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A systematic review of the efficacy of donepezil hydrochloride combined with nimodipine on treating vascular dementia

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Abstract

Background: Vascular dementia (VaD) is a comprehensive syndrome related to the damage of cognitive function and various cerebral vascular illnesses. VaD is also generally recognized as the second most common type of dementia after Alzheimer disease, contributing to 30% of the dementia population in Asia and developing countries. The ability of donepezil hydrochloride and nimodipine had been respectively proven in improving cognitive function in vascular dementia. However, whether the combined application of both drugs contribute to better efficacy remains as a research hotspot. Studies had shown definite satisfactory result with such combination, however evidence-based evaluation of the efficacy is still lacking. Therefore, meta-analysis is employed in this study to evaluate the efficacy and safety of using donepezil hydrochloride combined with nimodipine in treating VaD to provide references for clinical treatments. The efficacy of donepezil hydrochloride combined with nimodipine on treating vascular dementia is systematically reviewed to provide evidence-based references for clinical applications.

Methods: Both Chinese and English databases were searched from the start till August, 2020 for any RCT regarding the combined use of the 2 drugs in treating vascular dementia. Two investigators would later evaluate and screened out research and data based on an improved Jaded scale. Software Rev Man 5.3.0 was employed to carry out meta-analysis on clinical effifacy, mini-mental state examination (MMSE) ratings, activity of daily living (ADL) ratings, and clinical dementia scale (CDR) ratings.

Results: Donepezil hydrochloride combined with nimodipine had demonstrated satisfactory efficacy on the treatment of vascular dementia. Improvements were namely spotted on MMSE scale, ADL scale, and CDR scale, with the utmost efficacy by 12 weeks after intervention.

Conclusions: Donepezil hydrochloride combined with nimodipine had good efficacy in the treatment of patients with vascular dementia, mainly in terms of improving the Simple MMSE scores, the ability to use daily living scale (ADL) scores and the CDR, and the best results were obtained after 12 weeks of intervention. Such conclusion should be cautiously evaluated.

Abbreviations: ADL = activity of daily living, CDR = clinical dementia scale, MMSE = mini-mental state examination, VaD = vascular dementia.

Keywords: donepezil hydrochloride, efficacy, meta-analysis, nimodipine, vascular dementia

1. Introduction

Vascular dementia (VaD) is a comprehensive syndrome related to the damage of cognitive function and various cerebral vascular illnesses. VaD is also generally recognized as the second most common type of dementia after Alzheimer disease, contributing to 30% of the dementia population in Asia and developing countries.[1] The ability of donepezil hydrochloride and nimodipine had been respectively proven in improving cognitive function in vascular dementia.[2,3] However, whether the combined application of both drugs contribute to better efficacy remains as a research hotspot. Studies had shown definite satisfactory result with such combination, however evidence-based evaluation of the efficacy is still lacking. Therefore, meta-analysis is employed in this study to evaluate the efficacy and safety of using donepezil hydrochloride combined with

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Data Availability: All data compiled or analyzed during this study are included in this published article.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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nimodipine in treating VaD to provide references for clinical treatments.[4,5]

2. Data and Methods

2.1. Inclusion criteria

Studies that employed randomized or quasi-randomized controlled trial, with or without blinding methods. Research object fulfilled the diagnostic criteria of VaD.[6] Interventions: The observation group should employ a combination usage of donepezil hydrochloride and nimodipine, while the control group should employ a sole usage of either 1 drug. Efficacy indicators: general clinical efficacy; mini-mental state examination (MMSE); activity of daily living (ADL); clinical dementia scale (CDR).

2.2. Exclusion criteria

Combined with other types of dementia apart from VaD; duplicated researches; fundamental laboratory report; literature review; non-RCT researches; interventions incoherent with inclusion criteria; incomplete data; unclear diagnosis.

2.3. Research strategy

Research is conducted based on the following databases: China National Knowledge Infrastructure, Wanfang database, China Science and Technology Journal Database, China Biomedical Database, PubMed Embase, Cochrane Library. Studies were included from the time of start to October 30, 2020. Keywords: vascular dementia, vascular cognitive impairment, donepezil hydrochloride, nimodipine.

2.4. Selection of studies and data extractions

Studies and data were selected and extracted by 2 independent investigators. When the consensus on a certain piece of information cannot be reached, it would be discussed and consulted by a third party. The following components were extracted from the data: name of the first author, time of publish, sample size, ways of intervention, result indicators, and risk of bias related indicators.

2.5. Quality evaluation of studies

Clinical trials within the studies included were evaluated by Cochrane risk of bias tool[7]: whether it is randomized; whether allocation method was concealed; whether both the participants and investigators were blinded; whether the results were drawn under double blinding; whether the data throughout the process to conclusion was complete; selective reporting of research results; other source of bias. All items evaluated as correct would be considered as low risk of bias. One or more than one item evaluated as unclear would be considered as uncertain. One or more than one item evaluated as incorrect would be considered as high risk of bias.

2.6. Statistical method

Software RevMan5.3 by Cochrane was employed to conduct statistical analysis. Heterogeneity test would indicate studies with higher homogeneity ($P > .1$) and fixed effect model would be utilized for analysis. The remaining studies would be analyzed by random effect model. Odd ratio and 95% confidence interval of count data was calculated. When $P < .05$ and 1 was not included within 95% confidence interval, the point estimation differences of OR were considered as statistically significance. Mean difference and 95% confidence interval of count data were calculated. Funnel plot was drawn to analyze publication bias, the better completion and symmetricity of the plot would demonstrate lower publication bias to ensure the stability of the analytical results.

2.7. Ethical review

This study does not involve a clinical trial and ethical review is not applicable.

3. Results

3.1. Studies inclusion

One hundred thirteen studies were obtained through database searching. Forty nine studies including duplicated studies were than excluded through screening at title and abstract. Full text screening were then carried out to further exclude 46 studies. Eighteen RCTs with a sample size of 1647 patients were ultimately included in our study. See Fig. 1 and Table 1.

3.2. Quality evaluation of included studies

Eighteen studies[8–25] mentioned the word "randomized," 8 studies[8,9,17,20,21,23–25] mentioned specific randomization methods. Allocation concealment, blinding, and other risks were not mentioned in all studies. Eighteen studies had given detailed description on the baseline situation of included cases, and the employment of software RevMan5.3 on carrying risk of bias evaluation. Results on Figs. 2 and 3.

3.3. Results of meta-analysis

3.3.1. Results of the meta-analysis on MMSE. Seventeen studies[8–19,21–25] had compared the MMSE score before and after the combined usage of donepezil hydrochloride and nimodipine in the treatment of vascular dementia. Heterogeneity ($P < .000001$, $I^2 = 76\%$) were perceived in respective group of study, therefore meta-analysis was carried out by random effect model as shown in Fig. 4.

Results of the meta-analysis showed a statistically significant improvement on MMSE score (OR = 2.50, 95% CI [1.92, 3.09], $P < .00001$) on the experimental group than on the control group. Sub-group analysis was further conducted base on the duration of treatment (12, 8, 4 weeks). Eleven studies had observed the MMSE score after 12 weeks of intervention, heterogeneity ($P < .000001$, $I^2 = 74\%$) was detected in respective group of study, meta-analysis was than conducted through random effect model. Result had indicated statistically significant improvement on MMSE score (OR = 2.55, 95% CI [1.79, 3.31], $P < .00001$). Sensitivity analysis was further conducted: As the 11 groups of study regarding improvements of the MMSE score after 12 weeks had demonstrated a relatively higher statistical heterogeneity ($P < .000001$, $I^2 = 74\%$), study was therefore individually excluded respectively. The exclusion of the 3 studies conducted by Yangqin Kong, Kui Xiong, Zhiqiang Wang had induced a significant change in the heterogeneity among the remaining 8 studies, indicating absence of heterogeneity ($P = .31$, $I^2 = 15\%$). Therefore the 3 studies were highly considered as the source of heterogeneity in regard of this specific indicator. Seven studies had observed the MMSE score after 8 weeks of intervention, heterogeneity ($P = .0004$, $I^2 = 76\%$) was detected in respective group of study, meta-analysis was than conducted through random effect model. Result had indicated statistically significant improvement on MMSE score (OR = 2.33, 95% CI [1.52, 3.14], $P < .00001$). Sensitivity analysis was further conducted: as the 7 groups of study regarding improvements of the MMSE score after 8 weeks had demonstrated a relatively higher statistical heterogeneity

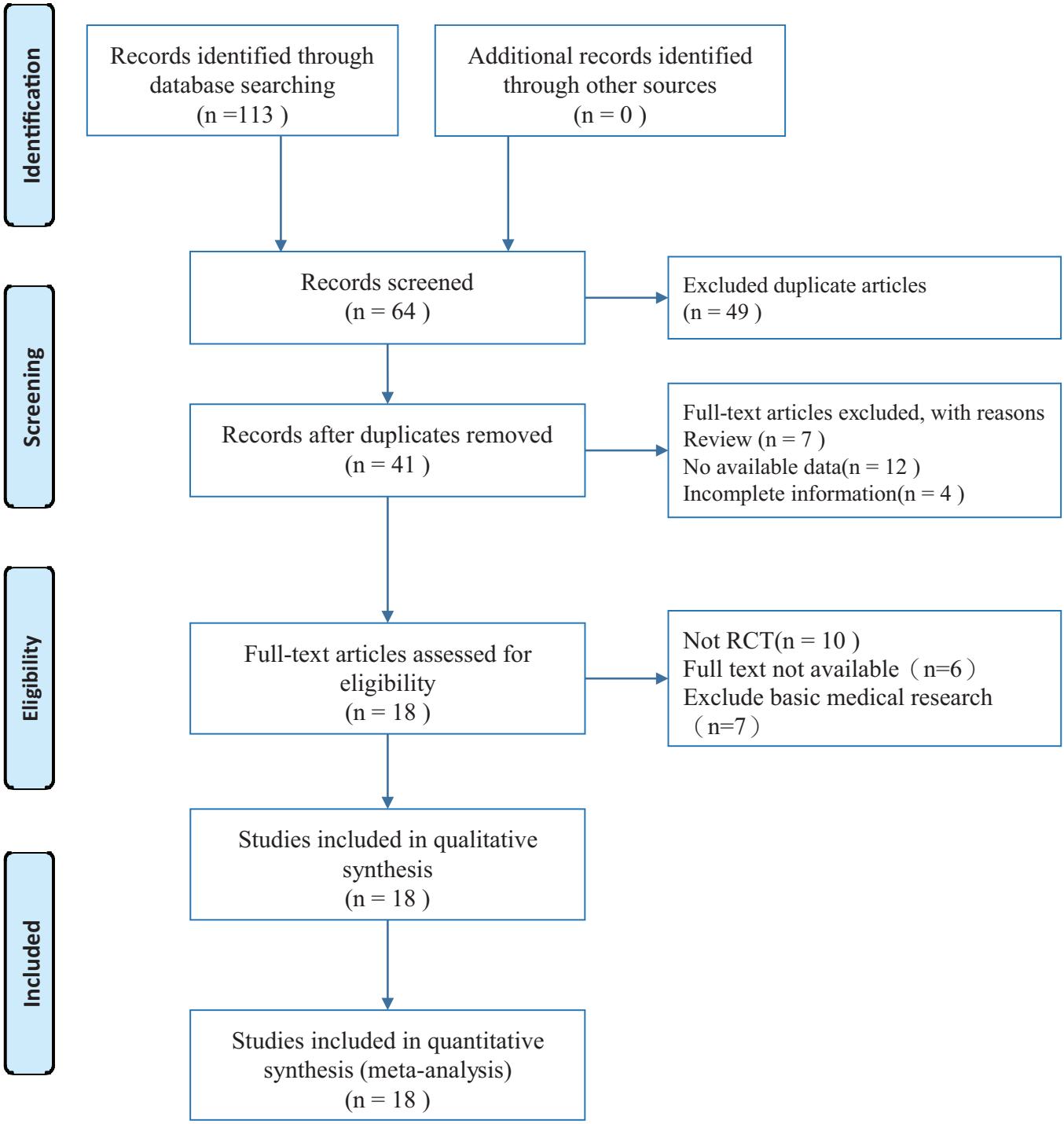

Figure 1. Flow chart of literature screening.

(P = .0004, I^2 = 76%), study was therefore individually excluded respectively. The exclusion of the 2 studies conducted by Xin He, Dandan Zhang had induced a significant change in the heterogeneity among the remaining 5 studies, indicating absence of heterogeneity (P = .84, I^2 = 0%). Therefore the 2 studies were highly considered as the source of heterogeneity in regard of this specific indicator. Eight studies had observed the MMSE score after 4 weeks of intervention, heterogeneity (P < .000001, I^2 = 81%) was detected in respective group of study, meta-analysis was than conducted through random effect model. Result had indicated statistically significant improvement on MMSE score (OR = 0.88, 95% CI [–0.15, 1.91], P < .00001). Sensitivity analysis was further conducted: as the 8 groups of study regarding improvements of the MMSE score after 4 weeks had demonstrated a relatively higher statistical heterogeneity (P < .000001, I^2 = 81%), study was therefore individually excluded respectively. The exclusion of the 1 study conducted by Dandan Zhang had induced a significant change in the heterogeneity among the remaining 5 studies, indicating absence of heterogeneity (P = .49, I^2 = 0%). Therefore the studies were highly considered as the source of heterogeneity in regard of this specific indicator. While at the same time, MMSE score improvement was considered most satisfactory with 12 weeks of combined usage of donepezil hydrochloride

Table 1

Basic information of the included literatures.

First author	Year of publication	Country	Number of cases		Basic information	Interventions		Random method	Observation target
			Control group	Treatment group		Control group	Treatment group		
Cuiyun Zhang[8]	2016	China	40	40	Similarity	A	A+B	Table of random numbers	
Jinxia Huo[9]	2015	China	65	59	Similarity	B	A+B	Table of random numbers	
Haibo Zeng[10]	2015	China	34	34	Similarity	A	A+B	Random	
Mahebula[11]	2012	China	34	34	Similarity	A	A+B	Random	
Lu Wang[12]	2015	China	30	30	Similarity	A	A+B	Random	
Jinsong Yang[13]	2014	China	150	150	Similarity	A	A+B	Random	
Zhiqing Wang[14]	2014	China	40	40	Similarity	A	A+B	Random	
Yanwei Zhu[15]	2018	China	48	48	Similarity	A	A+B	Random	
Erhen Ai[16]	2013	China	20	20	Similarity	A	A+B	Random	
Xin He[17]	2020	China	43	43	Similarity	A	A+B	Table of random numbers	
Xia Wang[18]	2012	China	19	20	Similarity	A	A+B	Random	
Xiaojing Sun[19]	2016	China	42	42	Similarity	A	A+B	Random	
Xiaohong Zhang[20]	2020	China	30	30	Similarity	A	A+B	Lottery	
Kui Xiong[21]	2020	China	60	60	Similarity	A	A+B	Lottery	
Yangqin Kong[22]	2017	China	25	25	Similarity	A	A+B	Random	
Dandan Zhang[23]	2018	China	76	76	Similarity	B	A+B	Random	
Shiying Zhao[24]	2019	China	40	40	Similarity	B	A+B	Random envelope method	
Yongwei Zhang[25]	2017	China	30	30	Similarity	B	A+B	Random	

and nimodipine in treating VaD through subgroup analysis. Detail as shown in Figs. 5 and 6.

3.3.2. Results of the meta-analysis on activity daily scale. Thirteen studies[10–18,20,22–24] had compared the CDR score before and after the combined usage of donepezil hydrochloride and nimodipine in the treatment of vascular dementia. Heterogeneity ($P < .000001$, $I^2 = 99\%$) were perceived in respective group of study, therefore meta-analysis was carried out by random effect model as shown in Fig. 7.

Results of the meta-analysis showed an improvement on ADL score among the experimental group compared with the controlled group but indicates no statistical significance (OR = 0.16, 95% CI [–3.55, 3.87], $P = .93$). Sub-group analysis was further conducted based on the duration of treatment (12, 8, 4 weeks). Eight studies had observed the ADL score after 12 weeks of intervention, heterogeneity ($P < .000001$, $I^2 = 99\%$) was detected in respective group of study, meta-analysis was than conducted through random effect model. Result had indicated improvement on ADL score among the experimental group compared with the controlled group but indicates no statistical significance (OR = 0.33, 95% CI [–3.97, 4.63], $P = .88$). Sensitivity analysis was further conducted: As the 8 groups of study regarding improvements of the ADL score after 12 weeks had demonstrated a relatively higher statistical heterogeneity ($P < .000001$, $I^2 = 99\%$), study was therefore individually excluded respectively. The exclusion of the 2 studies conducted by Yangqin Kong and Zhiqiang Wang had induced a significant change in the heterogeneity among the remaining 6 studies, indicating absence of heterogeneity ($P < .000001$, $I^2 = 0\%$). Therefore the 2 studies were highly considered as the source of heterogeneity in regard of this specific indicator. Six studies had observed the ADL score after 8 weeks of intervention, heterogeneity ($P < .000001$, $I^2 = 98\%$) was detected in respective group of study, meta-analysis was than conducted through random effect model. Result had indicated improvement on ADL score among the experimental group compared with the controlled group but indicates no statistical significance (OR = –2.4, 95% CI [–5.36, 4.87], $P = .93$). Sensitivity analysis was further conducted: as the 8 groups of study regarding improvements of the ADL score

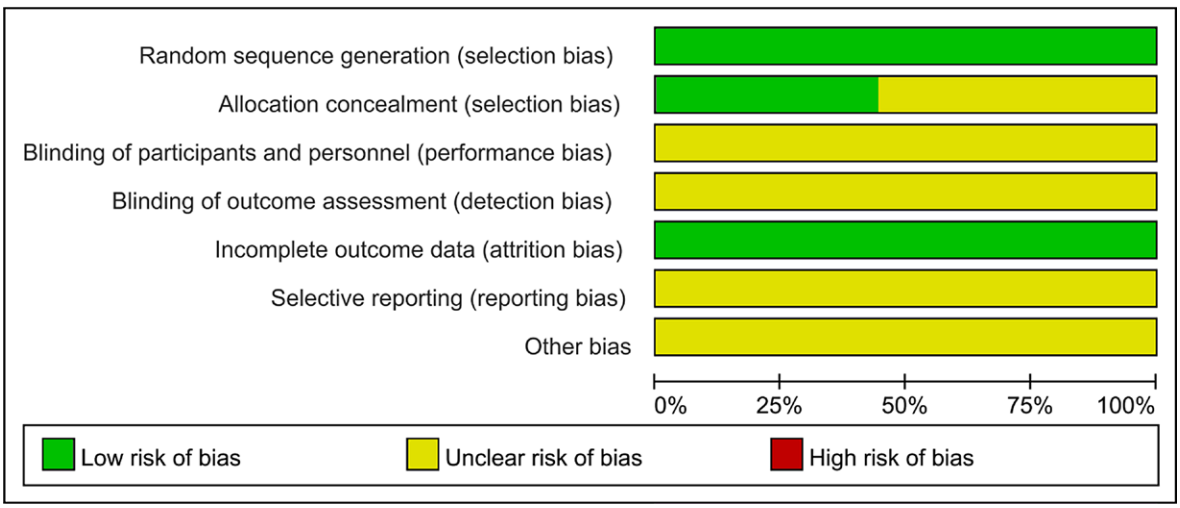

Figure 2. Risk of bias graph.

Figure 3. Risk of bias summary.

after 12 weeks had demonstrated a relatively higher statistical heterogeneity (P < .000001, I^2 = 98%), study was therefore individually excluded respectively. The exclusion of the 2 studies conducted by Xin He and Xiaotong Zhang had induced a significant change in the heterogeneity among the remaining 4 studies, but significant heterogeneity was still present (P = .04, I^2 = 63%). The improvement on ADL score within the experimental group was significantly higher than the controlled group (OR = −4.31, 95% CI [−5.90, −2.73], P < .000001). Therefore the 2 studies were highly considered as the source of heterogeneity in regard of this specific indicator. Five studies had observed the ADL score after 4 weeks of intervention, heterogeneity (P < .000001, I^2 = 89%) was detected in respective group of study, meta-analysis was than conducted through random effect model. Result had indicated improvement on ADL score among the experimental group compared with the controlled group but indicates no statistical significance (OR = −1.46, 95% CI [−4.91, 2.00], P = .41). Sensitivity analysis was further conducted: As the 5 groups of study regarding improvements of the ADL score after 4 weeks had demonstrated a relatively higher statistical heterogeneity (P < .000001, I^2 = 98%), study was therefore individually excluded respectively. The exclusion of the study conducted by Dandan Zhang had induced a significant change in the heterogeneity among the remaining 4 studies, indicating an absence of heterogeneity (P = .79, I^2 = 0%). Result from the meta-analysis had shown improvements on ADL score within the experimental group io comparison with the controlled group without statistical significance (OR = −0.16, 95% CI [−1.58, 1.26], P = .83). Therefore this study was highly considered as the source of heterogeneity in regard of this specific indicator. While at the same time, ADL score improvement was considered most satisfactory with 12 weeks of combined usage of donepezil hydrochloride and nimodipine in treating VaD through subgroup analysis. Detail as shown in Figs. 8 and 9.

3.3.3. Results of the meta-analysis on clinical dementia scale. Eight studies[8,12,13,19–21,23,24] had compared the ADL score before and after the combined usage of donepezil hydrochloride and nimodipine in the treatment of vascular dementia. Heterogeneity (P < .000001, I^2 = 84%) were perceived in respective group of study, therefore meta-analysis was carried out by random effect model as shown in Fig. 10.

Results of the meta-analysis showed a statistically significant improvement on CDR score (OR = −0.28, 95% CI [−0.40, −0.17], P < .000001) on the experimental group than on the control group. Sub-group analysis was further conducted based on the duration of treatment (12, 8, 4 weeks). Two studies had observed the CDR score after 12 weeks of intervention, heterogeneity (P = .06, I^2 = 72%) was detected in respective group of study, meta-analysis was than conducted through random effect model. Result had indicated statistically significant improvement on CDR score (OR = −0.32, 95% CI [−0.52, −0.11], P = .002) within the experimental group in comparison with the controlled group. Therefore the 2 studies were highly considered as the source of heterogeneity in regard of this specific indicator. Five studies had observed the CDR score after 8 weeks of intervention, heterogeneity (P < .000001, I^2 = 90%) was detected in respective group of study, meta-analysis was than conducted through random effect model. Result had indicated statistically significant improvement on CDR score (OR = −0.24, 95% CI [−0.42, −0.07], P = .006) within the experimental group in comparison with the controlled group. Sensitivity analysis was further conducted: as the 5 groups of study regarding improvements of the CDR score after 8 weeks had demonstrated a relatively higher statistical heterogeneity (P < .000001, I^2 = 90%), study was therefore individually excluded respectively. The exclusion of the 2 studies conducted by Dandan Zhang, Xiaohong Zhang had induced a significant change in the heterogeneity among the remaining 3 studies, but significant heterogeneity was still present (P = .27, I^2 = 24%). The improvement on CDR score was statistically significant within the experimental group in comparison with the controlled group (OR = −0.12, 95% CI [−0.21, −0.03], P = .001). Therefore the 2 studies were highly considered as the source of heterogeneity in regard of this specific indicator. Four studies had observed the CDR score after 4 weeks of intervention, heterogeneity (P = .01, I^2 = 73%) was detected in respective group of study, meta-analysis was

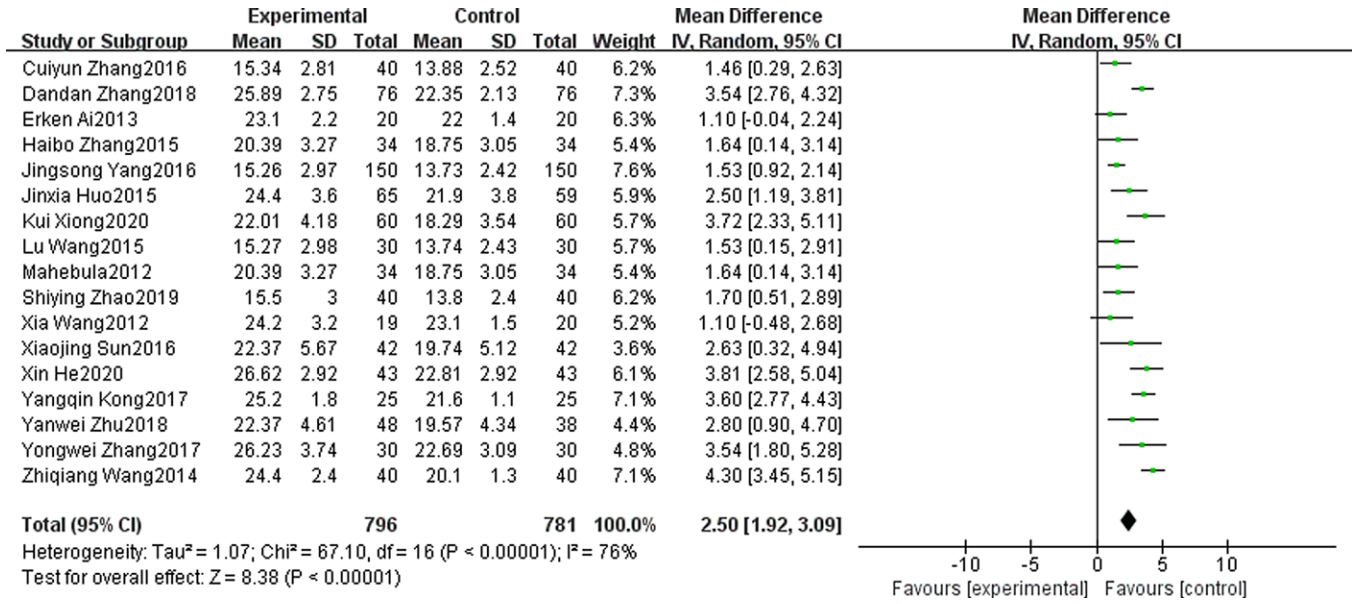

Figure 4. The forest plot of MMSE. MMSE = mini-mental state examination.

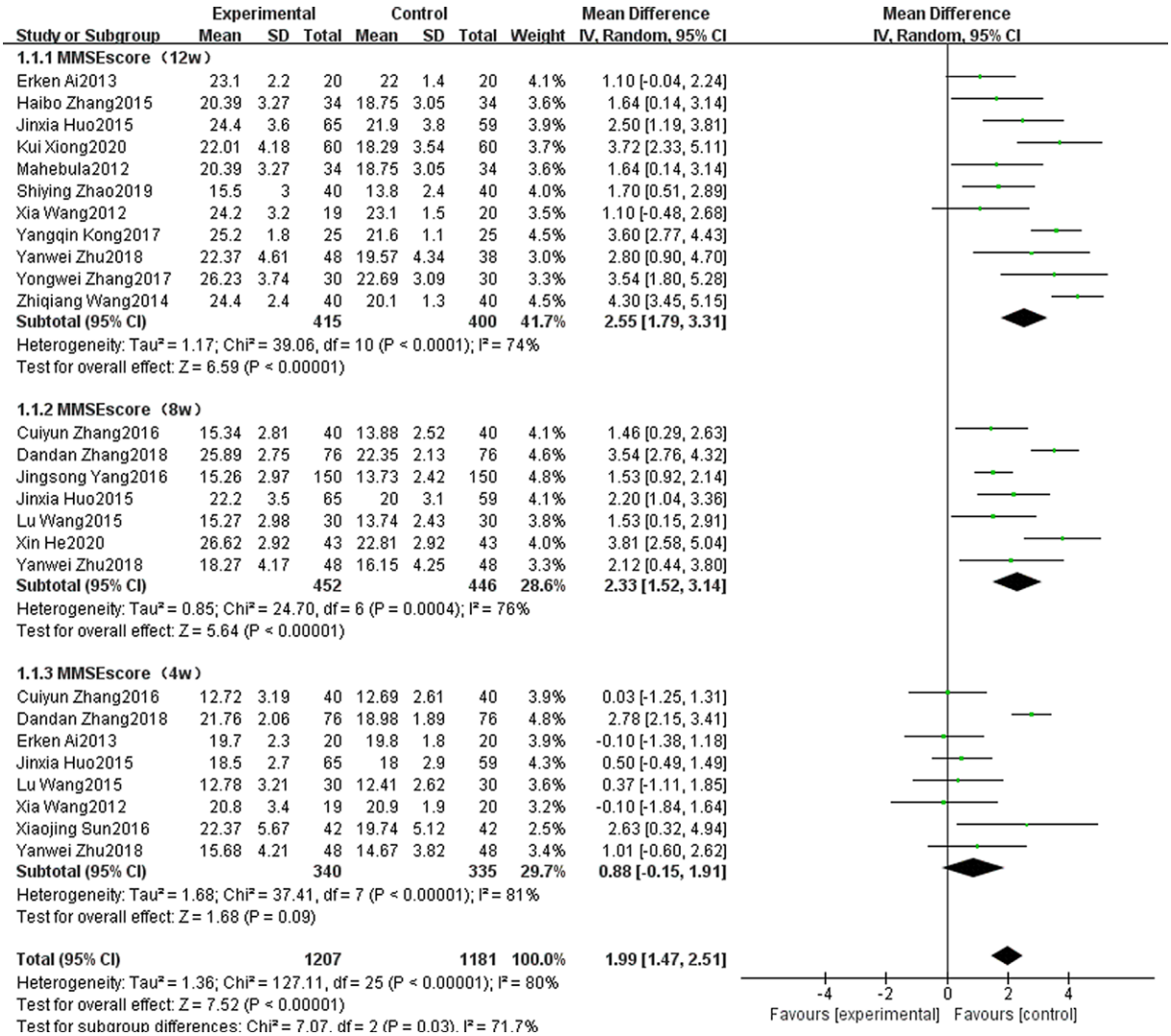

Figure 5. The forest plot of MMSE (subgroup analysis by duration of treatment: 12, 8, and 4 weeks). MMSE = mini-mental state examination.

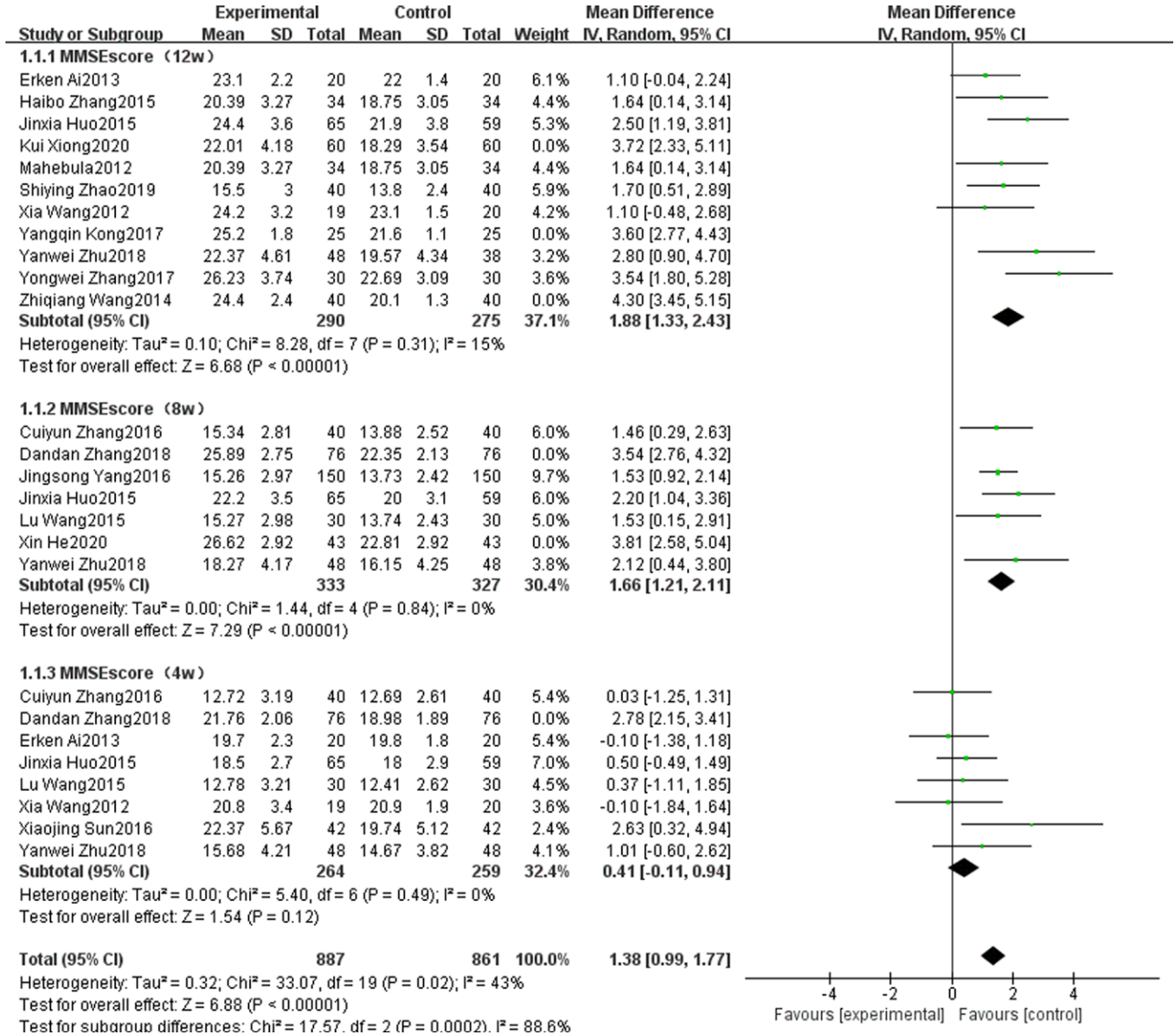

Figure 6. Sensitivity analysis of MMSE. MMSE = mini-mental state examination.

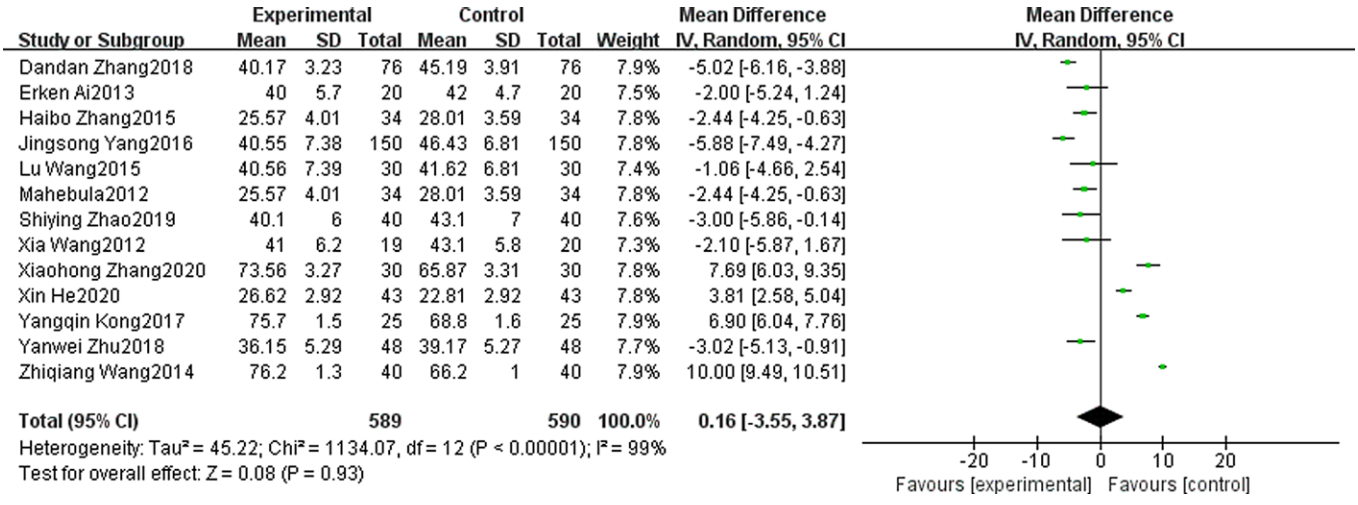

Figure 7. The forest plot of ADL. ADL = activity of daily living.

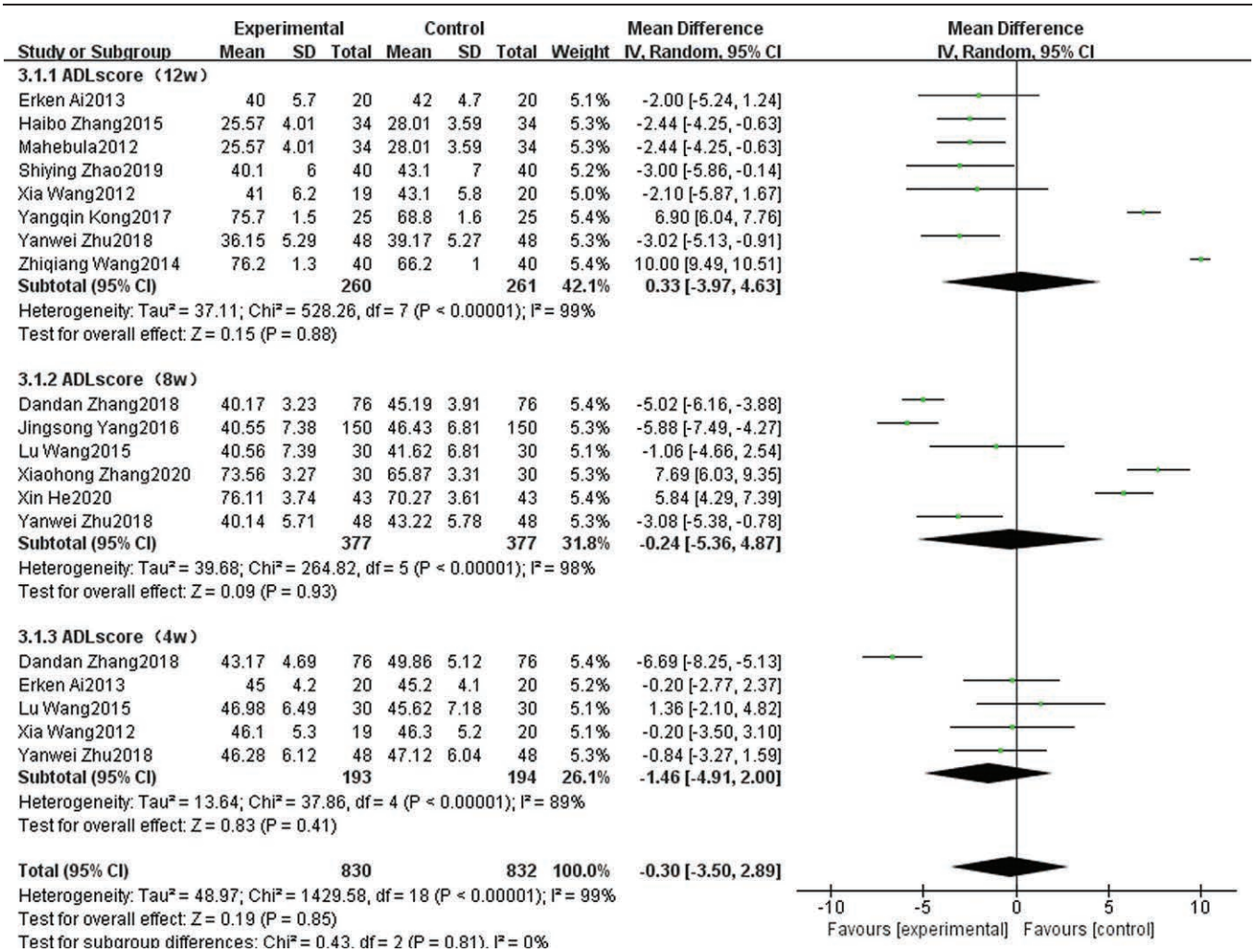

Figure 8. The forest plot of ADL (subgroup analysis by duration of treatment: 12, 8, and 4 weeks). ADL = activity of daily living.

than conducted through random effect model. Result had indicated statistically significant improvement on CDR score (OR = −0.24, 95% CI [−0.39, −0.08], P = .004) within the experimental group in comparison with the controlled group. Sensitivity analysis was further conducted: as the 4 groups of study regarding improvements of the CDR score after 4 weeks had demonstrated a relatively higher statistical heterogeneity (P < .000001, I^2 = 90%), study was therefore individually excluded respectively. The exclusion of the study conducted by Cuiyun Zhang had induced a statistically significant decrease (P = .14, I^2 = 50%) in the heterogeneity among the remaining 3 studies. Meta-analysis shown improvement in CDR score within experimental group in comparison with controlled group without statistical significance (OR = −0.31, 95% CI [−0.43, −0.18], P < .000001). This study is highly considered as the source of heterogeneity in regard of this specific indicator. CDR score improvement was considered most satisfactory with 12 weeks of combined usage of donepezil hydrochloride and nimodipine in treating VaD through subgroup analysis. Detail as shown in Figs. 11 and 12.

3.3.4. Results on the meta-analysis of clinical efficacy Seven studies[8–11,15,16,18] (n = 524) had compared the clinical efficacy of the combined usage of donepezil hydrochloride and nimodipine in VaD treatment, there were no heterogeneity among respective group of study (P = 81, I^2 = 0%). Therefore, meta-analysis was conducted through fixed effect model as shown in Fig. 13. The result indicates the efficacy of the experimental group was significantly higher than the controlled group (OR = 1.21, 95% CI [1.13, 1.29], P < .000001).

3.4. Publication bias

Funnel plot and result analysis: Funnel plot analysis is carried based on the MMSE score before and after the combined usage of donepezil hydrochloride and nimodipine in VaD treatment. The funnel plot was drawn based on using MD as the x-axis and standard error SE(MD) as the y-axis. Result has indicates a mostly symmetric funnel with true value as its symmetry, therefore the publication bias of studies included was considered relatively small. Funnel plot and result analysis as shown in Fig. 14.

4. Discussion

Vascular dementia (VaD) is an illness which specify in cerebral dysfunction after cerebral vascular disease. Blood flow of the brain decreased with the nutritional substances and oxygen which was originally carried into the brain cells. Therefore lowering the patient's cognitive function. Pathogenesis of VaD is considered in close relation with the hypothesis of calcium overload and cholinergic nerve damage.[26,27] Donepezil is 2nd generation cholinesterase suppressant; its curative effects is demonstrated through a reversible suppression of acetylcholinesterase. Acetylcholinesterase would induce the hydrolysis

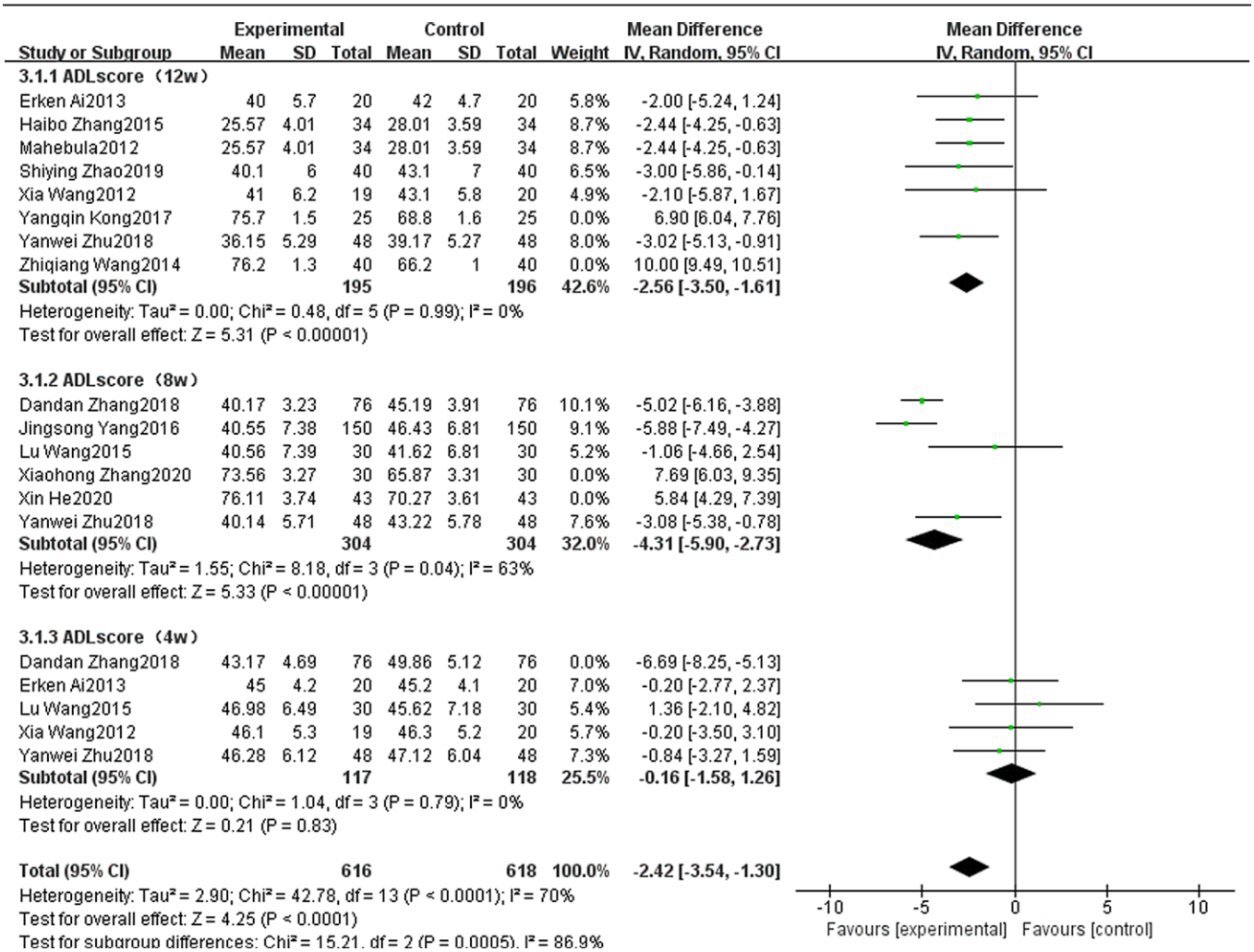

Figure 9. Sensitivity analysis of ADL. ADL = activity of daily living.

of cholinergic neuron while increasing the amount of cholinesterase within receptor. Nimodipine can change the functions of neurons, and perceived both neuroactive and psychoactive pharmacological property.[28] Nimodipine has high lipid solubility and demonstrates selective effects on cerebral vascular smooth muscle. This could ease the calcium overloaded within cell by preventing the inflow of calcium ions. The mechanism of the combined usage of both drugs on treating VaD is reasonable. Several clinical studies have confirmed the therapeutic efficacy of donepezil in combination with nimodipine in VaD, but as the results of these studies were derived from small single-center studies, there has been no systematic evaluation of donepezil in combination with nimodipine in the treatment of VaD. Therefore, we designed this study to provide a higher level of evidence-based clinical use of donepezil hydrochloride in combination with nimodipine for the treatment of VaD through systematic evaluation.

The results of this study show that donepezil combined with nimodipine can better improve the MMSE score, ADL score, and CDR score of patients with vascular dementia. Sensitivity

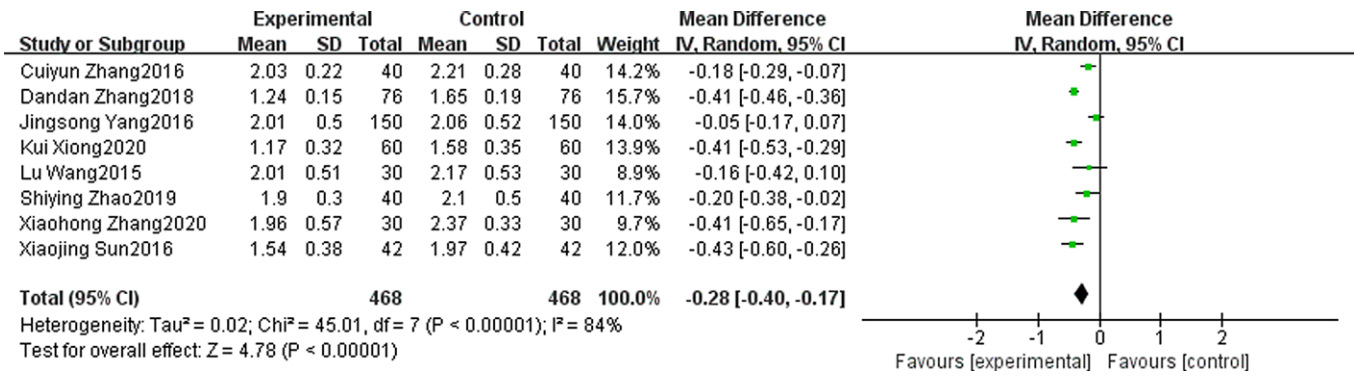

Figure 10. The forest plot of CDR. CDR = clinical dementia scale.

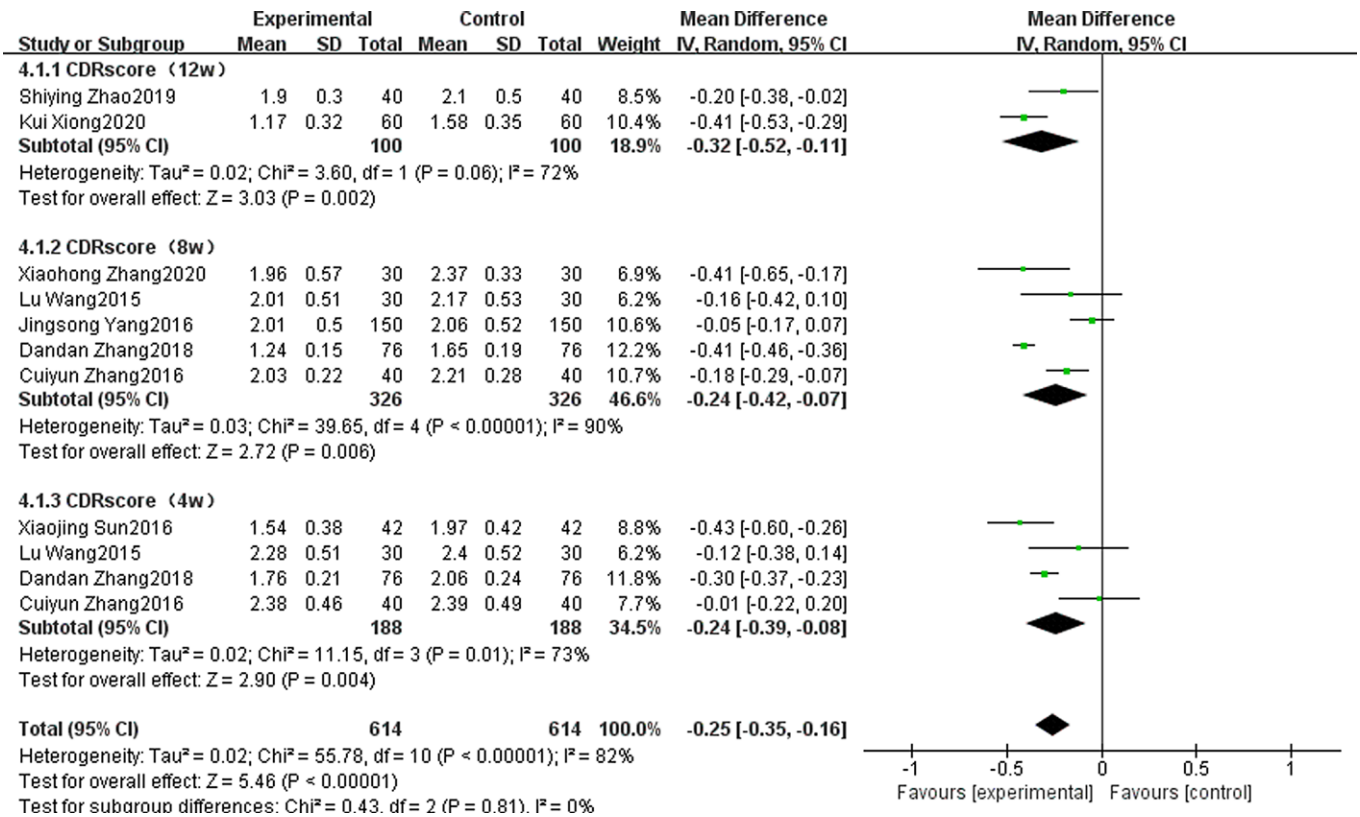

Figure 11. The forest plot of CDR (subgroup analysis by duration of treatment 12, 8, and 4 weeks). CDR = clinical dementia scale.

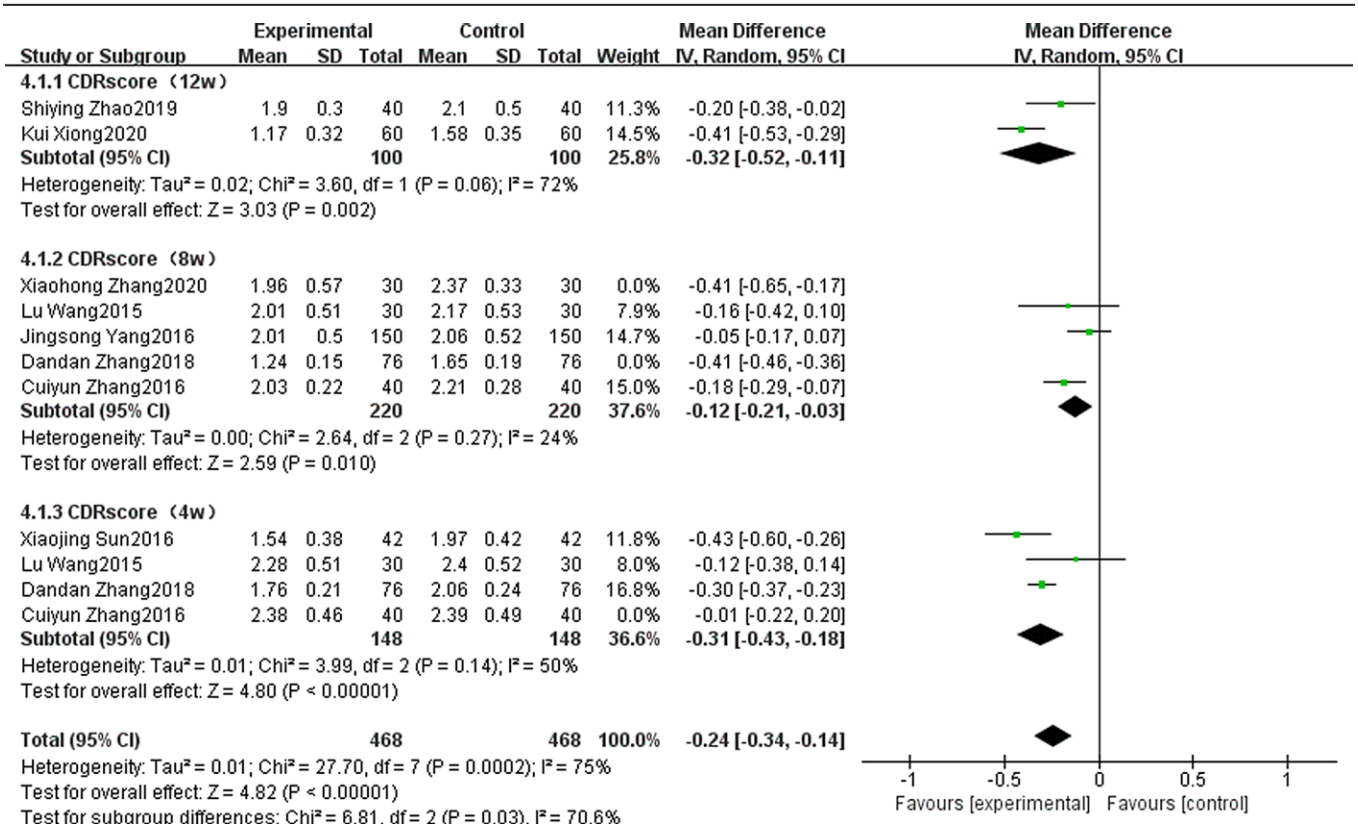

Figure 12. Sensitivity analysis of CDR. CDR = clinical dementia scale.

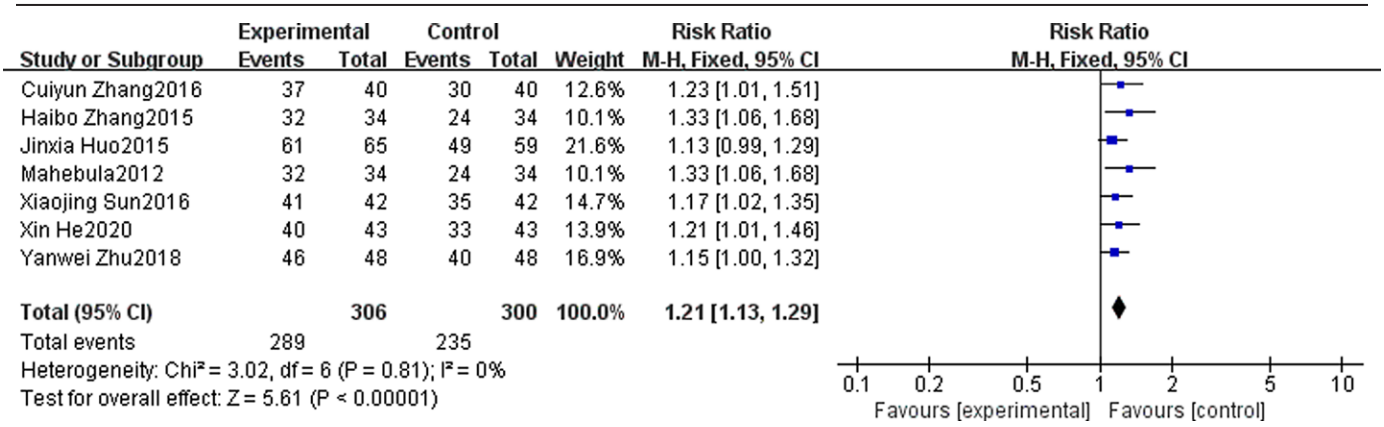

Figure 13. The forest plot of curative effect.

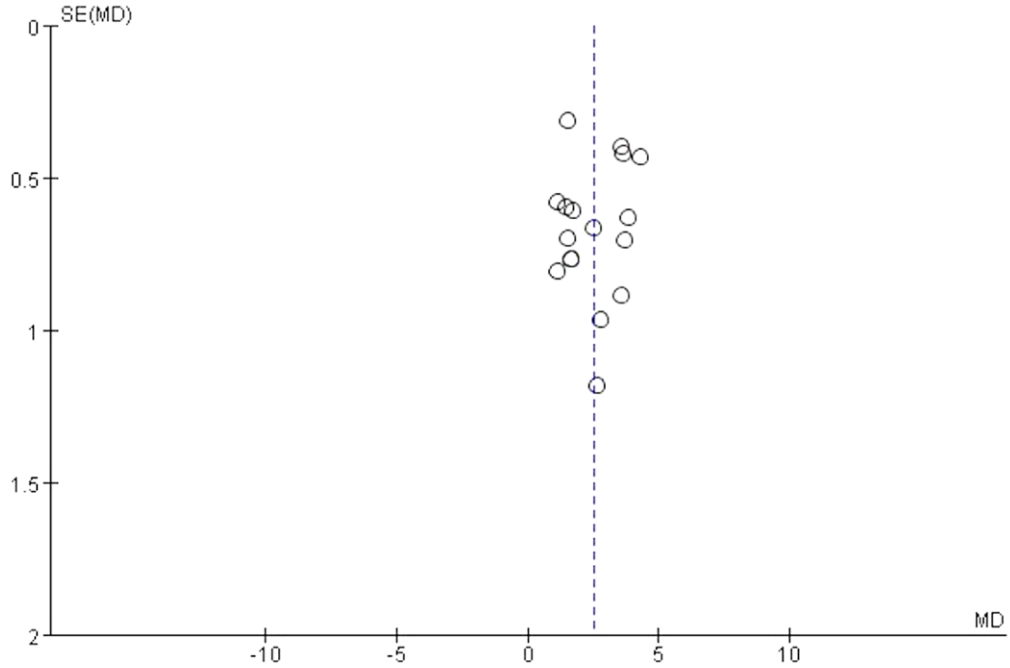

Figure 14. The funnel plot of MMSE scale scores before and after treatment. MMSE = mini-mental state examination.

analysis had proven efficacy is considered most satisfactory after 12 weeks of intervention. The possibility of publication bias perceived in this study is relatively lower.

Certain limitations are pertained to this meta-analysis: the quality of research methodologies included were relatively low, certain heterogeneity remained beyond explanations, the lack of strong evidence. The result should be clinically evaluated with cautiousness. The sample size of the respective studies is generally small, this may affect the authenticity of the research. Methodology of certain studies included was not explained in detail, this may contribute to a certain risk of bias. Therefore the above results should be perceived with cautious.

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Author contributions

All the authors have contributed to the topic selection, design, data retrieval, extraction, analysis, interpretation and drafting. Ai-hua Tan and Qiang Yang conceived the study. Si-miao Ran, Jia Liu, and Kai-lin Huang were responsible for the screening and data extraction and analysis of the literature; Jia Liu and Miyuan Wang drafted the draft; Guang-yao Wang interpreted and edited the analysis results; Ai-hua Tan and Si-miao Ran were responsible for writing the manuscript. All authors agree to the publication of this manuscript and agree to be responsible for it. Qiang Yang, Jia Liu and Kai-lin Huang are contribute equally to the article.

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References

[1] Wolters FJ, Ikram MA. Epidemiology of vascular dementia. Arterioscler Thromb Vasc Biol 2019;39:1542–9.
[2] Zhuo M, Yue CH, Wan-yu F. System review of efficacy of donepezil in treatment of vascular dementia. Chin J New Drugs 2013;22:569–76.
[3] Tao CH, Ling L, Deng CH, et al. Efficacy and safety of nimodipine in treatment of vascular dementia: a systematic review. Chin J Contemp Neurol Neurosurg 2015;15:546–53.

[4] Bing L, Dongmei L, Yin Zh. Efficacy of the combination of donepezil and nimodipine in the treatment of vascular dementia. Chin J Gerontol 2020;40:3279–81.
[5] Tao-zuo Zh. Clinical observation of 72 cases of vascular dementia patients treated with donepezil combined with nimodipine. Chin J Integr Med Cardio-/Cerebrovasc Dis 2020;18:1663–4.
[6] Qing-guo R, Bing L, Xiang-shui M. Overview of clinical diagnostic criteria for vascular cognitive impairment. J Pract Med 2019;35:1–3.
[7] Aftab RA, Sellappans R, Ming CK, et al. Taking a step further in identifying ideal blood pressure range among hemodialysis patients: a systematic review and a meta-analysis. Front Pharmacol 2020;11:1–8.
[8] Cui-yun Zh, Zu-neng L, Jun-jian Zh, et al. Effects of donepezil hydrochloride combined with nimodipine on cognitive function and self-care ability in patients with vascular dementia. Chin J Clin Healthcare 2016;19:236–9.
[9] Jin-xia H, Li-ping Z, Wen-feng L. Study on the efficacy of donepezil hydrochloride in combination with nimodipine in 65 cases of vascular dementia with moderate to severe mental retardation in the elderly. China Pharma 2015;24:65–7.
[10] Hai-bo Z, Yan L. Efficacy of donepezil hydrochloride in combination with nimodipine in 34 cases of vascular dementia in the elderly. World Latest Med Inform 2015;15:102–3.
[11] Bula M. Efficacy of donepezil hydrochloride in combination with nimodipine in 34 cases of vascular dementia in the elderly. Chin J Ethnomed Ethnopharm 2012;21:96–8.
[12] Lu W, Rong F, Jing Zh, et al. Efficacy of donepezil hydrochloride in combination with nimodipine in the treatment of vascular dementia. J Guiyang Med Coll 2015;40:291–3.
[13] Jin-song Y. Efficacy of donepezil hydrochloride in combination with nimodipine in the treatment of vascular dementia. Women's Health Res 2016;14:179–84.
[14] Zhi-qiang W. Efficacy and safety evaluation of donepezil hydrochloride in combination with nimodipine in the treatment of vascular dementia. Chin J Pract Nerv Dis 2014;17:96–7.
[15] Yan-wei Zh. Study of the efficacy of donepezil hydrochloride in combination with nimodipine in the treatment of vascular dementia. Clin Med Eng 2018;25:883–4.
[16] Mahemmuti E. Clinical observation of donepezil hydrochloride combined with nimodipine in the treatment of vascular dementia. Guide China Med 2013;11:245–6.
[17] Xin H. Clinical effects of donepezil hydrochloride in combination with nimodipine in the treatment of vascular dementia. China Mod Med 2020;27:80–2.
[18] Xia W, Zhuo-yan L, Hui-fang L. Clinical observation of donepezil hydrochloride combined with nimodipine in the treatment of vascular dementia. Clin Focus 2012;27:482–4.
[19] Xiao-jing S. Effectiveness of donepezil hydrochloride in combination with nimodipine in the treatment of vascular dementia. China Continu Med Educ 2016;8:134–5.
[20] Xiao-hong Zh. Analysis of donepezil hydrochloride combined with nimodipine in the treatment of vascular dementia and its effect on self-care ability in daily life. Med Aesthet Beauty 2020;29:92.
[21] Kui X. Effect of nimodipine combined with donepezil hydrochloride on the degree of dementia and cognitive function in patients with vascular dementia. J Clin Ration Drug Use 2020;13:73–5.
[22] Yang-qin K, Kun H, Yong-rong L. The effect of donepezil hydrochloride combined with nimodipine on the improvement of cognitive function in patients with vascular dementia. Contemp Med 2017;23:84–6.
[23] Dan-dan Zh, Yong L, Zu-yu Zh, et al. Effectiveness of donepezil hydrochloride in combination with nimodipine in the treatment of vascular dementia. Shandong Med J 2018;58:64–6.
[24] Shi-yin Zh. Analysis of the effect and incidence of adverse effects of donepezil hydrochloride in combination with nimodipine in the treatment of vascular dementia. J Mathem Med 2019;32:719–21.
[25] Yong-wei Zh. Efficacy and safety analysis of donepezil hydrochloride combined with nimodipine in the treatment of vascular dementia symptoms. World Latest Med Inform 2017;17:79–80.
[26] Erkinjuntti T, Román G, Gauthier S, et al. Emerging therapies for vascular dementia and vascular cognitive impairment. Stroke 2004;35:1010–7.
[27] Wang X, Zhang B, Xia R, et al. Inflammation,apoptosis and autophagy as critical players in vascular dementia. Eur Rev Med Pharmacol Sci 2020;24:9601–14.
[28] Li Y. Neuroprotective Effects of Nimodipine and Catalpol. 2009; China Dalian University of Technology, Dalian, China.