Systematic Evaluation of the Efficacy of Integrated Traditional Chinese and Western Medicine in Treating Mild Cognitive Impairment

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Abstracts: *Objective: To explore the effectiveness and safety of integrated traditional Chinese and western medicine in the treatment of MCI patients. Methods: Search three English databases, four Chinese databases, and assess the risk of bias according to Cochrane tools. Statistics will be used for heterogeneity assessment, sensitivity analysis, data synthesis, funnel chart generation and subgroup analysis. If a sufficiently uniform study is found, a meta-analysis will be performed and any differences will be described in groups. Results: A total of 15 studies were included, 11 studies treated MMSE as an outcome indicator, 7 studies used MoCA as an outcome indicator, 6 studies reported overall effectiveness, 3 studies used ADL as an outcome indicator, and 2 studies reported blood The data of markers and the results of 15 studies are beneficial to the traditional Chinese medicine combined with western medicine group. Conclusion: The conclusion shows that the treatment of mild cognitive impairment with integrated traditional Chinese and western medicine is superior to the single use of traditional Chinese medicine or western medicine in improving MMSE, MoCA, ADL, total effective rate score and reducing blood markers Aβ and IT-6, and the incidence of adverse reactions Lower, higher safety, for clinical reference. However, there are flaws in the research methodology, which need to be confirmed by more high-quality literature.*

Keywords: *mild cognitive impairment; integrated traditional Chinese and western medicine; MCI; systematic review; meta-analysis*

1. Background

Mild cognitive impairment (MCI) is a transitional state between normal aging and Alzheimer's disease (AD) [1], this state can develop into dementia, mainly manifested as Alzheimer's disease [2]. In the elderly 60-84 years old, the prevalence of MCI is about 6.7% to 25.2% [3]. Every year, 16% of MCI patients develop dementia [4]. MCI progresses to poor treatment effect after dementia and will bring a heavy economic burden to the family and society. Therefore, it is very important to effectively prevent and reverse the development of MCI to AD. In recent years, Chinese herbal medicine has shown great potential in preventing and treating cognitive decline [5-6]. In clinical practice, in addition to commonly used drugs such as cholinesterase inhibitors and ionotropic glutamate receptor antagonists, traditional Chinese medicines. It has also been widely used. The calcium channel blocker nimodipine, piracetam, aniracetam, oxiracetam and other drugs will also be used in conjunction with the above drugs to improve cognitive function. Neither Western medicine nor traditional Chinese medicine treatment can delay the conversion of mild cognitive dysfunction into dementia, and the advantages of integrated traditional Chinese and Western medicine treatment may be demonstrated [7].

2. Method

2.1 Data retrieval

Use the Chinese and English databases from the establishment of the database to December 20, 2020 to search for MCI clinical trials: Cochrane Library, EMbase, PubMed, China Biomedical

Literature Database (CBM), China National Knowledge Infrastructure Project (CNKI), Wanfang Medical database (WANFANG DATA), VIP database (VIP). The search terms are divided into four groups: Intervention (including: Integrated Chinese and Western medicine, Chinese medicine combined with Western medicine, etc.), Clinical conditions (including: cognitive impairment, memory impairment, cognitive impairment, memory loss, etc.), Research design (including: Clinical trials, placebo, randomized, double-blind, controlled, etc.) are searched in accordance with the requirements of the Cochrane Collaboration

2.2 Inclusion criteria

2.2.1 Types of participants

Participants diagnosed with MCI, according to valid standards: reported by patients or insiders, or experienced clinicians have found cognitive impairment, there is objective evidence of one or more cognitive functional domain impairments, and daily ability may be slight Damage, but can maintain an independent daily life, and has not yet reached the diagnosis of dementia. The inclusion of subjects in this study has no restrictions on age and gender. Diagnostic criteria include: Mayo diagnostic criteria [8], Petersen diagnostic criteria [9] and 2018 guidelines update [10], the National Institute of Aging (NIA) and The diagnostic criteria for MCI caused by Alzheimer's disease developed by the Alzheimer's Association (ADA) group[11], the 2013 American Diagnostic and Statistical Manual of Mental Disorders (DSM-VI), etc.[12];

2.2.2 Intervention measures

The intervention group includes: any form of herbal medicines, herbal preparations and non-herbal medicines in combination, and there are no restrictions on the dosage, dosage form, frequency of use, and course of treatment. The control group can be treated with traditional Chinese medicine or western medicine, and the mode of administration and dosage are not limited.

2.2.3 Outcome indicators

There are many outcome indicators for MCI, including neuropsychological assessment, biomarkers, and neuroimaging. Although biomarkers and neuroimaging methods have been well consolidated in the medical community, they are expensive, invasive, and potentially dangerous for the diagnosis and observation of this disease [13]. The most commonly used is neurology. Psychological assessment has the advantages of convenience, speed, and cost savings. It is the preferred observation index for large-sample MCI clinical trials. The disadvantage is that the results are subjective. This study selected the more commonly used Concise Mental Status Checklist MMSE, Montreal Cognitive Assessment Form (MoCA), Daily Living Ability Assessment Form (ADL), blood markers, and total effective rate as the outcome indicators.

2.2.4 Research design type

All randomized controlled trials of Chinese medicine combined with western medicine in the treatment of patients with mild cognitive impairment, regardless of whether blinding is used, have no restrictions on the duration of the study, background or language of publication.

2.3 Exclusion criteria

Studies with an average MMSE and MoCA baseline average score of less than 20 in the experimental group or control group were excluded, because participants with a score of less than 20 are usually classified as mild AD. In addition, there are studies on repeated publications, non-clinical randomized controlled trials, and other adjuvant treatments, such as yoga, massage, tai chi, qigong, acupuncture, etc. The research objects include AD, VaD, healthy young participants or other dementia patients. Research and research with missing data.

2.4 Screening and data extraction of included studies

According to the literature screening flow chart stated by PRISMA [14], two researchers independently conducted literature search. The documents that are obviously inconsistent are eliminated, the full text of the retrieved documents is read, and the inclusion and ranking criteria are re-screened. The full text of the research that meets the main criteria is evaluated. The test data that meets the inclusion criteria are extracted into a pre-built electronic form. The form includes the necessary

information required by the study, including the first author, title, year of publication, diagnostic criteria, sample size, average age of participants, and research duration Time, intervention measures, control measures, data information (baseline, end of treatment, follow-up), outcome indicators, number of dropouts, adverse reactions, etc. The information was extracted by two researchers independently. When the data of the original literature showed obvious deviation and incompleteness, the original author of the experiment must be contacted to obtain further relevant information, and the original literature for which specific data could not be obtained was excluded, and finally cross-checked , If there are disagreements, seek the opinions of third-party evaluators for review.

2.5 Bias risk assessment

According to the literature evaluation standards provided by Cochrane Handbook 5.1.0 [15-16], the methodological quality evaluation of the included studies mainly includes: random sequence generation, allocation hiding, blinding researchers and research subjects, and There are 7 factors including blindness of the outcome assessor, completeness of the outcome data, selective reporting, and other factors that may affect the authenticity of the results. The final results are divided into 3 levels: "low risk of bias", "unclear" and "high risk of bias". The quality evaluation is still independently cross-checked by two researchers. Any objections will be discussed with the third reviewer for a decision. , And finally reached an agreement, and the evaluation results will be reported in the grade summary of the final survey results table.

2.6 Data analysis

The RevMan 5. 3 software provided by the Cochrane Collaboration was used for statistical analysis. Binary data is represented by relative risk (RR) and 95% CI; continuous data is represented by weighted mean difference (WMD). First judge the heterogeneity between the studies. If there is no obvious heterogeneity ($P>0.1$, $I^2<50\%$), use the fixed effects model to calculate the combined effect size; if there is heterogeneity ($P<0.1$, $I^2>50\%$), but when it is clinically judged that the groups are consistent and need to be merged, the random effect model is used to calculate the combined effect size, and subgroup analysis is performed to find the source of heterogeneity; if the heterogeneity is too large, only descriptive analysis. This study included a large number of documents (more than 10 items), and a funnel chart was needed to detect publication bias.

3. Results
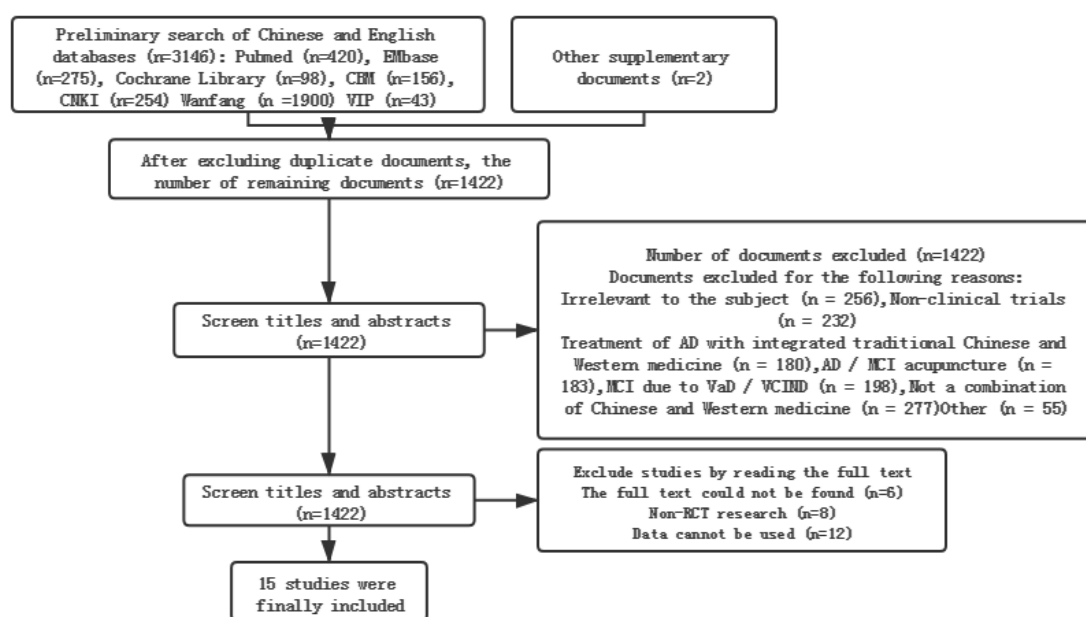
3.1 Document retrieval process

Fig 1 Document retrieval flow chart

According to the search strategy, 3146 documents were initially retrieved, all of which were obtained through electronic retrieval. After heavy weighting, 1422 documents remained. After reading the title, abstract, and keywords of the documents, there were 41 documents remaining; after reading the full text of the documents, 6 articles did not Found the full text, 8 non-RCT studies, 12 data could not be used, and finally 15 papers were included for data analysis, as shown in Figure 1.

3.2 General characteristics of the included studies

In the included 15 studies, all studies were published in Chinese journals, and a total of 1047 patients were included (treatment group: 524 cases, control group: 523 cases). No study followed up the subjects. The average age of the subjects was between 59-79 years old. Three studies reported the patients' years of education. Two of the studies reported the patients' average years of education, as shown in the table. 1

Table 1. General characteristics of the included literature

First author and publication time	Included		Intervention		Course of treatment	Observation index
	therapy group	Control group	therapy group	Control group		
Yang[17] 2011	34	34	Allison 5mg + Wuling Capsules	Donepezil 5mg	8	①②③
Zheng[18] 2016	30	30	Nimodipine 30mg+Buqi Tongmai Tablets	Nimodipine 30mg	16	①②③
Xie[19] 2015	30	30	Donepezil 5mg+Buyang Huanwu Decoction	Donepezil 5mg	8	①②⑤
Yu[20] 2016	40	40	Donepezil 5mg+Buyang Huanwu Decoction	Donepezil 5mg	8	①②⑤
Liu[21] 2020	43	43	Donepezil 5mg+Buyang Huanwu Decoction	Donepezil 5mg	8	①②⑤⑥
Wu[22] 2019	44	40	Oxiracetam intravenous drip + Guyuan Xingnao Decoction	Oxiracetam IV	3	①②③⑦⑧
Yang[23] 2015	30	30	Oxiracetam intravenous drip + Guyuan Xingnao Decoction	Oxiracetam IV	3	①②③⑦⑧
Yu[24] 2012	40	40	Galantamine 5mg+ Yindan Xinnaotong Capsules	Galantamine 5mg	12	①②③
Wu[25] 2013	23	23	Qingnao Yisui Buxue Decoction + Huperzine A 50μg	Qingnao Yisui Buxue Decoction	24	①⑨⑥
Wang[26] 2012	26	26	Allison 5mg+ Nimodipine 40mg+ Guipi Decoction	Allison 5mg + Nimodipine 40mg	12	①⑩⑪
He[27] 2017	40	40	Donepezil Hydrochloride 5mg + Huan Nao Yi Cong Decoction	Donepezil Hydrochloride 5mg	8	①④
Hu[28] 2015	30	30	Jiannao Bushen Pills + 6 ginkgo leaves	Donepezil hydrochloride 2.5mg	12	①③⑨
Liu[29] 2020	49	52	Aniracetam Capsule 0.2 g + Naokang II	Aniracetam capsule 0.2 g	12	④⑫⑨
Wang[30] 2010	25	25	Naofukang Capsule 2.4g+Tiaobuxinshen Recipe	Naofukang Capsule 2.4g	12	⑨
Yuan[31] 2017	40	40	Niergoline 10mg+ Naofukang Capsule 0.8g+ Tiaobuxinshen Decoction	Niergoline 10mg + Naofukang Capsule 0.8g	12	⑨

Note: ①. Concise Mental State Examination Scale (MMSE) ②. Montreal Cognitive Assessment Scale (MoCA) ③. Daily Living Ability Scale (ADL) ④. ADAS-cog ⑤. Daily Living Ability BI Score ⑥ TCM Syndrome Points (SDSVD) ⑦ Serum Aβ ⑧ Serum IL-6 ⑨ Clinical effective rate ⑩ Global Decline Scale (GDS) ⑪Clinical Dementia Scale (CDR) ⑫Auditory Word Learning Test (AVLT)

3.3 Quality evaluation of included studies

The included studies were generally of low quality. 15 studies were described as RCTs, 4 of which specified an appropriate sequence generation method, and none of the studies mentioned allocation concealment. One study mentioned blinding, but did not specifically describe the blinding method; the results of all studies are complete and there is no selective report on the results of the study; all studies did not declare conflicts of interest, as shown in Figure 2.
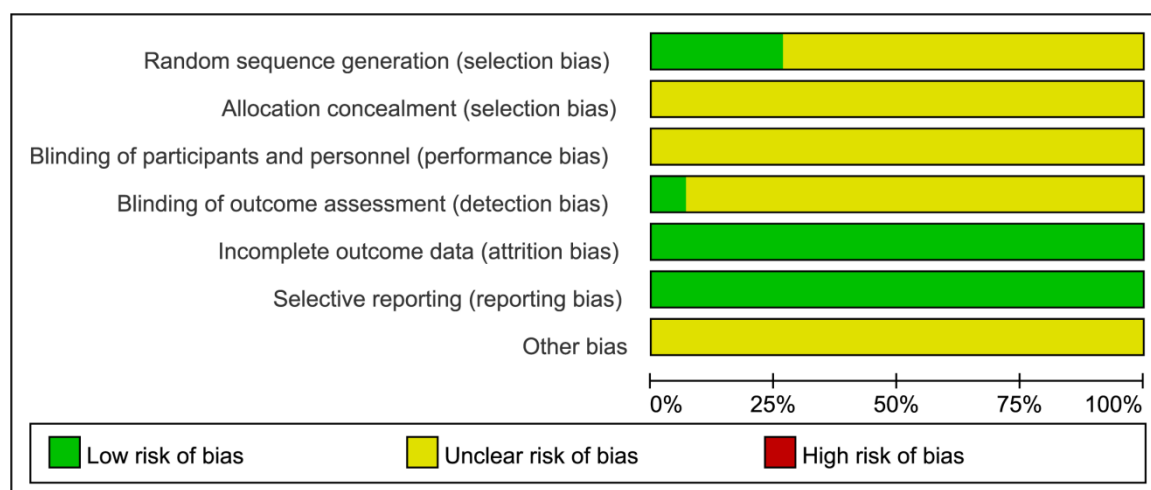
Fig 2 Methodological evaluation of the included literature

4. Compare the results

After sorting out, it was found that different studies used common outcome indicators, 11 studies used MMSE as an outcome indicator [17-27], 7 studies used MoCA as an outcome indicator [17,19,20-24], and 6 research reports The overall effective rate [25,27-31], 3 studies used ADL as an outcome indicator [19-21], and 2 studies reported blood marker data [22,23]. Among the studies using MMSE as an outcome indicator, three studies used Buyanghuanwu Decoction combined with donepezil to compare with donepezil [19-21], and 2 studies used Oxiracetam combined with Guyuan Xingnao Decoction and Ola Racetam contrast [22,23]. Based on this, it can be divided into two categories: continuous variables and binary variables: continuous variables are used to analyze the differences in the scores of MMSE, MoCA, ADL, and blood markers; subgroup analysis is performed for the same drug intervention studies. Use dichotomous variables to analyze the total effective rate difference.

4.1 Comparison of MMSE after treatment

A total of 10 studies in this group reported the MMSE score [17-27], the treatment time was 8-24 weeks, and there were 756 participants at baseline. One study used random number table grouping, and one study used lottery grouping; A total of 10 studies in this group used a funnel chart to assess publication bias. Most of the studies have good symmetry on both sides of the funnel chart, and 4 studies are obviously asymmetric, suggesting that there may be bias. The results are shown in Figure 3. After heterogeneity test, $I^2=89\%>50\%$, Q test P=0.0008<0.1, suggesting that there is heterogeneity between groups, random effects model is selected and subgroup analysis is performed according to intervention measures. For 3 groups (Buyang Huanwu Decoction combined with donepezil group P=0.36, $I^2=1\%$; Oxiracetam combined with Guyuan Xingnao Decoction group P=0.25, $I^2=26\%$; other traditional Chinese medicine combined with western medicine group P=0.0001, $I^2=82\%$;). It is found that the heterogeneity of the same subgroups of intervention drugs is very low, while the heterogeneity of different subgroups of intervention drugs is extremely high. Therefore, it is judged that the heterogeneity may come from different intervention measures. The results showed that Buyang Huanwu Decoction combined with donepezil combined effect size [MD=3.02,95%CI(2.15,3.89), P＜0.00001]; Oxiracetam intravenous infusion combined with Guyuan Xingnao Decoction and Oxiracetam group [MD=3.06,95%CI(2.40,3.71), P＜0.00001]; other traditional Chinese medicine combined with western medicine group [MD=1.68,95%CI(0.72,2.64), P=0.0006], statistically significant.
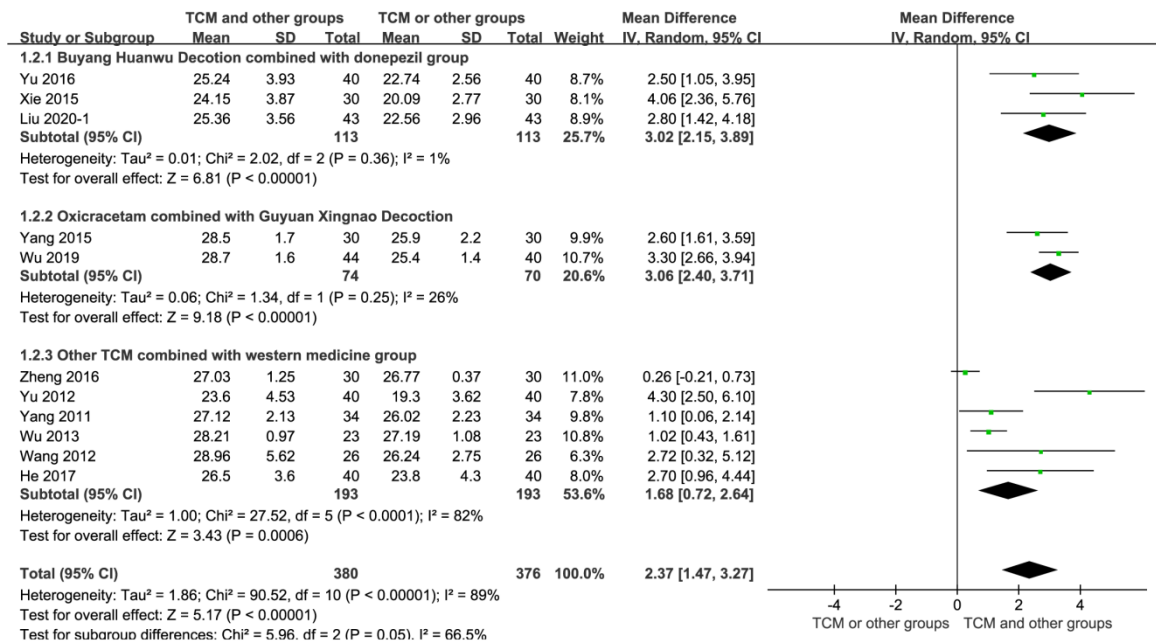
Fig 3 Forest diagram of comparison of MMSE after treatment

4.2 Comparison of MoCA after treatment

Seven studies reported the scores of the MoCA scale [17,19,20-24], the treatment time was 8-12 weeks, and a total of 518 participants were at baseline. 7 studies only mentioned randomization without specifying the method, and the risk is still unclear. After the heterogeneity test (I^2=0%, P=0.42), there is almost no heterogeneity between the groups. The fixed-effects model was selected for meta-analysis, and the results showed that [MD=2.57,95%CI(2.14,3.00),P< 0.00001], statistically significant, the results show that the combination of traditional Chinese medicine and western medicine in the treatment of MCI is significantly better than using traditional Chinese medicine alone in improving the MoCA score, as shown in Figure 4.
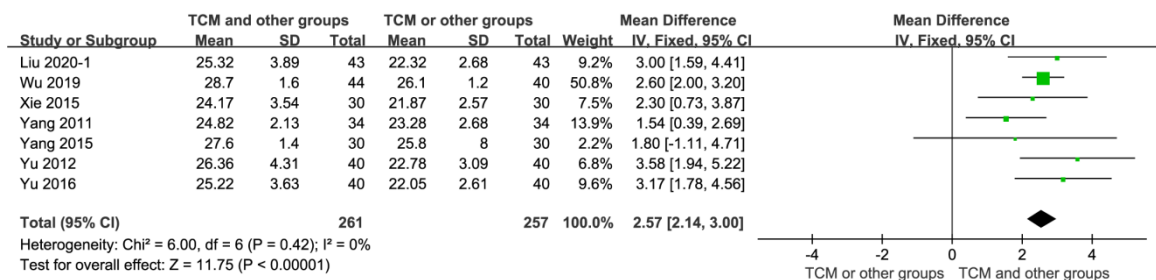

Fig 4 A forest map comparing the Montreal Cognitive Assessment Scale (MOCA) after treatment

4.3 Comparison of ADL after treatment

Three studies reported the scores of the MoCA scale [19-21], the treatment time was 8 weeks, and there were a total of 226 participants at baseline. The three studies only mentioned randomization without specifying the method, and the risk is not yet clear. After the heterogeneity test (I^2=87%, P=0.0004), indicating that there is heterogeneity between the groups, a random effects model was selected for analysis, and the results showed [MD=9.05,95%CI(2.72,15.38),P=0.005], indicating that Chinese medicine combined with western medicine treatment improves the MoCA score of MCI patients better than using Chinese medicine alone, but there is heterogeneity between the groups. The reason for the heterogeneity may be inconsistent with the selected version of the outcome index, and the sample size is small. The conclusion needs to be viewed objectively, See Figure 5.
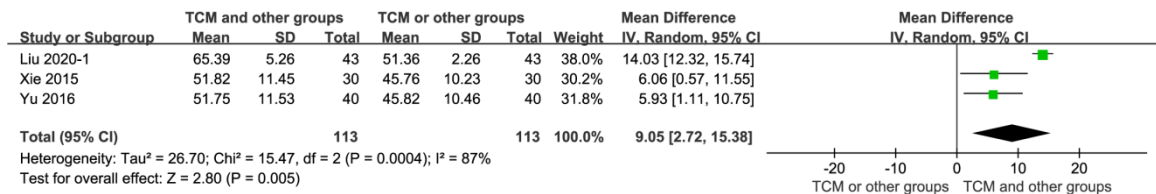
Fig 5 Forest chart comparing the ability of daily living scale (ADL) after treatment

4.4 Comparison of blood markers after treatment

Two studies reported the scores of the MoCA scale [22,23], and the treatment time was 3 weeks. Two studies only mentioned randomization without specifying the method, and the risk is not clear. After the heterogeneity test (I^2=91%, P=0.00001), it indicates that there is heterogeneity between the groups. The random effects model is selected for analysis. Because the two studies use two identical indicators and there is heterogeneity, the indicators are divided There are two subgroups (Aβ group I^2=93%, P=0.0001; IT-6 group I^2=86%, P=0.009). Both groups have heterogeneity. Analysis of the reasons for heterogeneity may be related to the small sample size. Short treatment time is related. The results showed that Aβ group [MD=-35.19,95%CI (-59.77,-10.60), P=0.005], IT-6 group [MD=-25,95%CI (-40.62,-10.96), P=0.009] It shows that traditional Chinese medicine combined with western medicine is superior to the traditional Chinese medicine treatment group in reducing Aβ and IT-6 in MCI patients, but there is a large heterogeneity between the groups, the treatment time is short, and the conclusion should be kept objective, as shown in Figure 6.
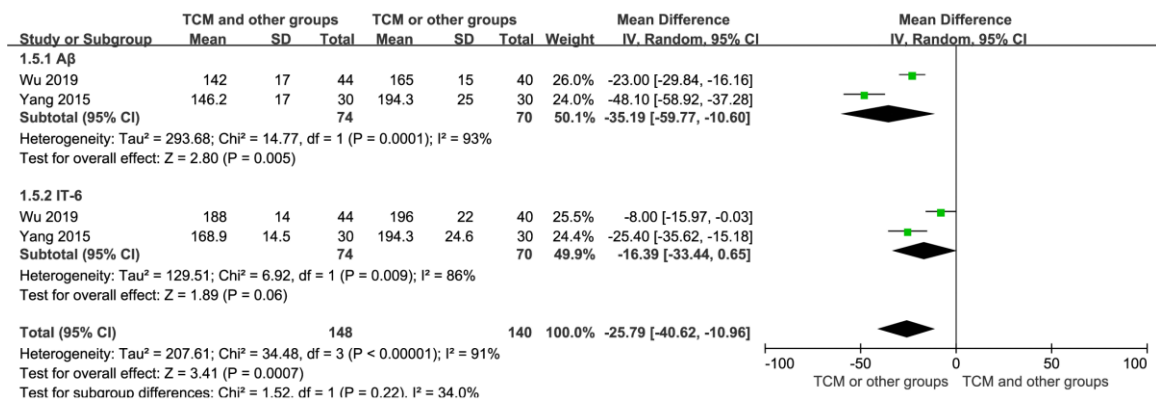

Fig 6 Forest plot comparing blood markers (Aβ, IT-6) after treatment

4.5 Comparison of total effective rate after treatment

Six studies reported the total effective rate [25,27-31]. The heterogeneity test found that there were statistically heterogeneous differences between the studies. Excluding documents with high heterogeneity [29], the heterogeneity test was performed again (I^2=12%, P=0.33), using a fixed effects model. Meta analysis results show that [RR=1.31,95%CI (1.16,1.48), P<0.0001], the total effective rate of Chinese medicine combined with western medicine group is higher than that of Chinese medicine group alone, as shown in Figure 7.
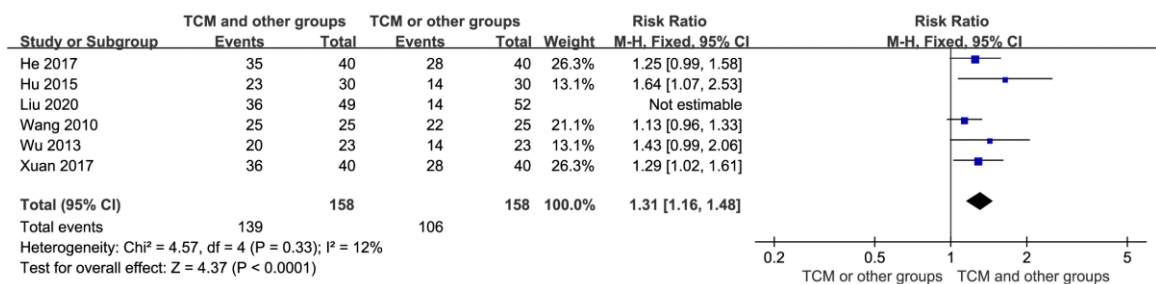

Figure 7 Forest diagram of total effective rate comparison after treatment

5. Adverse events

In 15 studies, no serious adverse events were reported, and 4 reported mild adverse events, mainly manifested in several adverse events such as excitement, insomnia, gastrointestinal reactions, muscle cramps, lethargy, dry mouth, and constipation. The number of adverse reactions in the western medicine group was greater than that in the traditional Chinese medicine group alone. After the adverse reactions occurred, there was no suspension of the test and no drug intervention, and the participants got better on their own. In a study. No adverse events were reported in 12 studies, and the safety data for statistical analysis was insufficient.

6. Discussion

Through the systematic evaluation of the treatment of mild cognitive impairment with integrated traditional Chinese and western medicine, it is found that the combination of traditional Chinese medicine and western medicine can increase the scores of MMSE, MoCA, ADL, and total effective rate, which is better than using traditional Chinese medicine or western medicine alone, and can also reduce the deposition of Aβ in the blood. , IT-6; the probability of adverse reactions is low, and the safety is high. Most studies use MMSE and MoCA as outcome indicators, and some use ADL. Only a few studies use blood markers as outcome indicators. Subjective scales have many uncontrollable factors. Future studies should use objective indicators as much as possible. At present, in addition to drug therapy, long-term adherence to non-drug therapy such as physical exercise, diet intervention, and cognitive training can also improve cognition, but there is insufficient evidence that it can delay the conversion of MCI to AD. Some European countries have included Ginkgo biloba extract (EGB761VR) in the guidelines for the treatment of mild cognitive impairment [32] as a drug for the prevention and treatment of MCI. Through systematic reviews, it is found that both traditional Chinese medicine and western medicine can have different effects on MCI patients, and the combination of traditional Chinese medicine and western medicine can improve cognitive function to a greater extent. The treatment of MCI with integrated Chinese and Western medicine is a direction that can be further studied.

The quality of the literature of the included studies is generally not high. These studies have large differences in the number of participants and treatment time. None of the studies has more than 100 people. Many studies have a small number of participants. Only one study lasted 24 weeks, and the rest The research observation time is relatively short. Only one study specifically elaborated on blinding, and many studies have flaws in law. There is obvious heterogeneity between the ADL group and the blood marker group during meta-analysis. In addition to the impact of the patient's education level, age, and gender, the scores of the objective scale will also be interfered with by many subjective factors. These weaknesses limit the power of the evidence. More high-quality, large-scale clinical studies with clear objective outcome indicators (such as biomarkers, imaging examinations, etc.) are needed to further explore the efficacy of integrated traditional Chinese and Western medicine in the treatment of mild cognitive impairment.

The results show that the treatment of mild cognitive impairment with integrated traditional Chinese and western medicine is better than using traditional Chinese medicine or western medicine alone in improving MMSE, MoCA, ADL, total effective rate score and reducing blood markers Aβ, IT-6, and the incidence of adverse reactions is lower. , The safety is high, and it can be used for clinical reference. However, there are flaws in the research methodology, which need to be confirmed by more high-quality literature.

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