 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**).

Sensitivity and subgroup analyses

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 BT + PA + CP, which showed no statistical difference in reducing the recurrence rate when compared to BT, BT + PA, and BT + SLC. Furthermore, MA and CTD showed no difference when compared to MA + CP. Besides, the results of NMA were consistent with both the random model and the fixed model (**Supplementary Table 15**), and the further results of sensitivity analysis are displayed in **Supplementary Tables 16 and 17** and **Supplementary Fig. 10**.

We performed a subgroup analysis based on PSP frequency and divided them into two groups. In the subgroup of the FPSP, 13 articles containing 7 interventions were included in the analysis. According to the results of FPSP-NMA, BT + AP ranked the highest in the prevention of recurrent pneumothorax. In the recurrent primary spontaneous pneumothorax (RPSP) subgroup, 11 studies with a total of 11 interventions were included for analysis. According to the results of RPSP-NMA, BT + CP ranked the highest in the prevention of recurrent pneumothorax. All the comparisons are displayed in **Supplementary Tables 18–21** and **Supplementary Fig. 11**.

Discussion

PSP is a common disease and undermines patients' quality of life due to high recurrence rates. There are many treatment options for PSP, including CT, MA, CTD, and surgical approaches. However, the best treatment option remains controversial and clinicians often choose the final treatment based on their previous experience or patient's preference. So as an answer to the shortage of high-grade evidence to guide clinical practice, we conducted this Bayesian NMA to clarify which treatment is the most optimal strategy for PSP.

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] CTD and MA are the first-choice treatment methods among various treatment options for PSP treatment in clinical practice. These two treatments are equally effective, and MA is related to decreased hospitalization time. Our study confirmed no statistically significant difference between these two procedures in terms of the recurrence rate. Furthermore, our study found that MA was associated with a 2.27-day reduction in hospitalization time and a lower rate of complications when compared to CTD. 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. Besides, our study also demonstrated that CT is an acceptable alternative to CTD or MA due to similar PSP recurrence rates but lower incidence of complications. However, because our NMA only included one RCT of CT, more research is needed to determine the accuracy of the conclusions.

Furthermore, our research showed that surgical methods had a significantly lower recurrence rate and were associated with a reduced hospitalization time compared to MA and CTD. On the other hand, MA and CTD had significantly lower complication rates. These findings are consistent with a paired meta-analysis published in 2019,[24] which compared CTD 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 (standardized MD, 95% CI: –2.19 [–4.34, –0.04]) was validated in this meta-analysis.

There are a variety of surgical options for PSP. The most common surgical method is BT, which can be performed alone or with additional procedures. Pleurodesis or SLC or a combination of both are common additional procedures. Pleurodesis is a procedure that involves mechanical pleurodesis (PA/AP) and CP. Besides, because of the high recurrence rate at the staple line, it can be covered with absorbable mesh to reduce the recurrence rate. Clinicians often perform these additional procedures on the basis of bullae excision to reduce the recurrence rate. Our study found that additional procedures could reduce the recurrence rate of PSP when compared to BT alone, 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 (**Fig. 4**) to balance efficiency and safety, which revealed that CP was more effective than mechanical pleurodesis and SLC. These findings were consistent with previous meta-analysis published in 2019,[25] which compared CP versus mechanical pleurodesis. According to this meta-analysis, CP 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 CP group spent less time in the

Fig. 4 Two dimensional plot. CT: conservative 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(mc): bullectomy + chemical pleurodesis with minocycline; BT + CP(talc): bullectomy + chemical pleurodesis with talc; BT + SLC: bullectomy + staple line coverage; BT + PA + CP: bullectomy + pleural abrasion + chemical pleurodesis; 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

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 CP is superior to mechanical pleurodesis and SLC.

The agents used for CP included in this study were minocycline, talc, Achromycin, dextrose solution, and talc–dextrose solution mixed. Our study found that CP with Achromycin had the best effect in terms of reducing recurrence, followed by talc, dextrose solution, talc–dextrose solution mixed, and minocycline.

As for other procedures, BT(TN) appears to be superior to BT alone, as BT(TN) is better than BT in reducing the recurrence rate and lowering complication rates. As for simple 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.

Combining the available research findings, we believe that in patients with an FPSP, 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, BT(TN) is a great option. For patients with recurrent PSP, to further reduce the recurrence rate, we recommend BT with CP as the optimal surgical option of choice. However, more RCTs 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.

Limitations

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 Materials and 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 do not have the support of pairwise meta-analysis. On the other hand, the methodological power of NMA is believable, because empirical evidence suggests that NMAs 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 MA, CTD, and CT in terms of recurrence reduction. There was no significant difference between MA and CTD in reducing the recurrence rate, but MA was linked to a shorter hospitalization time and a lower rate of complication. Moreover, CT is an acceptable alternative to CTD or MA due to similar PSP recurrence rates but lower incidence of complications. In addition, our study showed that BT combined with additional procedures such as CP, mechanical pleurodesis, or SLC can reduce the recurrence rate of PSP compared to BT alone, but none of them were statistically significant. Balancing efficiency and safety, chemical pleurodesis was more effective than mechanical pleurodesis and SLC. Additionally, we found that BT(TN) was superior to BT alone. However, more RCTs are needed to confirm these findings and raise the level of evidence.

Supplementary Material

The additional charts are included in the supplementary material.

Authors' Contributions

Conception and design: Muredili Muhetaer and Liwei Zhang; administrative support: Qingchao Sun; provision of study materials or patients: Liang Zong; collection and assembly of data: Muredili Muhetaer, Keriman Paerhati, and Haiping Zhang; data analysis and interpretation: Muredili Muhetaer, Keriman Paerhati, Qingchao Sun, and Desheng Li; manuscript writing: all authors; and final approval of manuscript: all authors.

Availability of Data and Materials

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

Ethics Approval

No ethical approval required as this research project is a systematic review of previous studies.

Disclosure Statement

The authors have no conflicts of interest to declare.

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