Explore 19 (2023) 509–518

Contents lists available at ScienceDirect

EXPLORE

journal homepage: www.elsevier.com/locate/jsch

Meta-analysis of the efficacy of acupuncture in the treatment of the vascular cognitive impairment associated with cerebral small vessel disease

Xiao-Ting Huang, Chu-Yun Chen *, Qu-Fei Zhang, Li-Hong Lu, Ya-Lin She, Xiao-Yi Fang

Department of Acupuncture and Moxibustion, The Traditional Chinese Medicine Hospital of Guangzhou Medical University, No.16 of Zhuji Road, Liwan District, Guangzhou 510130, China

ARTICLE INFO

Keywords:
Cerebral small vessel disease
Vascular cognitive impairment
Acupuncture
Meta-analysis

ABSTRACT

Objective: To systematically evaluate the efficacy and safety of acupuncture in the treatment of the vascular cognitive impairment (VCI) associated with cerebral small vessel disease (CSVD–VCI) and to provide a theoretical basis for clinical acupuncture treatment for CSVD–VCI.

Method: Various databases, including China National Knowledge Infrastructure, Wanfang Data, Chinese Science and Technology Journal Database, Chinese BioMedical Literature Service System, PubMed, the Cochrane Library, and EBSCOhost, were searched for randomized controlled trials (RCTs) related to acupuncture treatment for CSVD–VCI. The quality of the included trials was evaluated, and a meta-analysis was conducted using the Review Manager 5.4 software.

Results: Ten articles on RCTs were included, involving 761 patients, i.e., 381 in the acupuncture group and 380 in the control group. The meta-analysis results indicated that the use of acupuncture alone and acupuncture alongside other therapies for CSVD–VCI could improve the overall clinical response rate [odds ratio = 3.51, 95% confidence interval (CI) = (2.05, 6.00), $P < 0.00001$], increase the patients' Montreal Cognitive Assessment scores [mean difference (MD) = 3.33, 95%CI (2.98, 3.68), $P < 0.00001$], Mini-Mental State Examination scores [MD = 2.78, 95%CI (2.51, 3.06), $P < 0.00001$], and activities of daily living scores [MD = 6.30, 95%CI (4.22, 8.37), $P < 0.00001$], and shorten the latency of auditory evoked potential P300 [MD = −14.67, 95%CI (−19.54, −9.80), $P < 0.00001$].

Conclusion: Acupuncture alone and acupuncture alongside other therapies are superior to non-acupuncture-based therapies in the treatment of CSVD–VCI. However, due to the small number of relevant available articles and their general low quality, this conclusion may be biased. More clinical RCTs with a larger sample size and higher quality are needed to support this theory.

Introduction

Cerebral small vessel disease (CSVD) refers to a group of pathological processes that affect the small vessels in the skull and is currently a common syndrome identified in clinical, cognitive, neuropathological, and neuroimaging examinations.[1,2] Cerebral small vessels include two primary parts: a pial vascular network, which is a branch of a medium-sized artery with a diameter of 100–400 μm coming from the subarachnoid space and located in the superficial part of the dorsolateral surface, and deep perforators of the anterior, middle, and posterior cerebral arteries. Small arteries from the two different sources supply blood to deep cerebral white matter or gray matter nuclei.[3,4] Cerebral small arteries not only serve as channels for blood transportation but are also involved in the formation of the blood–brain barrier, the regulation of cerebral perfusion pressure, the production of intercellular fluid, and regurgitation.

Due to the insidious onset and slow course of CSVD, it has no specific clinical signs, with some patients exhibiting no clear symptoms at all. The uncertainty of the pathogenesis leads to great difficulty in diagnosis and a delay in effective treatment. However, with the promotion and popularization of various imaging techniques, CSVD is gradually being given increased attention. The disease involves complex and diverse clinical manifestations, and the attendant imaging results provide an important basis for its diagnosis.[5]

Head magnetic resonance imaging (MRI) is the most important method for detecting CSVD, which presents with white matter lesions,

* Corresponding author.
E-mail address: chenchuyunccy@126.com (C.-Y. Chen).

https://doi.org/10.1016/j.explore.2022.10.019
Received 14 July 2022; Received in revised form 18 October 2022; Accepted 25 October 2022
Available online 5 November 2022

lacunar infarction, cerebral microbleeds, microinfarction, and an enlarged perivascular space on imaging. Studies have demonstrated that the lesions have a certain impact on a patient's cognitive functioning, while white matter hyperintensity, lacunar infarction, and cerebral microbleeds can act as imaging markers associated with vascular cognitive impairment (VCI).[6–9]

Research has demonstrated that 20%–30% of patients develop ischemic stroke and cerebral hemorrhage due to CSVD.[10–12] Moreover, the disease is the most common cause of VCI, potentially responsible for up to 36%–67% of cognitive impairment due to vascular dementia. Moreover, its incidence increases with age.[13] In fact, the aging population is a global problem, and with the development of health services and the increasing aging of China's population, the incidence of CSVD in people over 70 years of age is currently over 80%, i.e., five times that of large vessel stroke.[14] While many elderly adults have VCI, they are often unaware that their cognitive ability is impaired, placing an invisible burden on both their families and society.

At present, there is no specific medicinal treatment for CSVD–VCI. In fact, most existing clinical treatments are based on vascular dementia and other types of dementia, so their efficacy is largely insufficient. Therefore, new therapies are urgently needed.

The concepts of CSVD and VCI are largely absent in articles related to traditional Chinese medicine (TCM). In fact, based on the clinical symptoms exhibited by the patients, CSVD–VCI is generally referred to in terms of "dementia symptoms," "dementia," "amnesia," and "forgetfulness" in TCM. Although there have been many cases in which the use of acupuncture has demonstrated good efficacy in the treatment of CSVD–VCI in clinical practice, numerous limitations exist in terms of the attendant research, including small sample sizes, a lack of relevant articles, and unreasonable experiment designs.

While various meta-analyses have been conducted on the treatment of post-stroke cognitive impairment and VCI with no dementia in China,[15,16] no meta-analysis has been conducted in relation to the treatment of CSVD–VCI using acupuncture. In fact, there is only one foreign meta-analysis related to this area.[17] The studies included here were not all related to acupuncture treatment for CSVD–VCI. With this in mind, the present study was aimed at conducting a meta-analysis related to RCTs pertaining to the treatment of CSVD–VCI via acupuncture to obtain direct and accurate evidence for the clinical treatment of the disease using acupuncture.

Thus, to further enhance the evidence-based treatment-related research, in this study, a meta-analysis is adopted as the statistical method for collecting published randomized controlled trials (RCTs) pertaining to the use of acupuncture for the treatment of CSVD–VCI to explore its efficacy and subsequently provide theoretical support for its clinical diagnosis and treatment.

Materials and methods

We performed the research in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[18]

Inclusion criteria

(1) Subjects

Biomedical diagnosis: According to the *Clinical practice guideline for cognitive impairment of cerebral small vessel disease*[13] and the *Cerebral small vessel disease and vascular cognitive impairment: from diagnosis to management,*[19] the subjects had to have the following characteristics: subjectively reported cognitive decline and cognitive impairment confirmed via objective tests; CSVD diagnosed via MRI (the disease is mainly diagnosed via MRI/computed tomography, which can identify the symptoms of CSVD, e.g., myelopathy, leukoaraiosis, lacunar infarction, polyischemic lesions, dilated perivascular spaces, and microbleeds); and CSVD as the direct cause of the cognitive impairment.

(2) Study type

The study had to be a clinical trial conforming to the randomized and controlled design principle and published in either Chinese or English. Terms such as "randomized allocation" and "randomized grouping" had to be used in the document.

Exclusion criteria

1 Non-randomized and controlled clinical trials.
2 In the case of two papers with the same data, the one with more complete data and a later publication date was chosen.
3 Any papers lacking full text or involving lost data.
4 Papers related to animal testing, meeting proceedings, reviews, and meta-analyses.

Literature search and sources

Databases

The literature pertaining to randomized and controlled clinical trials on the treatment of CSVD-related cognitive impairment via acupuncture was searched using the following databases: China National Knowledge Infrastructure, Wanfang Data Knowledge Service Platform, Chinese Science and Technology Journal Database, Chinese BioMedical Literature Service System, PubMed, the Cochrane Library, and EBSCOhost. The reference lists of the identified papers were screened to identify potentially related papers. The search period was from the establishment of the database to February 25, 2022.

Search terms and methods

The relevant search terms were determined based on the PICO principles, i.e., patient/problem, intervention, comparison, and outcome, and the keywords for the search included the following.

Search terms in Chinese: 脑小血管病 (CSVDs), "腔隙性脑梗死(lacunar infarction)", 认知功能障碍 (cognitive impairment), 痴呆"/"健忘 (dementia/amnesia), and "针灸"/"针刺"/"电针" (acupuncture therapy/acupuncture/electroacupuncture). Before being entered into the Chinese databases, dissimilar search terms were connected using the Boolean operator "AND", and similar search terms were connected with "OR".

Search terms in English: "cerebral small vessel diseases"/"cerebral microangiopathy"//"stroke, lacunar"/"lacunar infarct"/"cerebral microbleeds"; "vascular cognitive impairment"//"vascular dementia"; and "acupuncture"/"acupuncture points"/"acupuncture therapy"/"electroacupuncture." Before being entered into the English databases, dissimilar search terms were connected using the Boolean operator "AND", and similar search terms were connected with "OR".

Literature screening and data sorting

Two investigators conducted the initial screening of the literature. They assessed the titles and abstracts of the papers in terms of the inclusion and exclusion criteria, obtained the full text, excluded repeated papers using the NoteExpress software, read the full text, and selected the papers that complied with the inclusion criteria.

The data extracted included the following: (1) basic information, including the title, author(s), date of publication, and study method; (2) the description of the subjects, including the sample size, average age, gender, course of illness, intervention measures, course of treatment, and outcome indicators pertaining to the experimental and control groups. We referred to the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) checklist[20] to extract detailed information regarding acupuncture treatment for each included study. Any dispute was settled through negotiation on reaching a consensus, and if necessary, a third investigator was recruited to discuss and make the final decision.

Evaluation of the quality of the studies

The quality evaluation was conducted using the bias risk evaluation tool recommended in the *Cochrane System Evaluation Handbook*, which includes randomization, allocation concealment, implementation bias (blinding of investigators and subjects), measurement bias (blind evaluation of the study outcomes), follow-up bias (integrity of the resultant data), report bias, and various other biases. Based on the above indicators, the bias of the studies was classified into low-risk bias, unknown risk bias, and high-risk bias. Two investigators conducted the evaluation independently and compared their results to identify any discrepancies, with a third investigator recruited for discussion and decision-making when required.

Statistical analysis

The meta-analysis was conducted using the Review Manager 5.4 software. Here, the analysis indicators of the binary variables were expressed in terms of the odds ratio (OR) and 95% confidence interval (CI), while the indicators of the continuous variables were expressed in terms of the mean difference (MD) and 95%CI. When the heterogeneity among the studies was low ($P > 0.1$ and $I^2 \leq 50\%$), the statistical heterogeneity of the outcome indicators among the included studies was confirmed to be non-significant, meaning the fixed effect model could be used. However, when the heterogeneity was high ($P \leq 0.1$ and $I^2 > 50\%$), the outcome indicators demonstrated statistically significant heterogeneity, and the random effect model was used to identify the source of the heterogeneity via subgroup analysis, sensitivity analysis, and other methods. Meanwhile, when the clinical heterogeneity was high and it was not possible to identify the source of the heterogeneity, a meta-analysis was not performed, with only a descriptive analysis carried out. The meta-analysis results were expressed using forest plots; when the number of included studies was >10, the funnel plot method was used to determine whether potential publication bias existed.

Results

Literature search results

A total of 616 related papers were searched using the seven aforementioned databases. NoteExpress was initially used to identify and delete any duplicate papers, which resulted in a total of 465 papers. Following this, the titles and abstracts were assessed in view of excluding any papers pertaining to animal tests, reviews, or meta-analyses, with 445 papers excluded in this process, leaving a total of 20 papers. After the initial screening, the full text of the remaining papers was searched and read to exclude repeated publications, with the same intervention measures used in terms of the two groups to identify papers with non-conforming outcome indicators or a lack of complete data, which resulted in a total of 10 remaining papers (Fig. 1).

Basic characteristics of the included studies

A total of 10 papers on RCTs[21–30] were included in the study. The total sample size included 761 cases, with 381 cases in the experimental group and 380 cases in the control group, and all papers were written in Chinese. Statistical analysis was applied in terms of the interventions measures pertaining to the two groups. In the treatment group,

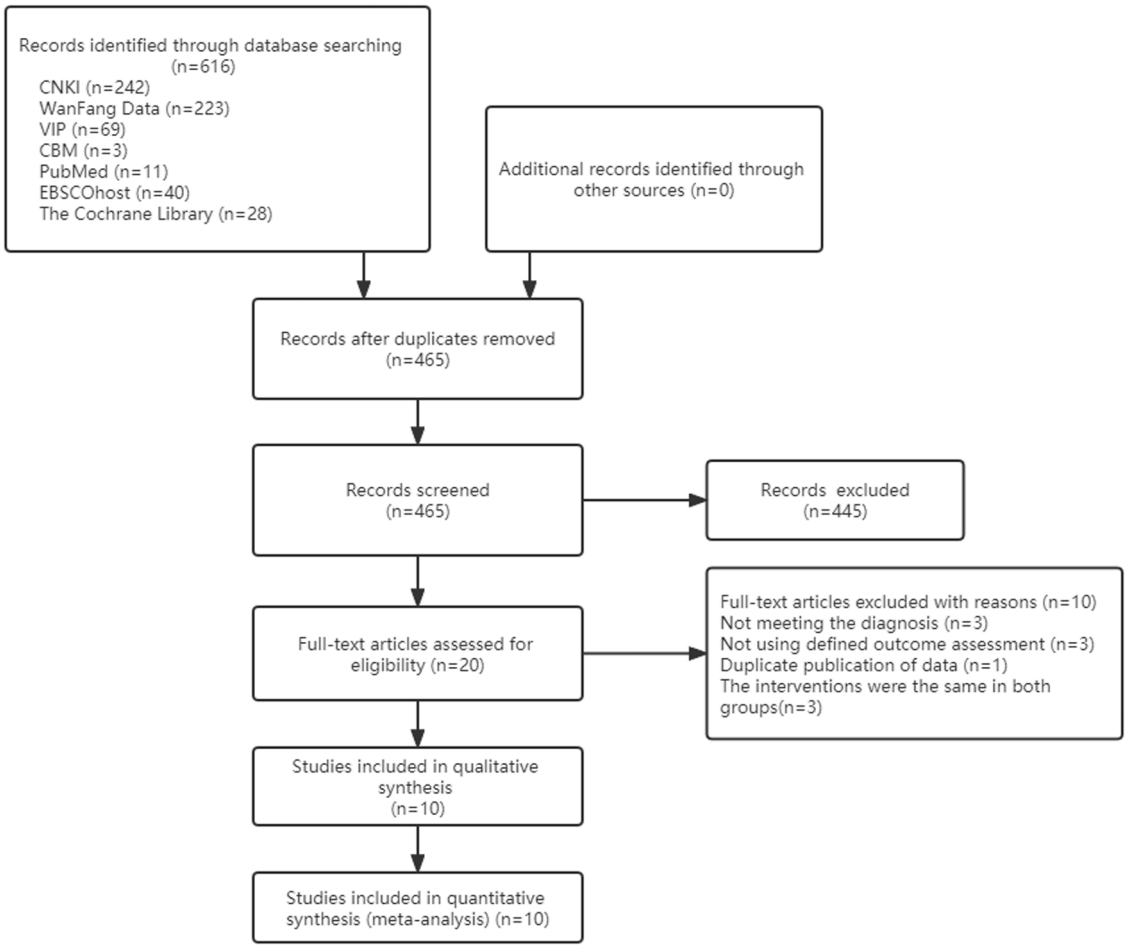

Fig. 1. Literature search flow and results.

acupuncture therapy, acupuncture combined with combined with medication, acupuncture plus taijiquan sport therapy, or acupuncture plus hyperbaric oxygen therapy was adopted,while in the control group, donepezil hydrochloride tablets (four papers[21,22,27,30]), hyperbaric oxygen therapy (three papers[24,25,29]), symptomatic treatment alone (two papers[26,28]), or taijiquan sport therapy (one paper[23]) was used for the treatment, with the average course of treatment being six weeks. The outcome indicators were as follows: the overall response rate (ORR) in five studies,[21,24,27–29] Montreal Cognitive Assessment (MoCA) scores in six studies,[23–26,29,30] Mini-Mental State Examination (MMSE) scores in six studies,[22,24–27,29] activities of daily living (ADL) scores in three studies,[21,26,27] and auditory event-related potential P300 latency change in three studies[22,23,25] (Tables S1 and S2 in the supplementary document and Table 1).

Quality evaluation of the included studies

Randomized design

The random number table method was adopted in four studies[22–24,30] and the computer randomizing method in one study[21]; these methods were determined to entail low-risk bias. Meanwhile, randomized grouping according to the admission sequence was used in one study,[26] which was deemed to entail high-risk bias. The mere expression of "random" was indicated in the remaining four studies,[25,27–29] with no description of the specific randomizing method; the studies were deemed to entail unknown risk bias (Fig. 2).

Allocation concealment

The non-transparent envelope method was used for the grouping in two studies[21,23] and was deemed to entail low-risk bias, while allocation concealment was not mentioned in the remaining eight studies, entailing unknown risk bias (Fig. 2).

Blinding

Only one study[23] reported the adoption of the blind control method for the evaluation and statistical analysis of the subjects, with the remaining studies not mentioning any such method, it is highly possible some implementation bias existed (Fig. 2).

Data integrity

Two studies[28,30] lacked outcome indicators, which was deemed to entail high-risk bias, while the remaining eight did include outcome indicators and were deemed to entail low-risk bias (Fig. 2).

Report publication

Five studies[21–23,26,28] provided the statistics and the reasons for any dropout during the tests, meaning they were deemed to entail low-risk bias. The remaining five did not indicate whether there were dropouts during the tests and were assessed in terms of unknown risk bias (Fig. 2).

Other biases

The bias source could not be identified in any of the papers, meaning this factor was determined to entail unknown risk bias (Fig. 2).

Meta-analysis

Analysis of clinical overall response rate

Five papers were included in this analysis,[21,24,27–29] with different criteria for the response rate adopted. The cases described in terms of "moderate response," "marked response," or "cured" were categorized as "response," while the cases described as "ineffective" or with no response were categorized as "no response," a process that was aimed at changing the variables into binary variables. The OR and 95%CI were used for the calculation, which resulted in a final total of 407 cases, including 204 cases in the experimental group, with 182 cases of response, and 203 cases in the control group, with 143 cases of response. The heterogeneity test results ($P = 0.82$ and $I^2 = 0\%$) indicated that the homogeneity among the studies was high, meaning the fixed effect model was adopted for the analysis. Here, the rhombus was on the right side, indicating that the test results favored the acupuncture treatment group, with the results of the meta-analysis after data merging indicating that the OR was 3.51 and the 95%CI (2.05, 6.00); the forest plot revealed an effect test value of $Z = 54.57$ ($P < 0.00001$), indicating a statistically significant difference between the two groups, implying that acupuncture therapy could effectively improve cognitive impairment following CSVD and increase the overall treatment efficacy (Fig. 3). A sensitivity analysis was conducted. After excluding any of the data, the response rate analysis presented in terms of the forest plots of the two

Table 1
Basic characteristics of included literature.

Included literature	Sample size CG	EG	Average age ($x \pm s$, years) CG	EG	Interventions CG	EG	Course of treatment	Outcome indicators	Dropout or withdrawal
Zhang 2020	35	35	61.38± 6.83	61.44 ± 6.75	Donepezil Hydrochloride Tablet	CG+ Acupuncture therapy	4 weeks	①②③④	Not mentioned
Ren 2019	30	30	64.50 ±4.90	65.7 ± 5.40	Donepezil Hydrochloride Tablet	CG+ Acupuncture therapy	4 weeks	①⑤⑥	3 dropout cases
Chen 2019	30	30	68.47 ±5.49	68.47 ±6.50	Donepezil Hydrochloride Tablet	Acupuncture therapy	12 weeks	⑦	Not mentioned
Wang 2021	32	33	70±6.79	71±5.04	Donepezil Hydrochloride Tablet	Acupuncture therapy	4 weeks	③④	No dropout cases
Xie 2017	40	40	63.60 ±5.87	62.84 ±6.38	Symptomatic treatment	CG+ Acupuncture therapy	6 weeks	④	No dropout cases
Liu 2015	30	30	54–80	50–85	Symptomatic treatment	CG+ Acupuncture therapy	2 weeks	①③⑦⑧	No dropout cases
Zhao 2016	56	56	62±3	61±3	Hyperbaric oxygen therapy	CG+ Acupuncture therapy	8 weeks	①⑥⑦	Not mentioned
Meng 2019	66	66	69.55 ±4.93	69.31 ±5.03	Hyperbaric oxygen therapy	CG+ Acupuncture therapy	4 weeks	①④⑦	Not mentioned
Zhang 2017	30	31	61.5 ± 2.5	58.1 ± 0.9	Hyperbaric oxygen therapy	CG+ Acupuncture therapy	2 weeks	①④⑦	Not mentioned
Shen 2021	31	31	65.19 ±4.41	62.61 ±5.89	Taijiquan	CG+ Acupuncture therapy	8 weeks	⑥⑦	No dropout cases

Note: CG: Control group EG: Experimental group Outcome indicators: ① Mini-Mental State Examination (MMSE); ② Vascular Dementia Assessment Scale-Cog (VaDAS-Cog); ③ Activity of Daily Living Scale (ADL); ④ Overall response rate (ORR); ⑤ Hastgawa Dementia Scale (HDS); ⑥ Auditory event-related potential P300 latency change; ⑦ Montreal Cognitive Assessment (MoCA); ⑧ Brainstem auditory evoked potential latency wave I, III and V (PL).

Fig. 2. Quality evaluation of included literature.

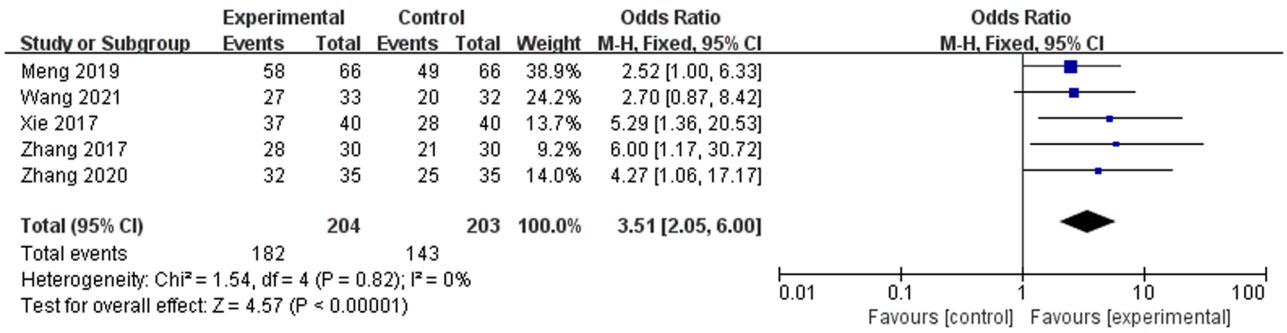

Fig. 3. Forest plot of clinical ORR.

groups favored the acupuncture treatment group; the conclusion underwent no change, indicating the high confidence level of the study and the stability of the results.

Montreal cognitive assessment score analysis

Here, six papers were included,[23–26,29,30] and since the included data presented continuous variables, the MD and 95%CI were used for the calculation, with the resultant number of cases being 486. The heterogeneity test results ($P = 0.14$ and $I^2 = 40\%$) indicated that the homogeneity among the studies was high, meaning the fixed effect model was adopted for the analysis. Here, the rhombus was on the right side, indicating that the test results favored the acupuncture treatment group, with the results of the meta-analysis after data merging revealing that the MD was 3.33 and the 95%CI (2.98, 3.67); the forest plot revealed that the effect test value was $Z = 18.68$ ($P < 0.00001$), indicating a statistically significant difference between the two groups, implying that acupuncture therapy is superior to non-acupuncture therapy in improving the MoCA scores of patients with CSVD–VCI (Fig. 4).

A sensitivity analysis was conducted. After excluding any of the data, the response rate analysis presented in terms of the forest plots of the two groups favored the acupuncture treatment group; the conclusion underwent no change, indicating the high confidence level of the study and the stability of the results.

Mini-Mental state examination score analysis

Here, six papers were included,[22,24–27,29] and since the included data presented continuous variables, the MD and 95%CI were used for the calculation, with the resultant number of cases being 494. The heterogeneity test results ($P < 0.00001$, $I^2 = 83\%$) indicated some homogeneity among the included papers, meaning the random effect model was used for the analysis. Here, the rhombus was on the right side, indicating that the test results favored the acupuncture treatment group, with the results of the meta-analysis after data merging revealing that the MD was 2.98 and the 95%CI (2.12, 3.83); the forest plot revealed that the effect test value was $Z = 6.83$ ($P < 0.00001$), indicating a statistically significant difference between the two groups, implying that acupuncture therapy is superior to non-acupuncture therapy in improving the MMSE scores in the treatment of CSVD–VCI (Fig. 5).

Due to the high heterogeneity found in the meta-analysis, a subgroup analysis was performed via comparing acupuncture therapy with hyperbaric oxygen therapy and the administration of donepezil hydrochloride tablets. In terms of the hyperbaric oxygen treatment group, $P = 0.00001$ and $I^2 = 93\%$, indicating a high heterogeneity among the included papers. The meta-analysis results revealed that the MD was 2.93 and the 95%CI (1.54, 4.32); the forest plot revealed that the effect test value was $Z = 4.13$ ($P < 0.00001$), indicating a statistically significant difference between the two groups, implying that acupuncture therapy is superior to hyperbaric oxygen therapy. The results of the donepezil hydrochloride tablet group indicated that $P = 0.82$ and $I^2 = 0\%$, indicating no statistical heterogeneity among the included papers. The meta-analysis results revealed that the MD was 3.02 and the 95%CI (1.59, 4.45); the forest plot revealed that the effect test value was $Z = 4.15$ ($P < 0.00001$), indicating a statistical difference between the two groups, implying that the therapeutic effect of acupuncture is superior to that of donepezil hydrochloride tablets. The subgroup analysis of the two control groups statistically demonstrated the benefits of acupuncture for the therapeutic effect, and high heterogeneity existed between the hyperbaric oxygen treatment groups; however, the source of the heterogeneity was not identified due to various unknown factors in the papers included for the quality evaluation (Fig. 5).

A sensitivity analysis was conducted to test the stability of the results, and after one study was excluded,[24] the heterogeneity disappeared ($P = 0.64$, $I^2 = 0\%$), with the source of the heterogeneity not identified. However, the conclusion underwent no significant change, indicating the high confidence level of the study and the stability of the results.

Analysis of P300 latency change

Here, three papers were included,[22,23,25] and since the included data presented continuous variables, the MD and 95%CI were used for the calculation, with the included number of cases being 234. The heterogeneity test results ($P = 0.29$ and $I^2 = 19\%$) indicated that the homogeneity among the studies was high, meaning the fixed effect model was adopted for the analysis. Here, the rhombus was on the left side, indicating that the test results favored the acupuncture treatment group. The

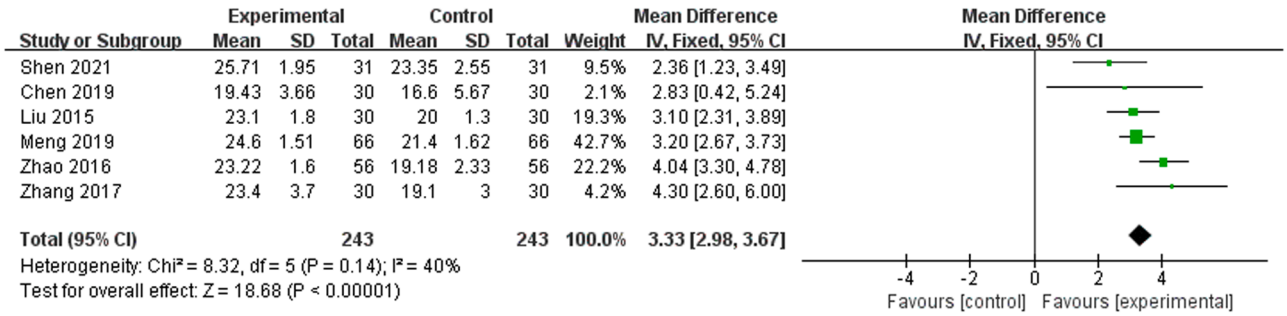

Fig. 4. Forest plot of MoCA scores.

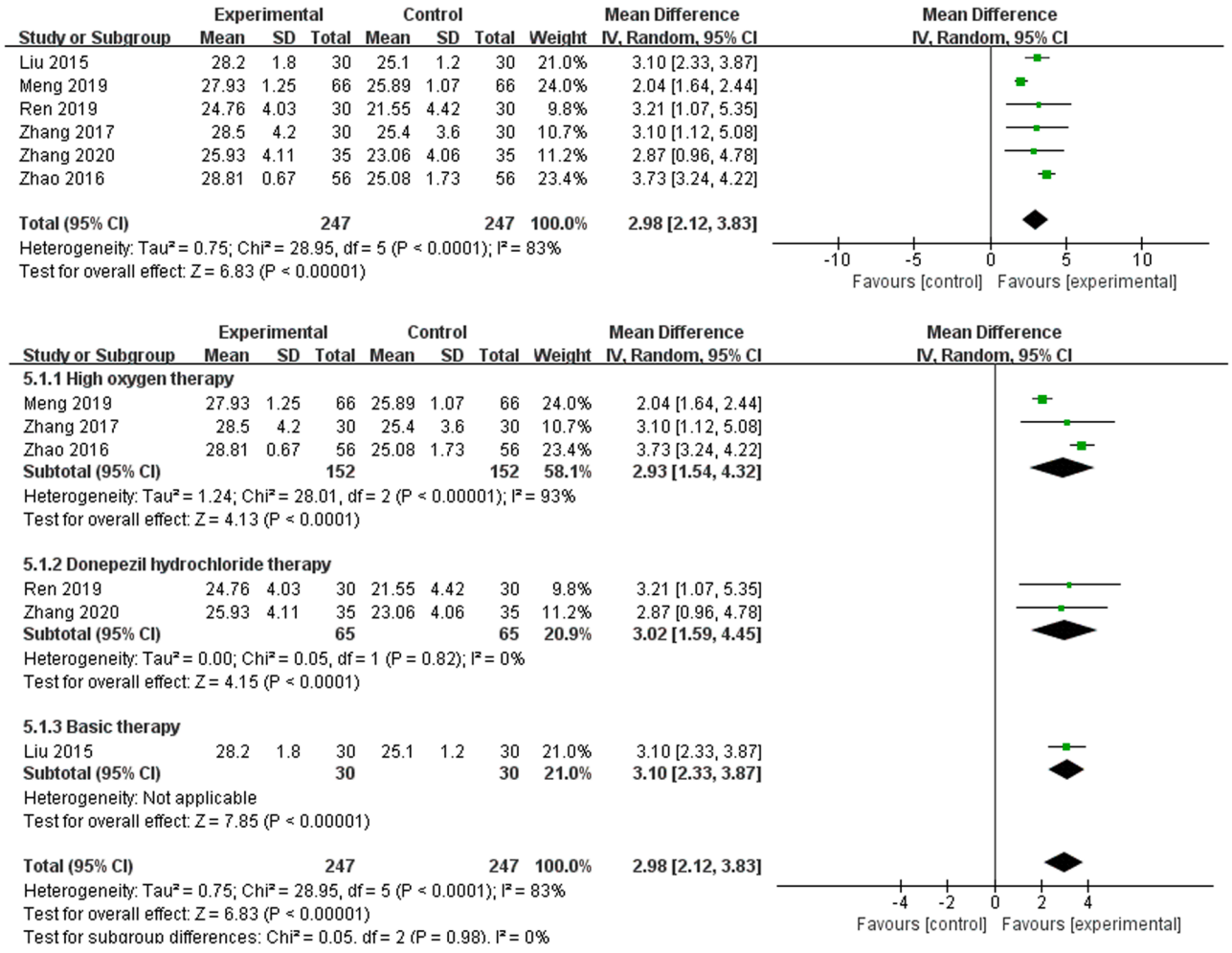

Fig. 5. Forest plot of MMSE scores and subgroup analysis.

results of the meta-analysis after data merging revealed that the MD was −14.67 and the 95%CI (−19.54, −9.80); the forest plot revealed that the effect test value was $Z = 5.91$, ($P < 0.00001$), indicating a statistically significant difference between the two groups, implying that acupuncture therapy is superior to non-acupuncture therapy in shortening the P300 latency in the treatment of CSVD–VCI (Fig. 6).

A sensitivity analysis was conducted. After excluding any of the data, the P300 latency change presented in the forest plots of the two groups favored the acupuncture treatment group. The conclusion underwent no change, indicating the high confidence level of the study and the stability of the results.

Activities of daily living score analysis

The outcome indicator of three studies[21,26,27] was the ADL score, but due to the different scoring criteria for the studies (in two,[21,27] the higher scores indicated the patient's higher ability for self-care, while in one,[26] the lower scores indicated the patient's low ability for self-care), only two were included.[21,27] Since the included data presented continuous variables, the MD and 95%CI were used for the calculation, with the included number of cases being 135. The heterogeneity test results ($P = 0.70$ and $I^2 = 0\%$) indicated that the homogeneity among the studies was high, meaning the fixed effect model was adopted for the analysis. Here, the rhombus was on the right side, indicating that the test results favored the acupuncture treatment group. The results of the meta-analysis after data merging revealed that the MD was 6.30 and the 95%CI (4.22, 8.37); the forest plot revealed that the effect test value was $Z = 5.95$ ($P < 0.00001$), indicating a statistically significant difference between the two groups, implying that acupuncture therapy is superior to non-acupuncture therapy in improving the ADL scores in the treatment of CSVD–VCI (Fig. 7).

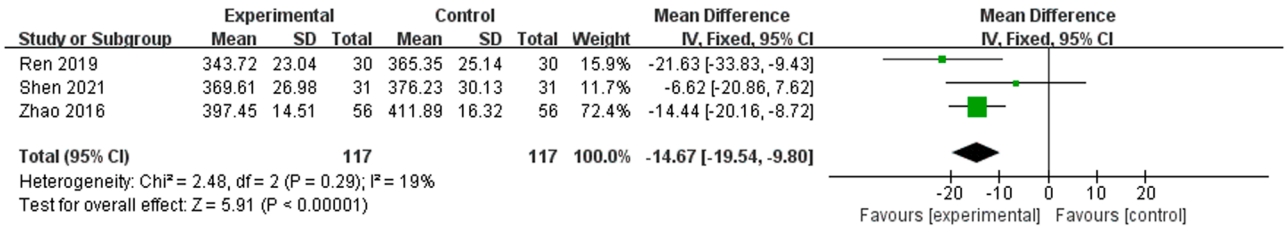

Fig. 6. Forest plot of auditory event-related potential P300 latency change.

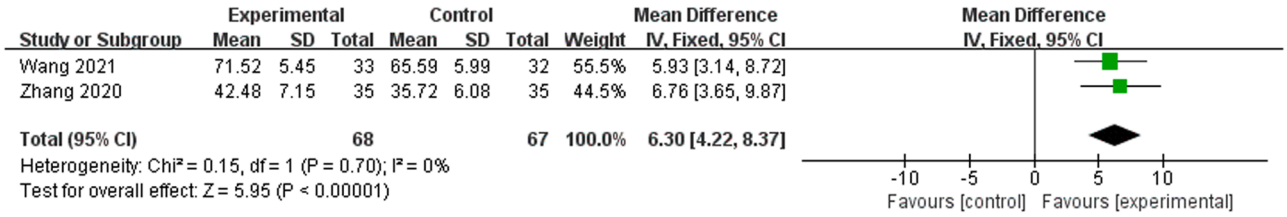

Fig. 7. Forest plot of ADL scores.

Discussion

The understanding of cerebral small vessel disease and the associated vascular cognitive impairment in the field of modern Western medicine

With the development of healthcare services, the aging society, and the increase in the percentage of elderly individuals, the morbidity of common diseases among the elderly is increasing annually, resulting in a gradual but significant impact on the economic development of society and the lives of many families.[4] In addition to Alzheimer's disease, vascular factors are a common cause of cognitive impairment and should not be ignored. Since the introduction of the concept of "small vessels, big problems,"[31] CSVD has gained widespread attention. It is characterized by insidious onset, varied clinical manifestations, and, generally, no marked change in the lives of patients apart from transient dizziness, blurred vision, or other mild symptoms.[32] Furthermore, a slow decrease in cognitive functioning is generally considered to be a part of the normal aging process and is often ignored by patients and their family members in the early stage, meaning a pathological examination will often indicate advanced-stage CSVD. Therefore, the cognitive impairment associated with CSVD leads to high morbidity and has gradually become a significant disease affecting the health of many people.[33]

Risk factors and common etiological factors

There are various risk factors for CSVD, including both non-interventive and interventive factors. The non-interventive risk factors are mainly associated with the age and genetic factors of the patient[34]; certain controversies remain in terms of the roles of gender and race, with no consensus having been reached in terms of the clinical conclusions. Meanwhile, the interventive risk factors include cerebral atherosclerosis, hypertension, diabetes, and hyperhomocysteinemia, among which hypertension is an important factor.[35–39] In fact, CSVD–VCI is also closely associated with hypertension, diabetes, and hyperlipidemia,[40–42] with its etiological factors classified into the following six types: arteriolosclerosis, also known as small vessel disease related to age and vascular risk factors; sporadic or congenital cerebral amyloid angiopathy; other genetic small vessel diseases; inflammatory or immune-mediated CSVDs; venous collagenization diseases; and other CSVDs.

Treatment

In general, treatments target acute and chronic CSVD. For acute ischemic stroke caused by CSVD, the current recommendation is to provide treatment with reference to the prevention and treatment regimens for acute ischemic stroke, i.e., blood-pressure-lowering therapy, thrombolytic therapy, antiplatelet therapy, and lipid-lowering therapy among others. Regarding chronic CSVD, CSVD–VCI is an important subtype of VCI, and current studies on the treatment of CSVD–VCI in the field of Western medicine have primarily been conducted with reference to that used for vascular dementia or other dementia types. According to the *2019 Chinese Guidelines for the Diagnosis and Treatment of Vascular Cognitive Impairment Associated with Cerebral Small Vessel Disease,*[13] appropriate intervention measures and medication should be provided to patients with CSVD–VCI. A reasonable diet, treatment of any complications, lifestyle changes, and the treatment of any underlying diseases are examples of relatively effective intervention measures. Meanwhile, the drugs used for the treatment of CSVD–VCI include cholinesterase inhibitors (e.g., donepezil, galanthamine, and rivastigmine[43–45] nimodipine, oxiracetam, Yangxueqingnao granule, memantine, ginkgo biloba extract, butylphthalide, and citicoline.[46–51] As current research indicates, cholinesterase inhibitors have a prominent therapeutic effect on CSVD–VCI.[52,53] Other drugs proven to be effective for the treatment of VCIs must be verified in further clinical trials.

Acupuncture for treatment of cerebral vessel disease and cognitive impairment

Huangdi Neijing presents the earliest records on the relationship between the brain and the meridians and collaterals. According to TCM theories, the bladder meridian of the foot-taiyang runs straight along the trunk from the head and backward to the occiput, whereupon it enters the cranial cavity and brain and then goes downward to the neck (*Tianzhu* acupoint). With any disorder of the meridian, the primary manifestations include headache, mania, and other cerebral issues.

With functions for dredging the channels (main and collateral channels, regarded as a network of passages, through which energy circulates and along which the acupuncture points are distributed), regulating the yin and yang, and adjusting the internal organs, acupuncture can stimulate the meridian qi to resist pathogens and restore the balance of qi and yin–yang in the body.[54] Peripheral inflammation and abnormal peripheral immune function may exacerbate neuroinflammation and cognitive dysfunction, and acupuncture may improve peripheral blood immune dysfunction in VD patients by regulate the distribution of lymphocyte subsets and the levels of Inflammatory cytokines.[55] Studies have demonstrated that acupuncture can improve cerebral function, increase cerebral blood flow, and promote the release of neurotransmitters, thereby regulating the intracranial metabolism, slowing any apoptosis of nerve cells in the brain, and improving CSVD–VCI.[56] In the treatment of cerebrovascular disease, acupuncture as either monotherapy or adjunctive therapy has a positive effect on improving the cognition and daily performance of people with VCI with few side effects.[57] In a meta-analysis of acupuncture for Alzheimer's disease, it was shown that acupuncture improves cognitive function, physical function and quality of life in patients with Alzheimer's disease.[58] Acupuncture can also improve the cognitive deficits of Alzheimer's disease or vascular disease by modulating neuroplasticity.[59]

There are no appropriate corresponding terms for CSVD or CSVD–VCI in ancient Chinese medical literature, although many cases with similar symptoms are described. As noted, CSVD exhibits varied clinical manifestations, and CSVD–VCI has been included in the category of "stroke" in a number of studies; however, it is in fact a mental disease, meaning it is more reasonable to include it in the category of "amnesia" or "dementia" in TCM. The site of the disease is the brain, though it can also affect the heart, kidneys, liver, and spleen.

Currently, various clinical methods are being actively explored to improve the CSVD–VCI patients using acupuncture-based therapy. For example, Chen Xulan[60] found that the MMSE and MoCA scores and carotid hemodynamic scores of patients with leukoaraiosis were

improved following acupuncture treatment, while Han Xu et al.[61] adopted *Tongdu Xingshen* acupuncture for the treatment of patients with CSVD–VCI and found that the therapy could significantly improve the patients' cognitive level and executive capability. Moreover, contemporary studies have demonstrated a high correlation between vascular inflammatory markers and CSVD in addition to a correlation between the expression level of systemic inflammatory factors and the severity of CSVD.[62] Gao Fengqing et al.[63] conducted a study on the treatment of CSVD using *Tongmai Yizhi* capsules combined with acupuncture and found that the hybrid method could result in an improvement in ET (endothelin), Hcy (homocysteine), TXA2 (thromboxane A2), and PGI2 (prostaglandin I2); its efficacy for cognitive impairment in the test group was found to be superior to that in the control group.

Conclusion

The aim of this study was to conduct a meta-analysis of the rct of CSVD-VCI treated by acupuncture to obtain direct and accurate evidence for the clinical treatment of the disease by acupuncture. Acupuncture alone and acupuncture alongside other therapies are superior to non-acupuncture-based therapies in the treatment of CSVD–VCI.

Study limitations

This study involved the following limitations:

(1) In the included papers, the choice of acupoints, insertion time, treatment frequency, and duration and application of electro-acupuncture differed to some degree in the acupuncture treatment group, which may have led to the inability to accurately interpret the heterogeneity in the analysis.
(2) The included studies were of low quality, with the method for generating random sequences ambiguous in 4 of the 10 studies, the utilization of allocation concealment clearly indicated in only 2 studies, and a blind control adopted for the evaluation and statistical analysis in only 1 study. The allocation concealment and blinding operation were not indicated in the remaining studies.
(3) The limited number of studies that met the study criteria may have led to false positive results in the subgroup analysis, with a lack of sufficient references for the conclusions.

Overall, while the efficacy of acupuncture therapy was found to be superior in the treatment of CSVD–VCI, especially in terms of improving the MoCA, MMSE, and ADL scores without marked side effects, the above limitations indicate that further studies involving high-quality support are required to better assess the efficacy of acupuncture in the treatment of CSVD–VCI and provide more reliable evidence-based insights for the attendant clinical diagnosis and medication.

Ethics approval and consent to participate

This study was conducted with approval from the Ethics Committee of Traditional Chinese Medicine Hospital of Guangzhou Medical University (No.2021NK051). This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request. We declared that materials described in the manuscript, including all relevant raw data, will be freely available to any scientist wishing to use them for non-commercial purposes, without breaching participant confidentiality.

Funding

This work was supported by the Administration of Traditional Chinese Medicine of Guangdong Province (No. 20223014).

CRediT authorship contribution statement

Xiao-Ting Huang: Writing – original draft, Conceptualization, Investigation, Writing – review & editing. **Chu-Yun Chen:** Writing – original draft, Conceptualization, Writing – review & editing, Investigation, Methodology. **Qu-Fei Zhang:** Writing – original draft, Funding acquisition, Data curation. **Li-Hong Lu:** Writing – original draft, Funding acquisition, Data curation. **Ya-Lin She:** Writing – original draft, Data curation, Formal analysis. **Xiao-Yi Fang:** Writing – original draft, Formal analysis.

Acknowledgments

We would like to acknowledge the hard and dedicated work of all the staff that implemented the intervention and evaluation components of the study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.explore.2022.10.019.

References

1 Wardlaw JM, Smith C, Dichgans M. Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging. *Lancet Neurol*. 2013;12(5):483~497.
2 Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol*. 2010;9(7):689~701.
3 Lau AYL, Ip BYM, Ko H, et al. Pandemic of the aging society - sporadic cerebral small vessel disease. *Chin Med J*. 2021;134(2):143~150.
4 De Silva TM, Faraci FM. Contributions of aging to cerebral small vessel disease. *Annu Rev Physiol*. 2020;82:275~295.
5 Cuadrado-Godia E, Dwivedi P, Sharma S, et al. Cerebral Small vessel disease: a review focusing on pathophysiology, biomarkers, and machine learning strategies. *J Stroke*. 2018;20(3):302~320.
6 Arba F, Quinn TJ, Hankey GJ, et al. Enlarged perivascular spaces and cognitive impairment after stroke and transient ischemic attack. *Int J Stroke*. 2018;13(1):47~56. official journal of the International Stroke Society.
7 Benjamin P., Trippier S., Lawrence A.J., et al. Lacunar infarcts, but not perivascular spaces, are predictors of cognitive decline in cerebral small-vessel disease. 2018:49, 586~593.
8 Jokinen H, Koikkalainen J, Laakso HM, et al. Global burden of small vessel disease-related brain changes on mri predicts cognitive and functional decline. *Stroke*. 2020;51(1):170~178.
9 Nannoni S, Ohlmeier L, Brown RB, et al. Cognitive impact of cerebral microbleeds in patients with symptomatic small vessel disease. *Int J Stroke*. 2022;17(4):415~424. official journal of the International Stroke Society.
10 Cannistraro RJ, Badi M, Eidelman BH, et al. CNS small vessel disease: a clinical review. *Neurology*. 2019;92(24):1146~1156.
11 Ryu W, Woo S, Schellingerhout D, et al. Stroke outcomes are worse with larger leukoaraiosis volumes. *Brain: a journal of neurology*. 2017;140(1):158~170.
12 Caprio FZ, Maas MB, Rosenberg NF, et al. Leukoaraiosis on magnetic resonance imaging correlates with worse outcomes after spontaneous intracerebral hemorrhage. *Stroke*. 2013;44(3):642~646.
13 Peng D. Clinical practice guideline for cognitive impairment of cerebral small vessel disease. *Aging Med*. 2019;2(2):64~73 (Milton (N.S.W)).
14 Thal DR, Grinberg LT, Attems J. Vascular dementia: different forms of vessel disorders contribute to the development of dementia in the elderly brain. *Exp Gerontol*. 2012;47(11):816~824.
15 Xie DL, Yang K, Xie HH, et al. Meta-analysis of the effectiveness of scalp acupuncture for post stroke cognitive impairment. *Guid J Tradit Chin Med Pharm*. 2021;27(12):130~136.
16 Wang YL, Zhang L, Li CR, et al. Meta analysis of clinical efficacy of acupuncture in the treatment of vascular cognitive impairment no dementia. *J Liaoning Univ Tradit Chin Med*. 2022;24(01):30~35.
17 Tang EC, Hung C, Lo SH, et al. Acupuncture on vascular cognitive impairment associated with cerebral small vessel disease: a systematic review and meta-analysis

of randomized and non-randomized controlled trials. *Eur J Integr Med*. 2022;49, 101403.
18 Wang X, Chen Y, Liu Y, et al. Reporting items for systematic reviews and meta-analyses of acupuncture: the PRISMA for acupuncture checklist. *BMC Complement Altern Med*. 2019;19(1):208. Aug 122019:19,208.
19 Zanon Zotin MC, Sveikata L, Viswanathan A, et al. Cerebral small vessel disease and vascular cognitive impairment: from diagnosis to management. *Curr Opin Neurol*. 2021;34(2):246~257.
20 Macpherson H, Altman DG, Hammerschlag R, et al. Revised STandards for reporting interventions in clinical trials of acupuncture (STRICTA): extending the CONSORT statement. *Acupunct Med J Br Med Acupunct Soc*. 2010;28(2):83~93.
21 Wang MJ. *Clinical Study on the Treatment of Cognitive Dysfunction Caused By Cerebrovascular Disease With Qi Huang Acupuncture*. Traditional Chinese Medicine Hospital of Guangzhou Medical University; 2021.
22 Ren X, Sun YZ. A randomized controlled study of Yuanluo Tongjing acupuncture in the treatment of mild cognitive impairment caused by Binswanger disease. *J Qiqihar Med Univ*. 2019;40(02):203~204.
23 Shen ZY. *Clinical Study on Acupuncture Combined with Taijiquan in the Treatment of Mild Cognitive Impairment Caused By Cerebrovascular Disease*. Fujian University of Traditional Chinese Medicine; 2021.
24 Meng YF. Effect of acupuncture combined with hyperbaric oxygen in the treatment of leukoaraiosis with mild cognitive impairment patients and its influence on neurotransmitter levels. *Asia Pac Tradit Med*. 2019;15(06):143~145.
25 Zhao YF, Wang XY. Clinical observation of needling plus hyperbaric oxygen for leukoaraiosis coupled with mild cognitive impairment. *Shanghai J Acupunct Moxibustion*. 2016;35(12):1414~1416.
26 Liu JM. Effect of acupuncture and moxibustion on cognitive function and brainstem auditory evoked potential of lacunar cerebral infarction. *Guid China Med*. 2015;13 (15):204~205.
27 Zhang JB, Cheng YZ, Suo LJ, et al. Therapeutic effect of acupuncture at Sishencong point combined with donepezil hydrochloride on mild cognitive impairment of subcortical arteriosclerotic encephalopathy. *J Med Theory Pract*. 2020;33(05): 739~741.
28 Xie C, Sun MH. Effect of acupuncture and moxibustion on cognitive impairment caused by cerebrovascular disease. *Health Guid*. 2017;33:232.
29 Zhang HQ. Clinical observation of needling plus hyperbaric oxygen for leukoaraiosis coupled with mild cognitive impairment. *Lab Med Clin*. 2017;14(z2):156~157.
30 Chen SN. *3d-asl Based Study on the Mechanism of Acupuncture Shenting Baihui to Improve Cognitive Dysfunction of Cerebrovascular Disease*. Traditional Chinese Medicine Hospital of Guangzhou Medical University; 2019.
31 Hachinski V. World stroke day 2008: "little strokes, big trouble". 2008:39, 2407~2420.
32 Rutten-Jacobs LCA, Markus HS. Vascular risk factor profiles differ between magnetic resonance imaging-defined subtypes of younger-onset lacunar stroke. *Stroke*. 2017; 48(9):2405~2411.
33 De Silva TM, Miller AA. Cerebral small vessel disease: targeting oxidative stress as a novel therapeutic strategy? *Front Pharmacol*. 2016;7:61.
34 Joutel A, Faraci FM. Cerebral small vessel disease: insights and opportunities from mouse models of collagen IV-related small vessel disease and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. *Stroke*. 2014;45(4):1215~1221.
35 Evans NR, Tarkin JM, Walsh J, et al. Carotid atheroinflammation is associated with cerebral small vessel disease severity. *Front Neurol*. 2021;12, 690935.
36 Petrea RE, O'Donnell A, Beiser AS, et al. Mid to late life hypertension trends and cerebral small vessel disease in the Framingham heart study. *Hypertension*. 2020;76 (3):707~714 (Dallas, Tex.: 1979).
37 Liu J, Rutten-Jacobs L, Liu M, et al. Causal impact of type 2 diabetes mellitus on cerebral small vessel disease: a mendelian randomization analysis. *Stroke*. 2018;49 (6):1325~1331.
38 Eriksson MI, Summanen P, Gordin D, et al. Cerebral small-vessel disease is associated with the severity of diabetic retinopathy in type 1 diabetes. *BMJ Open Diabetes Res Care*. 2021;9(1).
39 Li S, Li G, Luo X, et al. Endothelial dysfunction and hyperhomocysteinemia-linked cerebral small vessel disease: underlying mechanisms and treatment timing. *Front Neurol*. 2021;12, 736309.
40 Liu Y, Dong Y, Lyu P, et al. Hypertension-induced cerebral small vessel disease leading to cognitive impairment. *Chin Med J*. 2018;131(5).
41 Umemura T, Kawamura T, Umegaki H, et al. Association of chronic kidney disease and cerebral small vessel disease with cognitive impairment in elderly patients with type 2 diabetes. *Dement Geriatr Cogn Dis Extra*. 2013;3(1):212~222.
42 Wang Z, Chen Q, Chen J, et al. Risk factors of cerebral small vessel disease: a systematic review and meta-analysis. *Medicine*. 2021;100(51):e28229 (Baltimore).
43 Wilkinson D., Doody R., Helme R., et al. Donepezil in vascular dementia: a randomized, placebo-controlled study. 2003:61,479~486.
44 Auchus AP, Brashear HR, Salloway S, et al. Galantamine treatment of vascular dementia: a randomized trial. *Neurology*. 2007;69(5):448~458.
45 Narasimhalu K, Effendy S, Sim CH, et al. A randomized controlled trial of rivastigmine in patients with cognitive impairment no dementia because of cerebrovascular disease. *Acta Neurol Scand*. 2010;121(4):217~224.
46 Smith EE, Cieslak A, Barber P, et al. Therapeutic strategies and drug development for vascular cognitive impairment. *J Am Heart Assoc*. 2017;6(5).
47 Zhang J, Liu N, Yang C. Effects of rosuvastatin in combination with nimodipine in patients with mild cognitive impairment caused by cerebral small vessel disease. *Panminerva Med*. 2019;61(4):439~443.
48 Orgogozo J., Rigaud A., Stöffler A., et al. Efficacy and safety of memantine in patients with mild to moderate vascular dementia: a randomized, Placebo-controlled trial (MMM 300). 2002:33,1834~1839.
49 Wilcock G., Möbius H.J., Stöffler A. A double-blind, placebo-controlled multicentre study of memantine in mild to moderate vascular dementia (MMM500). 2002: 17,297~305.
50 Jia J, Wei C, Liang J, et al. The effects of DL-3-n-butylphthalide in patients with vascular cognitive impairment without dementia caused by subcortical ischemic small vessel disease: a multicentre, randomized, double-blind, placebo-controlled trial. *Alzheimer's Dement*. 2016;12(2):89~99. the journal of the Alzheimer's Association.
51 Demarin V, Bašić Kes V, Trkanjec Z, et al. Efficacy and safety of Ginkgo Biloba standardized extract in the treatment of vascular cognitive impairment: a randomized, double-blind, placebo-controlled clinical trial. *Neuropsychiatr Dis Treat*. 2017;13:483~490.
52 Román G.C., Salloway S., Black S.E., et al. Randomized, placebo-controlled, clinical trial of donepezil in vascular dementia: differential effects by hippocampal size. 2010:41,1213~1221.
53 Zhang DM, Zhang Y. Clinical evaluation of cholinesterase inhibitors in the treatment of vascular dementia. *J Brain Nerv Dis*. 2013;21(01):75~78.
54 Xiang J, Li H, Xiong J, et al. Acupuncture for post-stroke insomnia: a protocol for systematic review and meta-analysis. *Medicine*. 2020;99(30):e21381 (Baltimore).
55 Zhi H, Wang Y, Chang S, et al. Acupuncture can regulate the distribution of lymphocyte subsets and the levels of inflammatory cytokines in patients with mild to moderate vascular dementi. *Front Aging Neurosci*. 2021;13, 747673.
56 Lin Z.C., Jiang Y.J., Chen A.Z., et al. Therapeutic observation of acupuncture at Baihui (GV20) in improving executive dysfunction after cerebral stroke.,2017,36 (10):1164~1167.
57 Su X., Sun N., Zhang N., et al. Effectiveness and Safety of Acupuncture for Vascular Cognitive Impairment: a Systematic Review and Meta-Analysis. 2021:13,692508.
58 Lin C, Yeh M, Wu S, et al. Acupuncture-related treatments improve cognitive and physical functions in Alzheimer's disease: a systematic review and meta-analysis of randomized controlled trials. *Clin Rehabil*. 2022;36(5):609~635.
59 Ji S, Duan J, Hou X, et al. The role of acupuncture improving cognitive deficits due to Alzheimer's disease or vascular diseases through regulating neuroplasticity. *Neural Plast*. 2021;2021, 8868447.
60 Chen XL. Effect of mind-regulating and collateral-unblocking acupuncture on carotid hemodynamics in leukoaraiosis patients. *Shanghai J Acupunct Moxibustion*. 2015;(9): 811~813.
61 Han X, Wang M, Li Y. Clinical study of Tongdu Xingshen acupuncture in treating CSVD-VCI. *J Clin Acupunct Moxibustion*. 2022;38(02):25~28.
62 Li T, Huang Y, Cai W, et al. Age-related cerebral small vessel disease and inflammaging. *Cell Death Dis*. 2020;11(10):932.
63 Gao FQ, Ji YH, Cao HG, et al. Effect of Tongmai Yizhi capsule combined with acupuncture on cognitive impairment caused by cerebrovascular disease and its effect on TXA2, PGI2, et and Hcy. *Mod J Integr Tradit Chin West Med*. 2017;26(34): 3841~3843.