Clinical efficacy and safety of removing blood stasis and resolving phlegm in the treatment of epilepsy with cognitive impairment
A systematic review and meta-analysis

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Abstract

Backgrounds: Epilepsy is a chronic encephalopathy caused by abnormal discharge of neurons in the brain, resulting in brain dysfunction. Cognitive impairment is one of the most common complications of epilepsy. The current treatment of epilepsy in the control of symptoms at the same time cause a lot of side effects, especially the aggravation of cognitive impairment. Many literatures have stated that the efficacy and safety of integrated Traditional Chinese and western medicine in the treatment of epilepsy with cognitive impairment is superior to that of western medicine alone. In this systematic review and meta-analysis, we intend to evaluate the clinical efficacy and safety of removing stasis and resolving phlegm in the treatment of epilepsy with cognitive impairment.

Objective: To systematically evaluate the clinical efficacy and safety of removing blood stasis and resolving phlegm in the treatment of epilepsy with cognitive impairment.

Methods: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed to conduct this systematic review. The Chinese Journal Full Text Database (CNKI), Wanfang Database, CQVIP Database (CQVIP), Cochrane Library, EMbase, and Pubmed were searched by computer, and randomized controlled studies on the efficacy of removing blood stasis and resolving phlegm in the treatment of epilepsy with cognitive disorders were included. Retrieval was carried out until January 2022, and relevant data were extracted for meta-analysis using Rev Man5.3 software.

Results: Fourteen randomized controlled studies with a total of 1198 patients were included, including 601 patients in the control group and 597 patients in the treatment group (experimental group).

Results: Meta-analysis results showed that compared with the treatment of epilepsy with cognitive impairment in the western anti-epileptic drugs group alone, the treatment of epilepsy with cognitive impairment combined with the method of removing blood stasis and resolving phlegm could significantly improve the clinical efficacy of epilepsy (OR = 3.41, 95% CI 2.39–4.88, $P < .001$). Improved the TCM symptom score (OR = 3.99, 95% CI 1.72–9.26, $P < .001$). Increased the EEG improvement rate (RR = 1.39, 95% CI 1.05–1.84, $P = .02$). Improved MOCA score and cognitive function (MD = 3.54, 95% CI 1.68–5.40, $P < .001$). Improved QOLIE-31 cognitive function score. Improved cognitive function (MD = 7.22, 95% CI 3.35–11.08, $P < .001$). Improved the incidence of adverse reactions (RR = 0.50, 95% CI 0.33–0.76, $P = .001$).

Conclusion: Compared with the treatment of epilepsy with cognitive impairment by western anti-epileptic drugs alone, the treatment of epilepsy with cognitive impairment combined with the method of removing blood stasis and resolving phlegm is superior to the treatment of epilepsy with cognitive impairment by western anti-epileptic drugs alone.

Abbreviations: CI = confidence interval, EEG = electroencephalogram, MD = mean difference, MOCA = Montreal Cognitive Assessment, OR = odds ratio, QOLIE-31 = 31-item quality of life questionnaire in epilepsy, RCT = randomized controlled trial, RR = risk ratio, TCM = traditional Chinese medicine.

Keywords: epilepsy with cognitive impairment, integrated treatment of traditional Chinese and western anti-epileptic drugs, meta-analysis, removing blood stasis and resolving phlegm method

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1. Introduction

Epilepsy is a chronic encephalopathy with brain dysfunction caused by the abnormal discharge of neurons in the brain.[1] Long-term epilepsy brings great pain to patients. In addition, epilepsy patients are prone to complications, among which cognitive impairment is one of the most common, which leads to a series of social problems such as limited employment, reduced marriage rates, and reduced quality of life. At present, western drugs are mainly used to treat epilepsy, while western anti-epilepsy drugs cause many side effects while controlling symptoms, especially aggravation of cognitive impairment,[2,3] which brings a burden to patients and society. Therefore, it is particularly important to find new and effective antiepileptic drugs to relieve cognitive impairment.

Traditional Chinese medicine therapy is extensive and profound, and is the treasure of China. Due to its outstanding advantages in the treatment of clinical diseases, such as positive efficacy and less toxic and side effects, it is highly respected and accepted by the majority of patients and medical workers.

Many of the literatures showed that the efficacy and safety in the treatment of epilepsy with cognitive impairment by combining traditional Chinese and western anti-epileptic drugs is better than by western anti-epileptic drugs alone. Therefore, this study included a randomized observational control study on the treatment of epilepsy with cognitive impairment by removing blood stasis and resolving phlegm. To provide the basis for the prevention and treatment of epilepsy with cognitive impairment with traditional Chinese and western anti-epileptic drugs,[4–13] better play the advantages of traditional Chinese medicine.

2. Methods

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[14] Moreover, we have registered this systematic review and meta-analysis on the PROSPERO platform (PROSPERO registration number: CRD42021224893). This study was approved by the medical ethics Committee of Longhua Hospital Shanghai University of Traditional Chinese Medicine. The ethical number is 2021LCSY003.

2.1. Literature research

Literature searching was conducted by 2 researchers. Cochrane Library, Embase, PubMed, China National Knowledge Infrastructure, Wanfang database, and CQVIP database were searched by computer, and randomized controlled studies on the efficacy and observation of removing blood stasis and resolving phlegm in the treatment of epilepsy complicated with cognitive impairment were included. The retrieval time was up to January 2022. We manually searched relevant meeting minutes, eligible research reference lists, symposium abstracts, and grey literature such as degree papers, and conference papers.

The search terms were "blood stasis," "phlegm," "mutual association of phlegm and blood stasis," "epilepsy with cognitive impairment," and "epilepsy."

2.2. Inclusion criteria of the research

The inclusion criteria for this meta-analysis are as follows:

1. Type of studies: Type of study was randomized controlled trials (RCTS) on the clinical efficacy and safety of removing blood stasis and removing phlegm in the treatment of patients with epilepsy with cognitive impairment. No restriction were imposed on study dates or type and status. English and Chinese were applied as language restrictions. However, we will not consider literatures of animal studies, case report, case series, uncontrolled studies, nonclinical trials, non-RCTs, and quasi-RCTs

2. Type of participants: The patient diagnosed as epilepsy with cognitive impairment. Country, race, age, gender, educational background, and economic status, and duration and severity of epilepsy with cognitive impairment were not limited.

It conforms the following 2 diagnostic criteria (diagnosed by 2 researchers):

1. Diagnostic criteria for epilepsy[15,16]: Diagnostic criteria for epilepsy was referred to clinical diagnostic criteria and seizure classification of epilepsy from the International Anti-Epilepsy Alliance in 2015.

2. Diagnostic criteria for cognitive impairment: Diagnostic criteria for cognitive impairment were referred to the criteria of symptoms of mental disorders caused by epilepsy in the 《Classification and Diagnostic Criteria of Mental Disorders in China》,[17] and the diagnostic criteria of cognitive impairment in the 《Diagnostic and Statistical Manual of Mental Disorders》[18] of the American Psychiatric Association, and combined with clinical practice.

3. Types of interventions: The experimental group was treated with traditional Chinese medicine of removing blood stasis and removing phlegm combined with other traditional Chinese medicine combined with western anti-epilepsy medicine. However, we were not considered clear requirements on specific prescriptions, drug addition and subtraction, dosage form and dosage. The control group was treated with western antiepileptic drugs. The 2 groups were treated with western anti-epileptic drugs, such as carbamazepine, Sodium valproate, Lamotrigine, Levetiracetam, and so on.

4. Types of outcome measures: The study must have at least one of the following outcomes:

1. Major outcomes: 1. Clinical efficacy of epilepsy; (According to 《clinical treatment guidelines Epilepsy section》,[15] the effective number of epilepsy clinical curative effect includes the total number of cases of basic control 、significant effect、effective of epilepsy after treatment.)

2. Secondary outcomes:

1. TCM symptom score,

2. EEG improvement rate, (According to 《clinical electroencephalography》,[19] the EEG changes improved before and after treatment. The total number of cases of severe, moderate, and mild abnormal EEG can improve or become normal EEG after treatment.

3. Montreal Cognitive Assessment score, (MoCA[20] is the most commonly used screening tool in Chinese outpatient clinics, with sufficient sensitivity and specificity to allow useful stratification from average to abnormal with adequate consideration of age and education. The MOCA scale evaluates the cognitive function, focusing on the cognitive evaluation of visual spatial executive ability, memory, naming, attention, abstract thinking, language fluency, orientation, delayed memory and other aspects. There are 12 questions and 30 items in total. The person who answers each item correctly gets 1 point, and the person who answers don't know or wrong gets 0 points. The total score of the scale was 0 to 30, and the higher the score, the better the cognitive function.)

4. QOLIE-31, cognitive function score; (Epilepsy has a significant impact on patients' quality of life, which is manifested in various aspects such as physiology, psychology and social function. The QOLIE-31 scale has good reliability and validity.[21] The scale consists of 7 dimensions and 1 overall item: general quality of life, episode worry, mood, energy/fatigue, cognitive function, drug effects, social function/activity, and general feeling of health, with a higher total score for each item indicating better conditions in that item.)

3. Incidence of adverse reactions.

2.3. Exclusion criteria of the research

Relevant clinical trials were manually removed if any of the following factors was identified:

1. Non-clinical randomized controlled studies.
2. Literature which was with incorrect data or missing data.
3. Literature which was repeated publication.
4. The intervention measures of the control group were inconsistent.
5. The observed outcome indicators were inconsistent.
6. Animal or cellular basic studies.

2.4. Literature screening

Two researchers independently excluded literatures which were identical literatures, not related to the topic and did not meet the inclusion criteria by reading the titles, abstracts, and full-text. The full text of the remaining studies was read, and the studies were assessed for inclusion in the meta-analysis based on the inclusion and exclusion criteria in accordance with the PRISMA[14] recommendations. Any disagreement was resolved by the third adjudicated reviewer.

2.5. Data extraction

we extracted the following data from each selected study: the first author, time of the literature publication, the time of experiment, and sample size in each group (control and experimental group), the method of design of the study, intervention measures, the type of western anti-epileptic drugs selected by control and experimental group, intervention time, patient gender, patient age, disease stage, TCM syndrome types, complications, treatment results, Types of outcome measures, Other outcomes in the literature, etc.

The 2 researchers cross-checked their respective results, and any inconsistency was discussed with other reviewer authors who acted as arbiters.

2.5.1. Missing data. The lack of information was supplemented by contacting with the first author or correspondence author of the document. However, we did not receive correspondence. Thus, only available data were analyzed. Any disagreement was resolved by the third adjudicated reviewer.

2.6. Quality assessment of literatures

2.6.1. Risk of bias assessment. The risk of bias was independently assessed by 2 researchers according to the "Risk of bias" assessment tool provided in the Cochrane Manual version 5.1.0. The evaluation results are divided into 3 levels: "unclear judgment risk," "low bias risk," and "high bias risk." If there are different opinions, discuss them. If there is still a disagreement, a third reviewer will be consulted.

2.6.2. Heterogeneity assessment. Statistical heterogeneity across the included trials were examined using chi-square test and I^2 test. If $I^2 > 50\%$, $P < .1$ implies considerable heterogeneity, and a random-effects model (REM) was exploited. The extracted data were checked again, and the predetermined subgroups were analyzed to compare the efficacy of different subgroups. I^2 test was also conducted to evaluate the degree of heterogeneity between studies. While $I^2 \leq 50\%$, $P > .1$, manifested acceptable homogeneity, and a fixed-effects model (FEM) was exploited.

2.6.3. Report bias assessment. If 8 or more studies were included, funnel plots were drawn and possible reporting bias was verified by symmetry in the funnel plots.

2.7. Statistical analysis

2.7.1. Effect size selection. Statistical analysis was performed using Review Manager 5.3 software. The clinical efficacy of epilepsy and TCM symptom scores were represented by odds ratio (OR). The improvement rate of EEG and the incidence of adverse reactions were represented by risk ratio (RR). MOCA and QOLIE-31 cognitive function scores were expressed by mean difference (MD). To reduce reporting bias.

2.7.2. Subgroup analysis. The specific intervention time of removing blood stasis and resolving phlegm therapy was analyzed in subgroups such as 2, 3, and 6 months.

Forest maps were made to show the differences between the outcomes of the studies.

MOCA and QOLIE-31 cognitive function scores were used for meta-analysis using a random-effects model, and were divided into subgroups of 3 and 6 months and 2 and 3 months, respectively, according to the intervention time.

2.7.3. Sensitivity analysis. We used the one-by-one elimination method to analyze the sensitivity of the research results.

2.7.4. Statistical analysis. Meta-analysis was performed using RevMan 5.3 software provided by the Cochrane Collaboration.

For dichotomous variables, relative Risk Ratio (RR) or Odds Ratio (OR) values and 95% confidence interval (CI) evaluation statistics were used.

For continuous variables, mean difference (MD) and 95% confidence interval (CI) evaluation statistics were used.

Heterogeneity was tested by Q value and χ^2 test. When $P > .1$ and $I^2 < 50\%$, multiple studies were homogenous. The results were combined using a fixed-effects model for meta-analysis.

When $P \leq .1$ and $I^2 \geq 50\%$, multiple studies had great heterogeneity, and the removal of the single study method was adopted, and sensitivity analysis was conducted.

When one study was removed, the heterogeneity among the remaining studies decreased. It was necessary to reread the literature and reevaluate its quality bias and decide whether to include it or not.

If there was no obvious heterogeneity change, further analysis of the source of heterogeneity was needed.

When statistical heterogeneity was present but clinical heterogeneity was not, random-effects model was used for meta-analysis of the study results.

When there was high heterogeneity and the source of heterogeneity could not be analyzed, subgroup analysis was performed and only descripted the analysis of the outcomes.

3. Results

3.1. Literature results

3.1.1. Retrieval results. A total of 1318 literatures were found. Literature screening was conducted by 3 researchers. After reading the titles, 172 identical literatures were excluded, 326 unrelated literatures were excluded, and 820 literatures were screened initially. Read the abstracts, excluding 123 non-RCT studies; after reading the full text, 432 studies with inconsistent intervention measures and outcome indicators were excluded, 132 animal and cell studies were excluded, and 133 literatures were finally included. Then, a more careful screening was conducted, 32 literatures with inconsistent inclusion and exclusion criteria were excluded, and 87 literatures with data errors or missing data were excluded. 14 RCTS studies[22–35] with a total of 1198 patients were included, including 601 patients in the control group and 597 patients in the treatment group (experimental group). Meta-analysis was performed using RevMan5.3 software (Fig. 1).
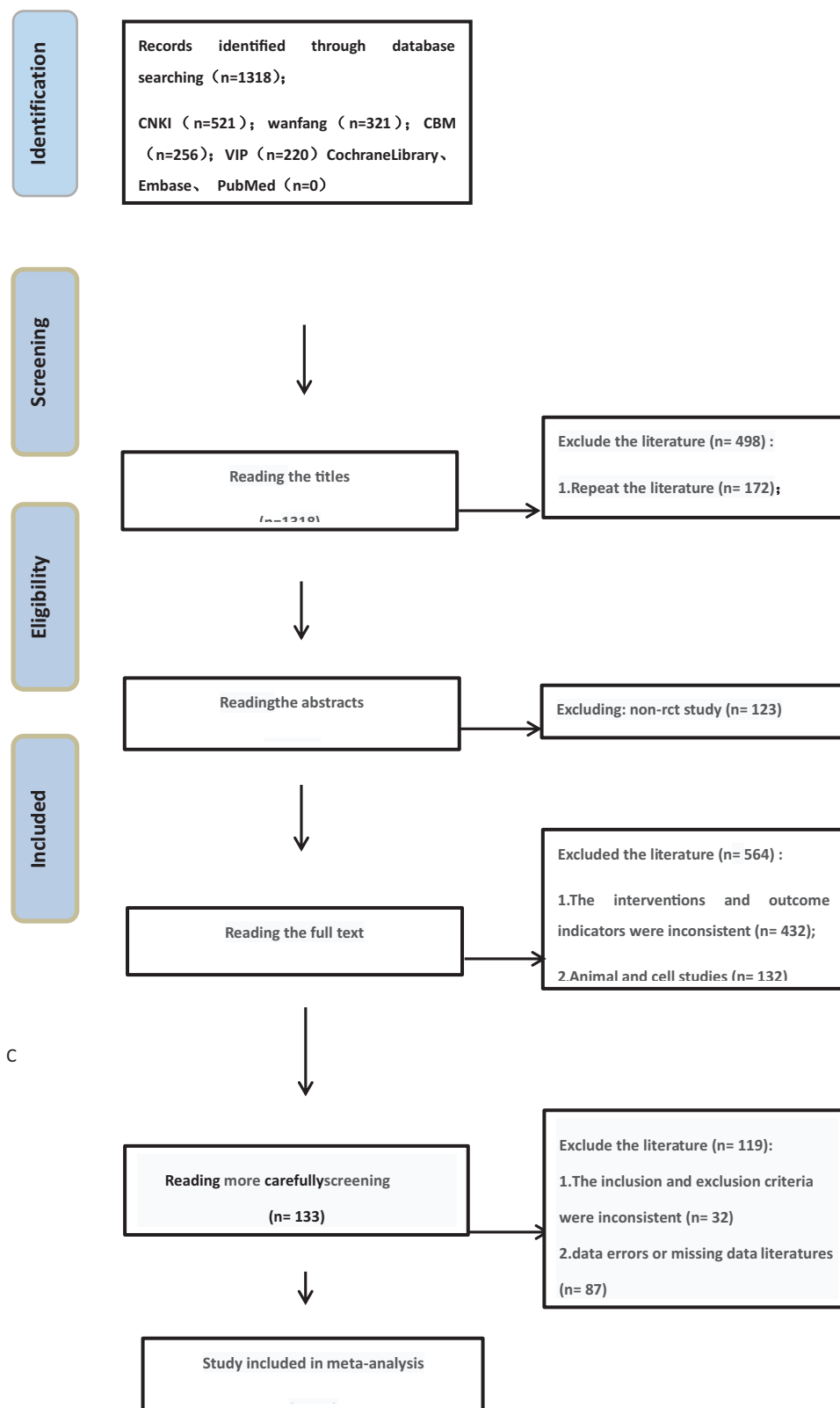
Figure 1. Flow chart of study selection process. Is the flow chart of literature selection process for meta-analysis (http://www.prisma-statement.org). CBM = China Biology Medicine disc, CBMdisc, CNKI = China National Knowledge Infrastructure, VIP = CQVIP.

3.1.2. Study characteristics. A total of 14 RCT studies[22–35] that met our criteria were included in the study (Table 1). These studies were published from 2015 to 2022 with 1198 patients involved, including 597 in the experimental group and 601 in the control group. The literatures were all from Chinese literature. Intervention measures of treatment group were traditional Chinese medicine for removing blood stasis and resolving phlegm, other traditional Chinese medicine, and western anti-epileptic drugs. The intervention measures of the control group were all kinds of western antiepileptic drugs. The course of treatment was 2, 3, and 6 months. About the observed outcome indicators, 11 studies measured clinical efficacy of epilepsy, 4 studies measured

Table 1

The study characteristics.

Author	Publication time	Sample size Treatment group/ Control group	Intervention measures (Treatment Group)	Intervention measures (Control Group)	Course of treatment Mo	Observe the outcome indicators	The other outcome indicators of the literature
Yan[22]	2019	47/46	1 + 2 + 3	3 Sodium valproate	2	1, 5	None
Xiaohui[23]	2018	28/32	1 + 2 + 3	3 Anti-ep conventional western medicine	3	3, 2, 6	1. Number of seizures of epilepsy2. Accompanying symptoms of epilepsy3. QOLIE-89 Total score
Huaqiong[24]	2019	31/33	1 + 2 + 3	3 Sodium valproate	2	1, 2, 5, 6	1. Number of seizures of epilepsy2. Duration of epilepsy3. Post treatment evaluation of EEG
Chunpeng et al[25]	2018	30/30	1 + 2 + 3	3 Lamotriazine	3	5, 6	1. Number of seizures of epilepsy2. Duration of epilepsy3. Evaluation of video EEG
Qiong[26]	2019	30/30	1 + 2 + 3	3 Sodium valproate	2	1, 2, 3, 6	QOLIE-31 total score
Kunmei[27]	2018	30/30	1 + 2 + 3	3 Anti-ep conventional western medicine	3	1, 2, 5, 6	None
Huifang[28]	2018	48/48	1 + 2 + 3	3 Camamasine	3	1, 4, 6	Number of seizures of epilepsy
Haiying et al[29]	2020	48/48	1 + 2 + 3	3 Occa	6	1, 4, 6	1. Number of seizures of epilepsy2. Duration of epilepsy3. EEG index
Lu et al[30]	2018	62/62	1 + 2 + 3	3 Occa	3	1, 3, 5	None
Kaiwei[31]	2015	27/26	1 + 2 + 3	3 Sodium valproate	6	1, 5	1. Onset frequency of epilepsy2. Course of illness of epilepsy
Jiancao et al[32]	2019	56/56	1 + 2 + 3	3 Sodium valproate	6	3, 4	Clinical symptom integral of Chinese medicine
Chan[33]	2016	68/68	1 + 2 + 3	3 Left ethyl latasi	6	1, 4	Number of seizures of epilepsy
Lisen et al[34]	2016	30/30	1 + 2 + 3	3 Anti-ep conventional western medicine	3	1, 4	1. Number of seizures of epilepsy. QOLIE-31 total score
Yabing[35]	2017	30/30	1 + 2 + 3	3 Anti-ep conventional western medicine	3	1, 3, 6	MOCA Grade rating

Intervention measures: 1. Traditional Chinese medicine for removing blood stasis and resolving phlegm; 2. Traditional Chinese medicine; and 3. Western anti-epileptic drugs.
Observe the outcome indicators: 1. Clinical efficacy of epilepsy; 2. Therapeutic effect of TCM symptom scores; 3. Improvement rate of EEG; 4. MOCA score; 5. QOLIE-31 cognitive function score; and 6. Incidence of adverse reactions.
EEG = electroencephalogram, MOCA = Montreal Cognitive Assessment, QOLIE-31 = 31-item Quality of life questionnaire in epilepsy, TCM = traditional Chinese medicine.

therapeutic effect of TCM symptom scores, 5 studies measured improvement rate of EEG, 5 studies measured MOCA score, 6 studies measured QOLIE-31 cognitive function score, 8 studies measured incidence of adverse reactions. Other outcome measures mentioned in the literature were also recorded (Table 1).

3.1.3. Literature quality assessment. The quality of the included literature was assessed by 2 investigators using Cochrane risk of bias assessment. Including selection bias (Random sequence generation, allocation concealment), performance bias (Blinding of participants and personnel), detection bias (Blinding of outcome assessment), attrition bias (Incomplete outcome data), reporting bias (Selective reporting), Other biases.

Among the 14 included literatures:
Randomization was mentioned in all included literatures. Nine of the studies[22,23,25–30,33] described random number table grouping. One study[35] was randomized according to the order in which

patients were presented. One study[32] was randomized in order of admission. One study[22,24,26–31,33–35] was randomized by Dollar's. These 12 studies were assessed as low risk. In addition, 2 other studies[24,31] did not provide specific random grouping methods.

About the allocation concealment, three of the studies[32,34,35] were assigned high risk. One study[24] was assigned low risk. Other studies did not mention it.

About the blinding of participants and personnel, none of the studies mentioned specific protocols, so systematic evaluation was not possible.

Eight studies[22–27,31,35] records mentioned loss of follow-up, shedding, withdrawal, etc. But it had no effect on the results. The other literatures were not mentioned.

None of the 14 studies mentioned selective reporting outcomes.

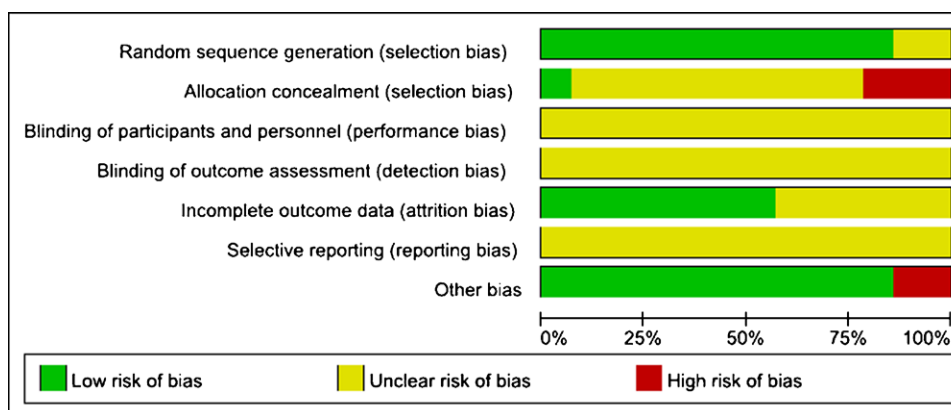In 2 of the studies,[27,34] other biases were high risk, while the others were low risk (Figs. 2 and 3).
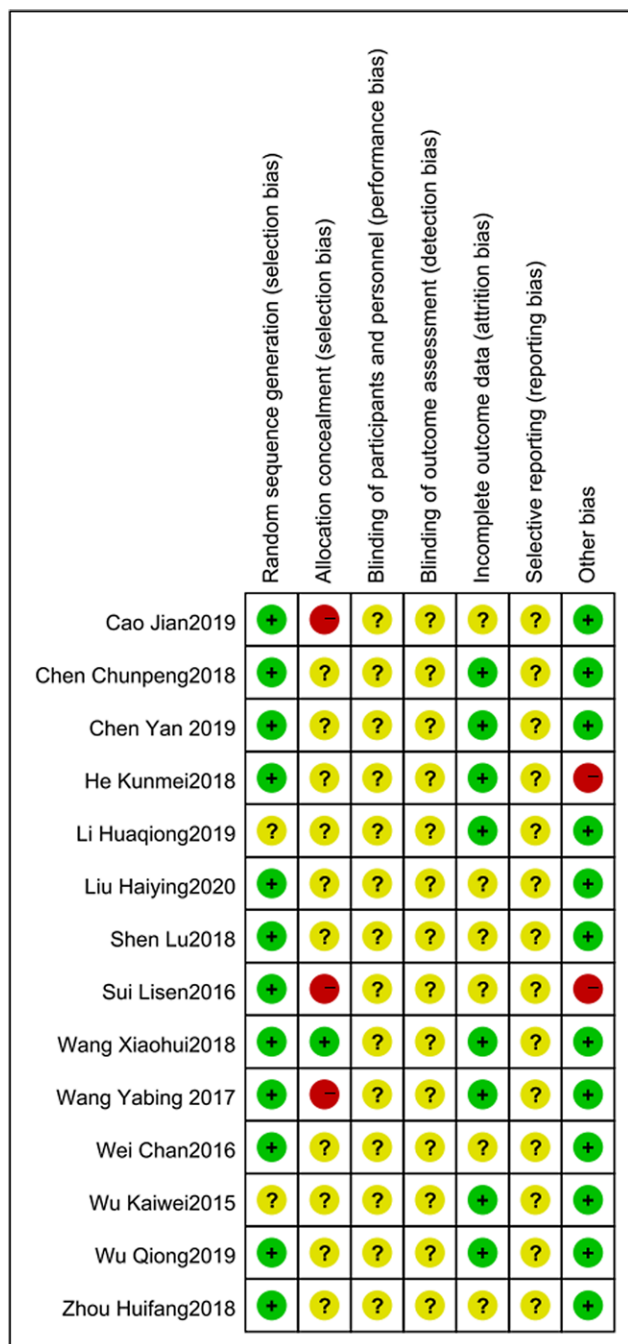

Figure 2. Risk of bias summary.

Figure 3. Risk of bias graph.

3.2. Meta-analysis results

3.2.1. Major outcomes.

3.2.1.1. Effectiveness on epilepsy clinical. Eleven literatures[22,24,26–31,33–35] on clinical efficacy of epilepsy as an outcome indicator were included, including 451 cases in the treatment group and 451 cases in the control group.

Heterogeneity test showed that there was no heterogeneity among the studies ($I^2 = 0\%$, $P = .88$), and the clinical efficacy of epilepsy in each study was homogenous. The combination of study results was analyzed by the fixed-effect model. Meta-analysis results showed that the clinical efficacy of epilepsy in the treatment group was better than that in the control group. The difference was statistically significant (OR = 3.41, 95% CI 2.39–4.88, $Z = 6.72$, $P < .00001$) (Fig. 4).

3.2.2. Secondary outcomes.

3.2.2.1. TCM symptom scores. Four literatures[23,24,26,27] with TCM symptom scores as an outcome indicator were included, including 119 cases in the treatment group and 125 cases in the control group. Heterogeneity test showed that there was no heterogeneity among the studies ($I^2 = 0\%$, $P = .86$), and the TCM symptom scores of each study were homogenous. The combination of the study results was analyzed by the fixed-effect model. Meta-analysis results showed that, compared with the control group, the treatment group had better efficacy of TCM symptom scores. The difference was statistically significant (OR = 3.99, 95% CI 1.72–9.26, $Z = 3.22$, $P = .001$) (Fig. 5).

3.2.2.2. Improvement rate of EEG. Five literatures[23,26,30,32,35] with EEG improvement rate as an outcome indicator were included, including 206 cases in the treatment group and 210 cases in the control group.

Heterogeneity test showed that there was no heterogeneity among the studies ($I^2 = 45\%$, $P = .12$), and the EEG improvement rate of each study was homogeneous. The combination of the study results was analyzed by the fixed-effect model. Meta-analysis results showed that the EEG improvement rate of the treatment group was better than that of the control group. The difference was statistically significant (RR = 1.39, 95% CI 1.05–1.84, $Z = 2.33$, $P = .02$) (Fig. 6).

3.2.2.3. MOCA scores. Five literatures[28,29,32–34] with MOCA score as an outcome indicator were included, including 250 cases in the treatment group and 250 cases in the control group. Heterogeneity test showed that there was great heterogeneity among the groups ($I^2 = 99\%$, $P < .0001$), so the random-effect model was used for analysis. Meta-analysis results showed that the improvement rate of MOCA score in the treatment group was better than that in the control group. The difference was statistically significant, (MD = 3.54, 95% CI 1.68–5.40, $Z = 3.73$, $P = .00002$) (Fig. 7).

3.2.2.3.1. Subgroup analysis. Five literatures with MOCA score as the outcome indicator were included, and subgroup analysis was performed according to the time of intervention.

Two studies[28,34] with the intervention time of 3 months were included, and 3 studies[29,32,33] with the intervention time of 6 months were included.

The intervention time was 3 months in 2 literatures, including 78 cases in the treatment group and 78 cases in the control group. Heterogeneity test showed that there was great heterogeneity among each group ($I^2 = 100\%$, $P < .00001$), so the random effects model was used for analysis.

Meta-analysis results showed that there was no statistically significant difference in MOCA score between the control group and the treatment group in the intervention period of 3 months (MD = 1.26, 95% CI –1.79 to 4.31, $Z = 0.81$, $P = .42$) (Fig. 7).

The intervention time was 6 months in 3 literatures, including 172 cases in the treatment group and 172 cases in the control group. Heterogeneity test showed that there was great heterogeneity among all groups ($I^2 = 91\%$, $P < .0001$), so a random effects model was used for analysis. Meta-analysis results showed that, compared with the control group, the improvement rate of MOCA score was better than the treatment group at the intervention time of 6 months. The difference was statistically significant (MD = 5.1, 95% CI 3.78–6.43, $Z = 7.56$, $P < .00001$) (Fig. 7).

Therefore, the improvement of MOCA score may be related to the time of intervention.

3.2.2.4. QOLIE-31 cognitive function score. Six studies[22,24,25,27,30,31] were included, including 227 cases in the treatment group and 227 cases in the control group, using QOLIE cognitive function score as an outcome indicator.

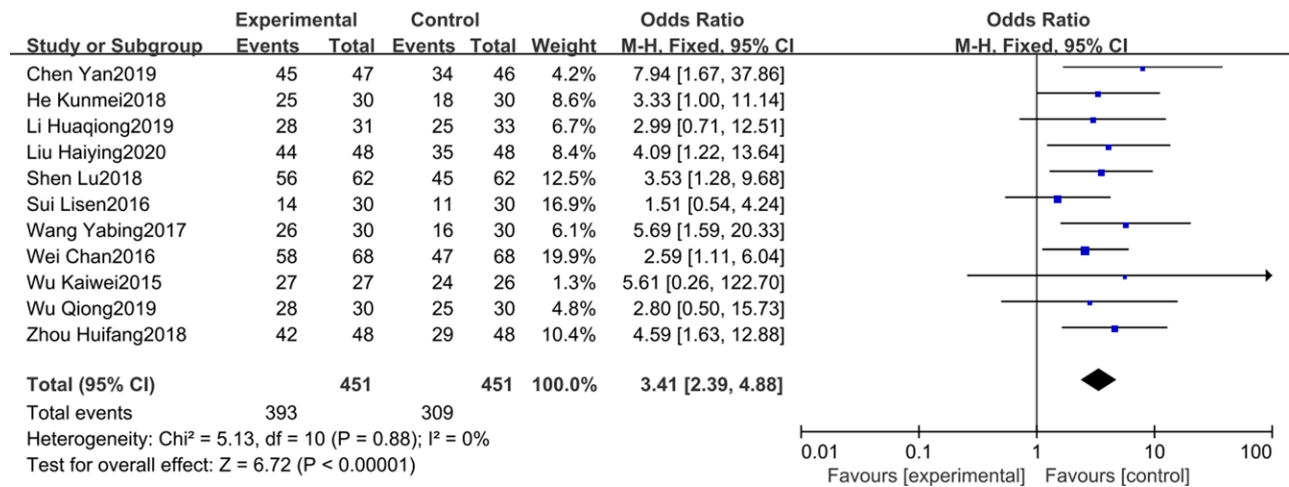Heterogeneity test showed that there was great heterogeneity among the groups ($I^2 = 99\%$, $P < .000001$), so the

Figure 4. Meta-analysis results of effectiveness on epilepsy clinical. CI = confidence interval.
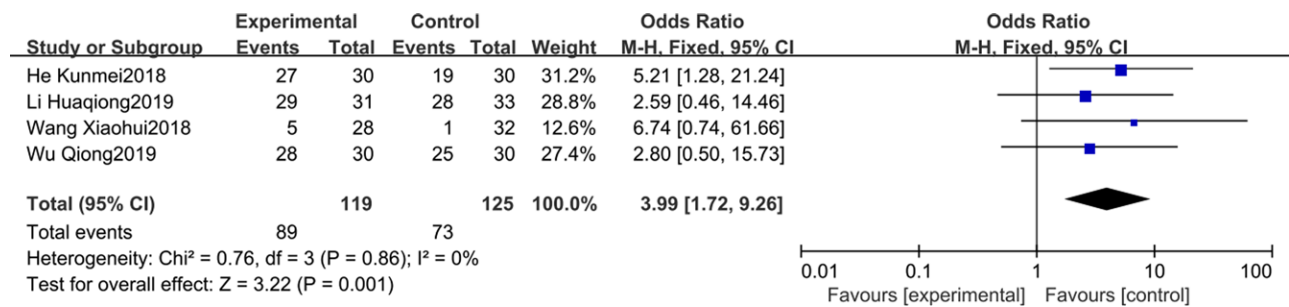

Figure 5. Meta-analysis results of the TCM symptom scores. CI = confidence interval, TCM = Traditional Chinese medicine.
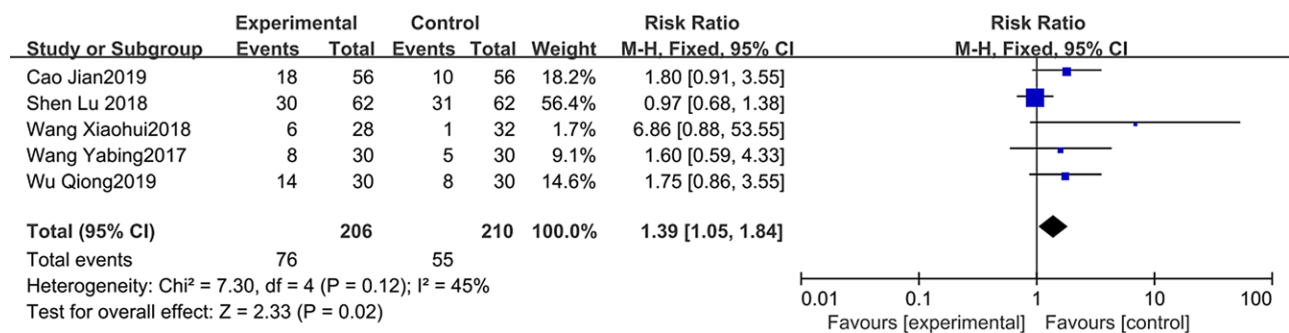

Figure 6. Meta-analysis results of the improvement rate of EEG. CI = confidence interval, EEG = electroencephalogram.

random-effect model was used for analysis. Meta-analysis results showed that the improvement rate of QOLIE-31 cognitive function score in the treatment group was better than that in the control group. The difference was statistically significant, (MD = 7.22, 95% CI 3.35–11.08, $Z = 3.66$, $P = .00003$) (Fig. 8).

3.2.2.4.1. Subgroup analysis. Subgroup analysis was performed based on the duration of the intervention in 6 studies that used the QOLIE-31 cognitive function score as an outcome indicator.

Two studies[22,24] with the intervention time in 2 months were included, and 4 studies[25,27,30,31] with the intervention time in 3 months were included.

The intervention time was 2 months in 2 literatures, including 78 cases in the treatment group and 79 cases in the control group.

Heterogeneity test showed that there was great heterogeneity among the groups ($I^2 = 99\%$, $P < .00001$), so the random-effects model was used for analysis. Meta-analysis results showed that the QOLIE-31 cognitive function score improved better in the treatment group compared with the control group at the intervention time of 2 months. The difference was statistically significant (MD = 14.84, 95% CI 9.53–20.16, $Z = 5.48$, $P < .00001$) (Fig. 8).

The intervention time was 3 months in 4 literatures, including 149 cases in the treatment group and 148 cases in the control group.

Heterogeneity test showed that there was significant heterogeneity among all groups ($I^2 = 99\%$, $P < .00001$). Therefore, the random effects model was used for analysis.

Results of the meta-analysis showed that QOLIE-31 cognitive function score improved more in the treatment group than in the control group at 3 months of intervention. The difference
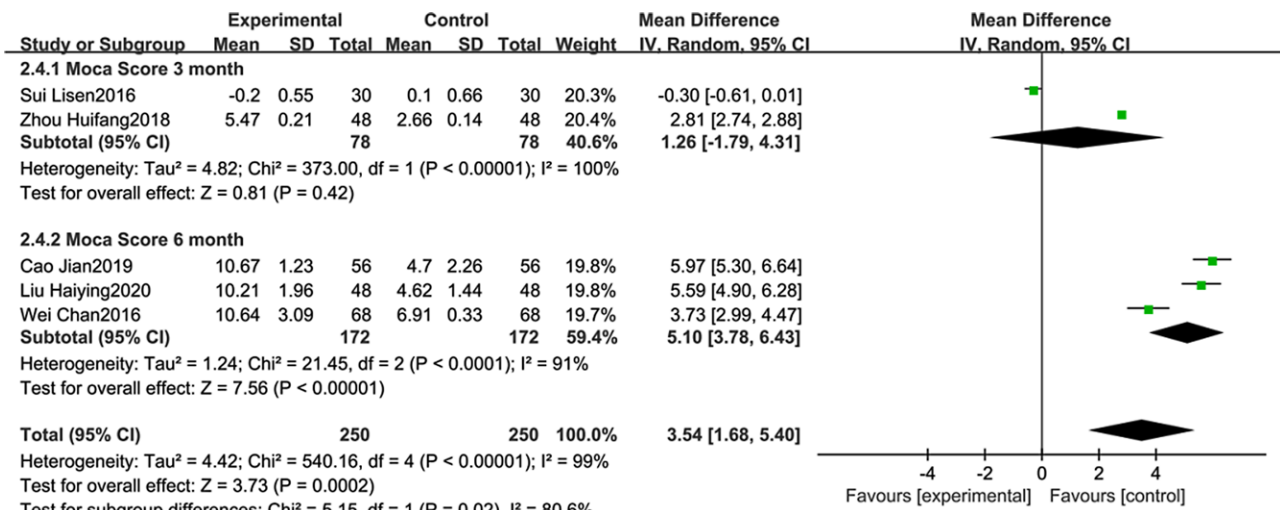
Figure 7. Meta-analysis results of MOCA score. CI = confidence interval, MOCA = Montreal Cognitive Assessment.
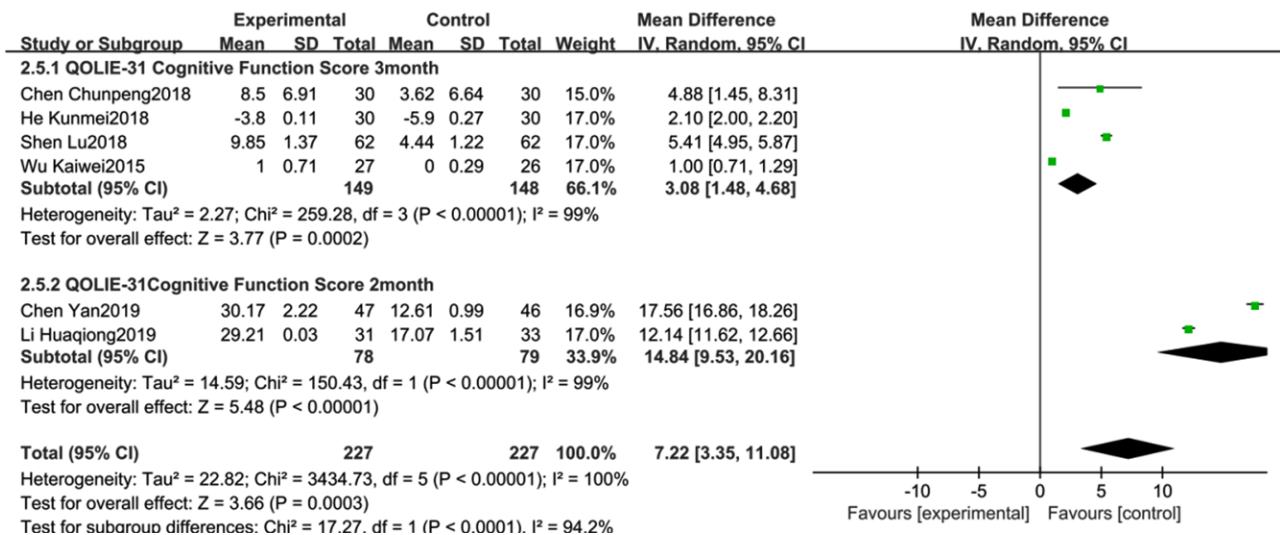

Figure 8. Meta-analysis results of QOLIE-31 cognitive function score. CI = confidence interval, QOLIE-31 = 31-item Quality of life questionnaire in epilepsy.

was statistically significant (MD = 3.08, 95% CI 1.48–4.68, Z = 3.77, P = .0002) (Fig. 8).

3.2.3. Adverse reactions. Eight studies[23–29,35] with the incidence of adverse reactions as an outcome indicator were included, including 247 cases in the treatment group and 249 cases in the control group.

Heterogeneity test showed that there was no heterogeneity among the studies (I^2 = 0%, P = .61), and the incidence of adverse reactions among the studies was homogeneous. The results were combined using a fixed effects model.

Meta-analysis results showed that the incidence of adverse reactions in the treatment group was lower than that in the control group. The difference was statistically significant (RR = 0.50, 95% CI 0.33–0.76, Z = 3.3, P = .001) (Fig. 9).

3.3. Sensitivity analysis

The above-mentioned outcome indicators were all eliminated one by one for sensitivity analysis. After eliminating the included studies one by one, the change in effect size and value was small. This shows that the results of the meta-analysis are stable and credible.

3.4. Publication bias

Among the 11 literatures[22,24,26–31,33–35] that used the method of removing blood stasis and removing phlegm to treat epilepsy complicated with cognitive impairment, the clinical efficacy of epilepsy was used as the outcome indicator to evaluate the publication bias of the included studies, and the OR value was used to evaluate the publication bias of the included studies, and funnel plots were drawn.

The funnel plot showed that the distribution positions of the effect estimates were all within the 2 oblique lines, which were partial to the upper and middle part and symmetrical to the left and right sides, suggesting that the possibility of publication bias was small. The result of the funnel plot was ideal (Fig. 10).

In the 8 literatures[23–29,35] evaluated with adverse reactions as an outcome indicator, RR value was used to evaluate the publication bias of the included studies, and funnel plots were drawn. The funnel plot showed that the distribution positions of the effect estimates were all within the 2 oblique lines, which were skewed to the upper and middle part and symmetrical to the left and right sides, suggesting that the possibility of publication bias was small. Due to the limited literature data on adverse reactions, the result of funnel plots was not ideal (Fig. 11).
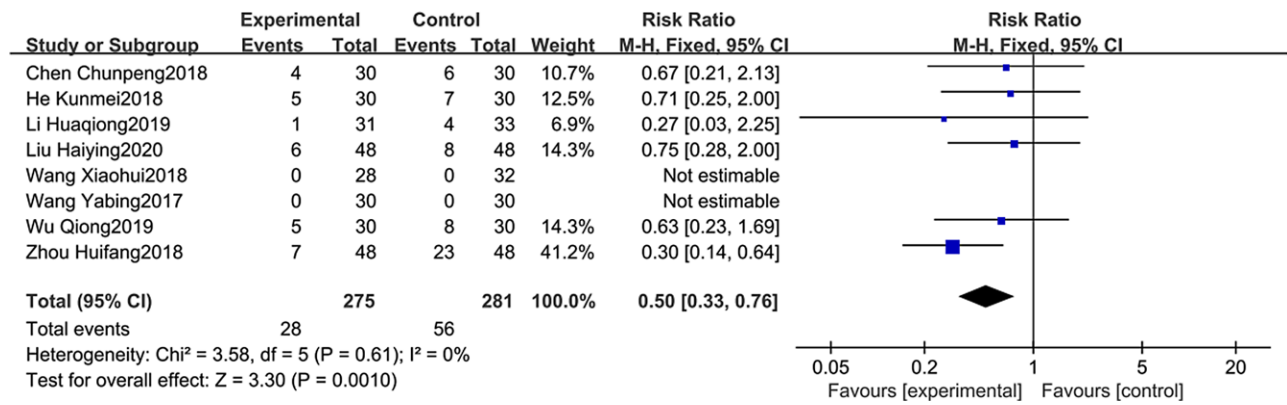
Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chen Chunpeng2018	4	30	6	30	10.7%	0.67 [0.21, 2.13]
He Kunmei2018	5	30	7	30	12.5%	0.71 [0.25, 2.00]
Li Huaqiong2019	1	31	4	33	6.9%	0.27 [0.03, 2.25]
Liu Haiying2020	6	48	8	48	14.3%	0.75 [0.28, 2.00]
Wang Xiaohui2018	0	28	0	32		Not estimable
Wang Yabing2017	0	30	0	30		Not estimable
Wu Qiong2019	5	30	8	30	14.3%	0.63 [0.23, 1.69]
Zhou Huifang2018	7	48	23	48	41.2%	0.30 [0.14, 0.64]
Total (95% CI)		275		281	100.0%	0.50 [0.33, 0.76]
Total events	28		56			

Heterogeneity: Chi² = 3.58, df = 5 (P = 0.61); I² = 0%
Test for overall effect: Z = 3.30 (P = 0.0010)

Figure 9. Meta-analysis results of adverse reactions. CI = confidence interval.
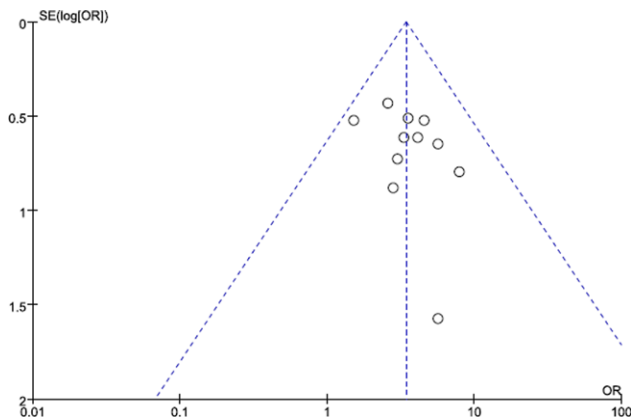

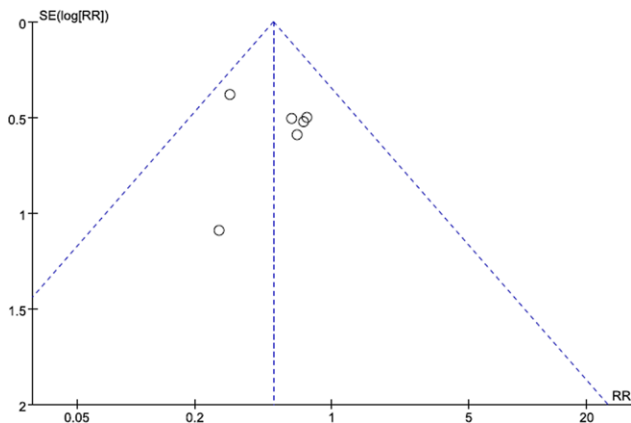**Figure 10.** Funnel plot of effectiveness one epilepsy clinical.

Figure 11. Funnel plot of effectiveness on adverse reactions.

4. Discussion

4.1. Knowledge of traditional Chinese and western medicine on epilepsy and cognitive impairment

TCM called epilepsy as "the disease of eclampsia," which is a chronic and recurrent disease. Prolonged illness leads to diseases entering the collateralization, resulting in poor qi and blood operation, stagnation of blood stasis, and eventually phlegm and blood stasis forming diseases. Or because of blood stasis give birth to epileptic seizure, or other external cause causes blood not to walk meridian, appear from the blood of the meridian, namely for blood stasis attack heart, bring about consciousness to be in a coma or unconscious. Based on the above theory, the pathological products of epilepsy should be responsible for phlegm and blood stasis. Its disease location is in the brain, and the core pathogenesis is "the spiritis out of control"

TCM called cognitive impairment as "dementia"; its location of disease is in the brain. The basic pathogenesis is that the physical weakness has substantial pathogenic factors on the surface, which is mostly due to the lack of Qi and blood essence in the viscera, and the surface fullness of pathogenic factors and fullness mostly involves blood stasis and phlegm turbidity. Disturbance of zang-fu organs, abnormal circulation of qi and blood, essence, and body fluid will further lead to blood stasis and phlegm turbidity. Phlegm and blood stasis interconnect each other, go up to deceive clear brain can trigger senile dementia.

Epilepsy with cognitive impairment is not clearly recorded in the historical literature of traditional Chinese medicine. However, a large amount of literature shows that both eclampsia and dementia are located in the brain. The pathogenesis is mainly due to insufficiency of innate endowment, imbalance of emotion, brain trauma, etc, or other diseases resulting in dysfunction of organs and imbalance of qi and blood, blood stasis and endogenous block of phlegm and turbidism, and turbidism into poison, which eventually leads to the out of control of spirit and the reduction of the essence of the brain. The etiology is mainly due to pathogenic factors, often with stasis, phlegm and other pathogenic factors. Or to this deficiency, spleen and kidney and other viscera function decline. ZhuDanxi wrote 《DanxiXinfa ·eclampsia》 recorded: "All because of the phlegm choking, resulting in blind hole." Emphasize that the disease is caused by phlegm that blinds the mind. It is pointed out in the book 《100 questions for infants and children > that "the blood probably stasis the mind, the evil wind in the heart, and accumulate the shock into epilepsy," and puts forward the method to treat epilepsy "through the heart meridian, regulate the blood, smooth the qi and clear the phlegm." In 《Treatises on Febrile Diseases》, it is recorded that "those who are easy to forget must have blood stasis." It is also recorded in 《Jing Yue Complete Book》 that "Ordinary minds have blood stasis, which must be cause forgetfulness."

It can be seen that eclampsia and dementia have a lot in common, their disease sites are in the brain, and the causes are mainly blood stasis and phlegm.

Moreover, when Wang Yue discussed the distribution law of epilepsy syndrome elements, he concluded that the common TCM syndrome types of epilepsy were blood stasis syndrome, wind-phlegm syndrome, phlegm heat syndrome, deficiency of liver and kidney Yin syndrome, and deficiency of heart and spleen syndrome.[36,37]

Epilepsy patients with blood stasis syndrome, phlegm syndrome accounted for the majority.

Therefore, both of them can be treated with the traditional Chinese medicine of removing blood stasis and resolving phlegm at the same time. It is consistent with the principle of co-treatment of different diseases.

The literature included in this paper mainly used the method of removing blood stasis and removing phlegm, and the drugs mainly included (Acorustatarinus, Dillong, Salvia miltiorrhiza, Radix Paeoniae Paeoniae, Ligusticum chuanxiong, Safflower, Radix Araceae, etc), which were then added or subtracted according to the patient's specific disease changes.

A large number of literatures also indicate that the pathogenesis of blood stasis or phlegm turbidity runs through the pathogenesis of epilepsy and cognitive impairment.

The pathogenesis of epilepsy complicated with cognitive impairment[38–40] is not clear, and it is believed to be caused by heredity, emotional stimulation, drugs, surgery, and other diseases.

At present, western anti-epileptic drugs mainly treat epilepsy combined with cognitive impairment by oral drugs, diet control, psychological education, and surgery when the disease is serious. However, because of long-term use of western medicine for epilepsy, there are many side effects, which will aggravate cognitive impairment, and western medicine for cognitive impairment will cause aggravation of epilepsy.[41–44]

Therefore, the treatment of traditional Chinese medicine has fewer side effects, longer duration of action, and better efficacy, which opens up new ideas and methods for the treatment of epilepsy complicated with cognitive impairment.

Moreover, some literatures showed that stone and calamus, a Chinese resolving phlegm medicine[45,46]: Modern pharmacological studies have confirmed that α-asaryl ether, the active ingredient in Acoruscalamus, has an anticonvulsant effect. While, β-Asarone can reduce abnormal discharge and inhibit epileptic seizures by regulating central neurotransmitter metabolism and preventing nerve cell apoptosis, to protect the nervous system and improve cognitive function.

The traditional Chinese medicine Paeoniapaeoniae for removing blood stasis[47] has the effects of sedation, analgesia, enhancement of memory ability, improvement of cognitive impairment, anti-depression and alleviation of ischemia reperfusion injury on the nervous system. Previous studies have shown that Paeoniaalba has anti-epileptic effects and can increase the blood concentration of lumina.

Therefore, TCM treatment of removing blood stasis and resolving phlegm is worth popularizing in clinics.

4.2. Summary of study

In the meta-analysis results of this study, compared with the western anti-epileptic drugs group alone, the treatment of epilepsy patients with cognitive impairment by removing blood stasis and resolving phlegm can significantly improve the clinical efficacy and safety. Fourteen studies were included, and 6 selected outcomes were observed. Literature on the clinical efficacy of epilepsy, TCM symptom score, EEG improvement rate and incidence of adverse reactions were included as outcome indicators. The heterogeneity test showed that all of them were homogenous, and fixed effect model was used for analysis. Meta-analysis results showed that, compared with the control group, the treatment group had better clinical efficacy of epilepsy, improvement of TCM symptom score, improvement rate of EEG, and reduced incidence of adverse reactions. The differences were statistically significant.

In the included literatures, MOCA score and QOLIE-31 cognitive function score were used as the outcome indicators to observe, the heterogeneity test showed that there was great heterogeneity among all groups, and a random effect model was used to analyze. Meta-analysis results showed that the improvement rate of MOCA score and QOLIE-31 cognitive function

score in the treatment group was better than that in the control group. The differences were statistically significant.

MOCA score subgroup analysis was performed according to the time of intervention. Heterogeneity test of MOCA scores for 3 and 6 months of intervention showed that there was great heterogeneity among all groups, which was analyzed by random effects model. Meta-analysis results showed that there was no statistically significant difference between the control group and the experimental group in the MOCA score of the intervention time of 3 months. In the MOCA score of the intervention time of 6 months, the improvement rate of MOCA score was better than that of the control group, and the difference was statistically significant. It can be seen that the improvement of cognitive function in MOCA score may be related to the intervention time.

Subgroup analysis was performed for the QOLIE-31 cognitive function score based on the duration of intervention. The heterogeneity test of the intervention time at 2 and 3 months showed that there was great heterogeneity among all groups, and the random effects model was used to analyze. Results of the meta-analysis showed that QOLIE-31 improved more when the intervention lasted for 2 and 3 months compared to the control group. The differences were statistically significant.

The outcome of the 8 or more studies included was the clinical efficacy of epilepsy and the incidence of adverse reactions. Therefore, funnel plots were drawn, in which the funnel plots were drawn with the clinical efficacy of epilepsy as the observation outcome index, and the distribution of funnel plots suggested that there was little possibility of publication bias. The result of the funnel plot is ideal. Funnel plots were drawn with the incidence of adverse reactions as the outcome index, and the distribution of funnel plots suggested that there was a small possibility of publication bias, but the production was not very ideal, which may be related to the small number of literatures.

4.3. Limitations

The literature included in this meta-analysis mainly had the following problems:

1. The symmetry distribution of funnel plots produced by the 8 included literatures with the incidence of adverse reactions as the outcome indicator was slightly poor, which may be related to the small number of included literatures.
2. The literature included in this study was all Chinese literature, and the number of cases was small. The concealment of allocation mode was not mentioned in many literature. Whether investigators and subjects administered blind, selective outcome reporting were not mentioned in any of the studies. Mayaffect on the results of the study.
3. The included studies did not fully unify the specific types of Chinese medicine, types of western anti-epileptic drugs, dosage, treatment period and dosage form of Chinese medicine in the treatment of epilepsy complicated with cognitive impairment by removing blood stasis and resolving phlegm. Whether these factors will affect the efficacy of removing blood stasis and resolving phlegm in the treatment of epilepsy complicated with cognitive impairment needs further confirmation.
4. The included outcome indicators of MOCA score and QOLIE-31 cognitive function score showed great heterogeneity in the heterogeneity test, which may be related to the basic diseases of patients, the number of included cases, specific drug types, drug dosage, medication duration and other factors between different studies.
5. The MOCA score with the intervention time of 3 months was used as the outcome indicator, and the results of meta-analysis showed $P = .42$, suggesting that the difference was not statistically significant, which may be related to the small number of included literatures.

6. Only 6 observation outcome indicators were selected in this paper, which may be related to the lack of literature. In addition, although there were the same observed outcome indicators in some literatures, these outcome indicators had to be removed because of the different evaluation methods.

4.4. Implications for clinical practice and future research

Therefore, the conclusions of this study need to carry out more large-sample and high-quality RCTs to verify, to provide a higher quality evidence-based basis for clinical practice. It is hoped that in the future, more detailed TCM syndromes, unified Chinese medicine and western anti-epileptic drugs, standardized treatment plan and unified evaluation and observation of outcome indicators will be adopted, to better evaluate the clinical efficacy of TCM and make the results more objective and accurate. It is also hoped that a unified treatment scheme and a scientific and reasonable large-sample, multi-center, double-blind, completely randomized controlled clinical trial can be adopted in the future to further confirm the efficacy and safety of the method of removing stasis and removing phlegm in the treatment of epilepsy complicated with cognitive impairment. It is expected that more high-quality RCTS literatures will provide more evidence-based evidence in the future.

5. Conclusion

In this study, it was suggested that turbidities of phlegm, blood stasis, or the combination of phlegm and blood stasis were the core etiology and pathogenesis of epilepsy complicated with cognitive impairment. Taking removing blood stasis and removing phlegm as the main treatment method, and applying TCM for removing blood stasis and removing phlegm to treat epilepsy complicated with cognitive impairment has better clinical efficacy and safety in the experimental group than In the control group which used western anti-epileptic drugs alone in the improvement of clinical efficacy of epilepsy, the improvement of TCM symptom score, the improvement rate of EEG, the improvement of MOCA and QOLIE-31 cognitive function score and the reduction of the incidence of adverse reactions. Traditional Chinese medicine starts from the holistic concept and syndrome differentiation. It provides a new idea and method for clinical prevention and treatment of epilepsy combined with cognitive impairment.

Author contributions

YYY, CG, and CXY had full access to all study data and take responsibility for its integrity and the accuracy of the analysis. YYY and CG were responsible for the study concept and design. YYY and CG were responsible for data acquisition and extraction. The assessment of bias risk was performed by YYY and CG; data analysis and interpretation were performed by YYY and CG, YYY drafted the paper, which was revised by CG and CXY. Statistical analyses were performed by YYY. CG and CXY supervised the study.
Conceptualization: Yang Yang Yu.
Data curation: Yang Yang Yu.
Formal analysis: Yang Yang Yu.
Funding acquisition: Chao Gu.
Investigation: Yang Yang Yu.
Methodology: Yang Yang Yu.
Project administration: Yang Yang Yu, Can Xing Yuan, Chao Gu.
Resources: Yang Yang Yu.

Supervision: Yang Yang Yu, Can Xing Yuan, Chao Gu.
Validation: Yang Yang Yu.
Visualization: Yang Yang Yu, Can Xing Yuan.
Writing – original draft: Yang Yang Yu.
Writing – review & editing: Yang Yang Yu, Can Xing Yuan, Chao Gu.

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