Systematic Review and Meta-Analysis

Medicine

OPEN

Acupuncture and related therapies for diabetic retinopathy

A systematic review and network meta-analysis

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Abstract

Background: Diabetic retinopathy (DR) is a significant long-term consequence of diabetes mellitus and is the primary cause of blindness in people of working age. Although acupuncture (AC) and medication are effective, the optimal treatment regimen for DR remains to be further defined. Consequently, we conducted a network meta-analysis to compare the efficacy of AC and the related treatments with that of medicines for DR.

Methods: We searched 8 academic electronic databases for randomized controlled trials published before December 1, 2023. The main outcome was the overall effective rate, and the secondary outcomes were the best corrected visual acuity and the central fovea of macula thickness. Two independent researchers identified eligible studies and collected data using pre-made forms. We conducted a network meta-analysis within a Bayesian framework to compare different interventions. The assessment of risk of bias and quality of literature was conducted using the risk of bias assessment tool recommended by the Cochrane Risk of Bias Tool 2 and the Jadad scale. Intervention ranking probabilities for all treatments were performed using the surface under the cumulative ranking curve.

Results: Twenty-eight studies published between 2012 and 2023 were included, involving 2801 patients. Interventions included AC, traditional Chinese medicine (TCM), electroacupuncture (EA), acupoint injections, and calcium dobesilate. In terms of the overall effective rate, EA + AC + TCM was the best treatment ($P < .05$) and for the best corrected visual acuity, AI + TCM was the best treatment ($P < .05$). In terms of the central fovea of macula thickness, AC + TCM was the best treatment ($P < .05$). An integration of AC and the related treatments is more effective than a single therapy.

Conclusion: EA combined with AC combined with TCM may be the most effective treatment for DR. AC and the related treatments have significant efficacy in treating DR, improving vision, and reducing macular edema with relatively few adverse effects. The use of integrative therapies combining AC and its related therapies can be promoted.

Abbreviations: CI = confidence intervals, AC = acupuncture, AGEs = advanced glycation end products, AI = acupoint injections, CD = calcium dobesilate, DR = diabetic retinopathy, EA = electroacupuncture, I2 = Cochran's I-square, MCMC = Monte Carlo Markov chains, MD = mean difference, NMA = network meta-analysis, RCTs = randomized controlled trials, RR = relative risks, SUCRA = surface under the cumulative ranking, TCM = traditional Chinese medicine.

Keywords: acupuncture, Bayesian network meta-analysis, diabetic retinopathy, systematic review

1. Introduction

Diabetic retinopathy (DR) is a common chronic microvascular consequence of diabetes. As the number of people with diabetes has increased, the prevalence of DR and the number of people with the disease have risen at the same time. The global prevalence of DR reached 103.12 million adults in 2020, and it is estimated to rise by 57.4 million individuals from 2020 to 2045.[1] DR is the major factor contributing to adult blindness and visual impairment aged 20 to 74 years globally, especially in economically developed countries.[2] Blindness due to

S-JC and Z-YZ contributed to this article equally.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

All participants included in the original RCT of this study have signed an informed consent form, which was reviewed and allowed by the local ethics committee. All data were anonymized and made publicly available for researchers. All data and analysis in this study will comply with all relevant laws and standards. Written informed consent and ethics committee review will not be required for this study.

Supplemental Digital Content is available for this article.

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How to cite this article: Che S-J, Zhang Z-Y, Wang S-A, Hu X-Y, Xu Y-H, Li L. Acupuncture and related therapies for diabetic retinopathy: A systematic review and network meta-analysis. Medicine 2025;104:20(e42431).

Received: 25 January 2024 / Received in final form: 4 August 2024 / Accepted: 24 April 2025

http://dx.doi.org/10.1097/MD.0000000000042431

DR is the only reason for the increase in the prevalence of age-standardized blindness in the last 30 years.[3] The development of DR greatly affected the quality of life of patients and brought a heavy economic burden. Direct medicare costs associated with DR in the U.S. in 2019 are estimated at $2.025 billion/yr.[2] Based on the cost of illness modeling, Indonesia is expected to invest a total of US$8.9 billion towards healthcare for DR in 2025.[4] Early screening as well as intervention in DR is important as it can effectively stop the progression of the disease and improve the prognosis.

The clinical features of DR are fundus microaneurysms, retinal hemorrhages, cotton wool version, hard exudates, and macular edema. At present, the treatment of DR is mainly based on controlling risk factors. On the basis of controlling blood glucose, blood pressure, and serum lipids, vasoprotective drugs, antioxidant drugs, and anti vascular endothelial growth factor drugs are applied.[5,6] Surgical treatments such as retinal laser photocoagulation and vitrectomy are used in patients with proliferative DR and diabetic macular edema.[7] However, there are limitations to the main treatment options currently available. Calcium dobesilate (CD) is widely used as a vasoactive and vasoprotective drug in the treatment of DR. CD is associated with adverse effects such as fever, gastrointestinal reactions, and granulocyte deficiency,[8] and studies have shown that not all DR patients benefit from CD.[9] There is a risk of disease progression, traction retinal detachment, or neovascular glaucoma if antivascular endothelial growth factor therapy is interrupted.[7] Choroidal detachment, elevated intraocular pressure, macular cystoid edema, and a decrease in the patient's peripheral vision, color vision, and night vision may occur after retinal laser photocoagulation treatment.

Acupuncture (AC) is a widely used complementary and alternative medicine. AC and its related treatments are widely used for ophthalmic diseases, including macular degeneration, dry eye, glaucoma and optic nerve atrophy.[10] Studies have shown that AC and its related therapies can effectively lower blood glucose, enhance insulin sensitivity, modulate inflammation-related factors, and reduce inflammatory responses.[11–13] AC and its related therapies are safe, low-cost treatments with few side effects. Investigation has demonstrated that AC and related therapies can improve vision, reduce macular edema, play an important role in the treatment of DR, and improve patients' quality of life.[10,14] The effectiveness of AC and the related treatments in ophthalmic diseases has been demonstrated, and further studies are still needed to compare the effectiveness and safety of AC and the related treatments in the management of DR. Based on this, we conducted a network meta-analysis (NMA) comparing AC and its related therapies for treating DR. The objective was to assess the effectiveness of various therapies for DR and to provide a theoretical foundation for clinical treatment options for Dr

2. Materials and methods

The investigation has been registered on the PROSPERO system with the registration number: CRD42024501856. This NMA was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension Statement for systematic reviews and meta-analyses,[15] and the full Preferred Reporting Items for Systematic Reviews and Meta-Analysis list is presented in the Supplementary Material S1, Supplemental Digital Content, https://links.lww.com/MD/O886.

2.1. Search strategies

Eight academic databases were searched from the time of library construction to December 1, 2023, including Pubmed, Embase, Cohrance Library, Web of Science, China National Knowledge Infrastructure, Vip Information, Wanfang Database, and China Biomedical Literature Service System. The detailed search methodology is described in the Supplementary Material S2, Supplemental Digital Content, https://links.lww.com/MD/O886.

2.2. Eligibility criteria

1 Study type: The randomized controlled trials (RCTs) of AC-related treatment for DR with language restriction to Chinese and English.
2 Participants: Patients diagnosed with DR according to an international[16] or Chinese diagnostic standard[17] based on fundus fluorescein angiography and fundus photography.
3 Interventions: In the treatment group, interventions included AC-related therapies (AC, electroacupuncture [EA], and acupoint injections [AI]) or AC combined with other treatments (basic Western medicine, traditional Chinese medicine [TCM]). The control group intervention was another AC-related therapy or medication (no restriction on time or duration of AC).
4 Outcomes: The outcome event must contain at least one of the subsequent: overall effective rate, best corrected visual acuity, and central fovea of macula thickness. Adverse events were also recorded.
5 Exclusion criteria: Literature review, animal experiment, case report, meta-analysis, protocol, and other such types of literature were excluded.

2.3. Definition of outcome events

The primary outcome event was the overall effective rate, which was assessed on the basis of the number of patients with improved best-corrected visual acuity and retinal vascular abnormalities. The overall effective rate is defined as the sum of the number of significant effective persons and the number of effective persons divided by the total number of persons. The definitions of significant effect, effective, and ineffective were as follows: significant effect: visual acuity improved by ≥ 2 lines, and there was a decrease in the score of 2 or more of the 3 symptoms with no increase in the score of the other symptom; effective: 2 > 1 line of visual acuity improvement, a decrease in the points of 1 of the 3 symptoms and no increase in the points of the other 2 symptoms; ineffective: visual acuity did not improve or decrease, and the fundus did not show any significant change compared with the pretreatment period. The scoring criteria for retinal vascular abnormalities were developed in accordance with the "Guidelines for Clinical of New Drugs Research in Chinese Medicine,"[18] as described in the Supplementary Material S3, Supplemental Digital Content, https://links.lww.com/MD/O886. Measurement and improvement of best-corrected visual acuity was assessed by clinicians in accordance with the "Guidelines for Clinical of New Drugs Research in Chinese Medicine"[18] or the "Diagnostic Efficacy Criteria for Chinese Medicine Internal Medicine Diseases."[19] The thickness of the central fovea of macula is assessed by the physicians through fundus photography examination.

2.4. Data collection and extraction

Two researchers independently extracted relevant information and screened it. After excluding duplicates, the title and abstract of the other literature were read. Following the inclusion and exclusion criteria, the literature was thoroughly reviewed to determine which ones should be included. Two independent researchers extracted the data that were ultimately included in the study, extracting information such as: authors, publication

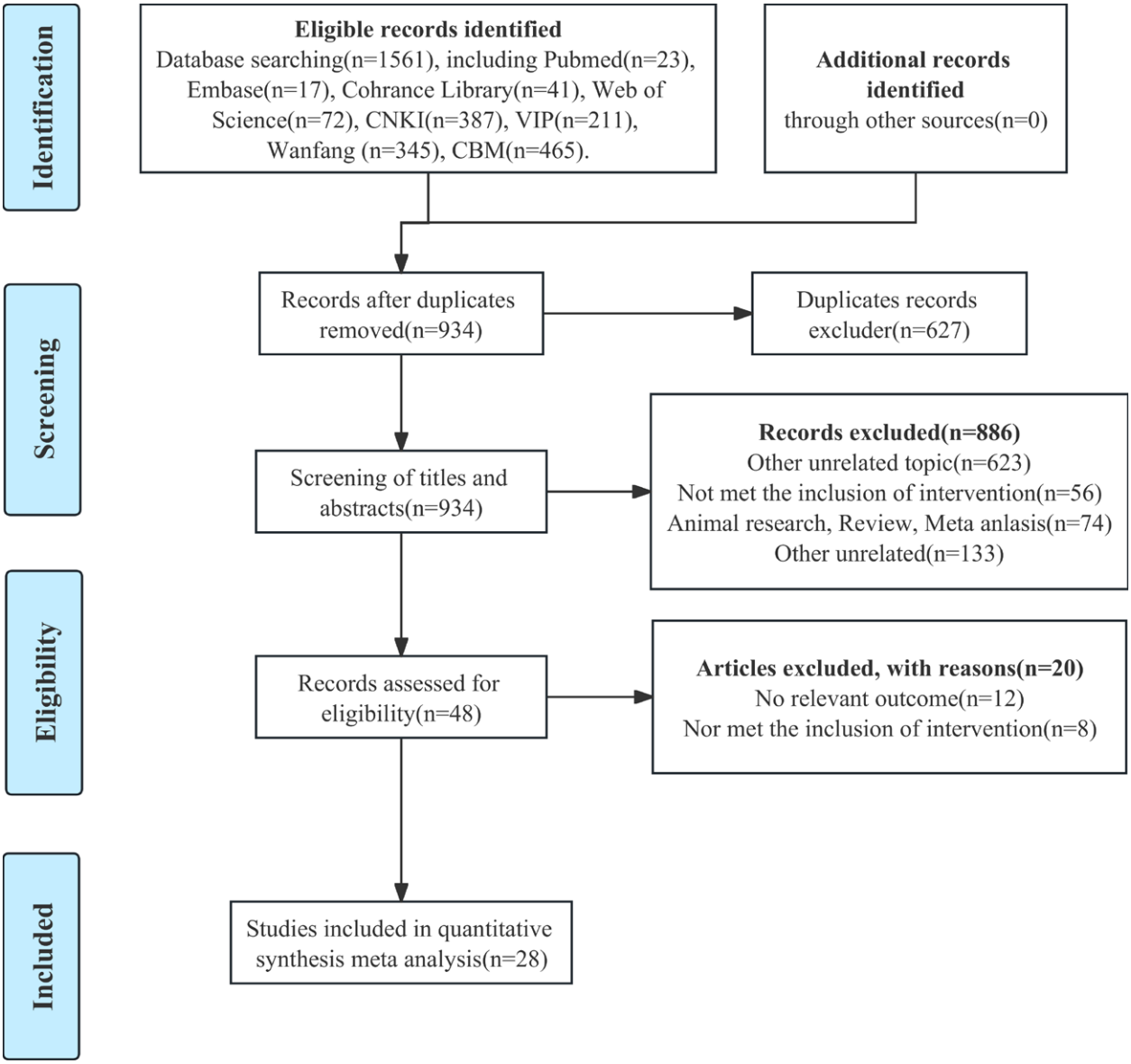

Figure 1. Flow chart of study selection.

year, country of research, intervention, demographic characteristics, sample size, and outcome events. Disagreements that arose during the process were discussed together with a third researcher.

2.5. Quality assessment

Two independent investigators evaluated the risk of bias of the studies included in the review using Review Manager 5.3 software according to the Risk of Bias Tool 2 recommended in the Cochrane manual.[20] The risk of bias of the included research was evaluated in 7 dimensions: randomized sequence generation, allocation concealment, use of participant blinding, use of outcome evaluator blinding, outcome data completeness, selective reporting, and other biases. Risk of bias was categorized as high, low, or unclear risk. Two investigators independently assessed the quality of the included research using the Jadad scale.[21] The quality of the literature was evaluated according to randomization, blinding, and reporting of dropouts and lost visits. The detailed Jadad scale is shown in the Supplementary Material S4, Supplemental Digital Content, https://links.lww.com/MD/O886. Two researchers evaluated independently and disagreement was discussed with a third researcher.

2.6. Statistical analysis

The binary variables were examined using relative risks (RR) and 95% confidence intervals (95% CI), and the continuous variables were examined with mean difference (MD) and 95% CI. Heterogeneity was tested using Cochran's *I*-square (I^2). The process of pairwise meta-analysis was conducted utilizing Review Manager 5.3 software. The fixed effects model was applied to the analysis when $I^2 < 50$, and the random effects model was applied when $I^2 > 50$.

NMA was performed using R software and Stata 12.0 software to analyze the effectiveness of different interventions for DR. Network evidence plots were generated using the "mvmeta" package of the Stata 12.0 software, and when closed loops existed in the network plots, the node splitting approach was used to contrast the inconsistency among indirect as well as direct comparisons. Monte Carlo Markov

Table 1

Characteristics of the included studies.

Study ID	Country	Sample size (T/C)	Age (yr, T/C)	Duration of treatment (mo)	Intervention: Treatment	Intervention: Control group 1	Intervention: Control group 2	Outcomes	Jadad
Fan-Ning Liu[24]	China	32/33	56.47 ± 8.504/59.42 ± 8.058	1	AC + TCM	TCM	–	①②④	2
Xiao-Ru Ma[38]	China	57/60	52.1 ± 7.42/52.13 ± 8.12	1	AC	EA	–	①②	4
Feng Yuan[25]	China	41/41/41	54 ± 6/52 ± 6/53 ± 6	1	AC	TCM	AC + TCM	①	3
Yun Zhao[39]	China	55/56	56.12 ± 5.15/54.36 ± 4.95	1	AC + CD	CD	–	②④	3
Jun-Yu Sheng[26]	China	77/78	63.25 ± 6.5/64.18 ± 5.51	3	AC + TCM	CD	–	①②④	2
Cheng Meng [41]	China	40/40	59 ± 5/56 ± 6	3	AC + CD	CD	–	②③	3
Neng Li[28]	China	41/41	NR	2	AC + TCM	TCM	–	①②③④	3
Kun Nie[40]	China	80/76	55 ± 6/54 ± 6	1	AC + TCM	TCM	–	①	3
Chen Meng[41]	China	40/40	60.960 ± 7.738/58.783 ± 6.802	1	AC	EA	–	①②	3
Hai-Qin Wang[30]	China	40/40	56.92/56.31	1	AC + TCM	TCM	–	①④	3
Xi-Qiang Lou[42]	China	64/64	69.10 ± 2.35/67.72 ± 3.53	0.3	AC + CD	CD	–	①	1
Wen-Tao Feng[43]	China	88/86	54. 57 ± 7. 51/54. 51 ± 7. 47	4	AC + CD	CD	–	①②	1
Xiao-Yan Yuan[48]	China	43/43	57. 38 ± 8. 97/57. 45 ± 8. 69	1	AI + TCM	AI	–	①	3
Cun-Liang Shi 2020[49]	China	68/68	52.49 ± 7.94/52.64 ± 8.64	1.5	AI + TCM	TCM	–	①②	3
Li-Na Zhou[31]	China	36/36	47.2 ± 4.0/46.7 ± 4.1	1.5	AC + TCM	TCM	–	①	2
Hai-Ye Guo[32]	China	65/65	49.64 ± 10.50/49.93 ± 10.68	3	AC + TCM	TCM	–	①②③	3
Shi-Zhong Zhang[50]	China	60/60	60.02 ± 4.11/60.04 ± 4.13	1.5	AI + TCM	AI	–	①	1
Yong Wang[44]	China	79/80	54.2 ± 6.5/54.4 ± 6.2	1	AC + CD	CD	–	①②	1
Jun-Peng Ren[33]	China	94/90	45.19 ± 3.38/45.28 ± 3.41	1	AC + TCM	CD	–	①②③④	1
Da-Zhen Zhang[34]	China	30/30	60.64 ± 10.09/53.53 ± 9.80	1	EA + AC + TCM	AC + TCM	–	①②	1
Le-Jun Cao[35]	China	66/66	54.67 ± 11.20/55.48 ± 11.13	1.5	AC + TCM	TCM	–	①②④	1
Zeng-Qiang Zhao[45]	China	48/48	56.2 ± 5.8/55.7 ± 6.4	1	AC + CD	CD	–	①	2
Xiao-Hong Xu[51]	China	42/42	52. 5/53	1	AI + TCM	TCM	–	①	3
Jiang-Xia Zhou[36]	China	40/36	50.74/51.15	1	AC + TCM	CD	–	①②	1
Fei-Xue Dong[37]	China	30/30	57.25 ± 9.52/61.53 ± 8.25	1	EA + TCM	TCM	–	①②	3
Zhi-Yan Wang[46]	China	34/34	46–59/45–57	0.5	AC	TCM	–	①	1
Li-Xia Shang[47]	China	34/34	56.06 ± 5.71/56.32 ± 5.85	2	AC + AI	AI	–	①	1

①Total effective rate; ②Best corrected visual acuity; ③Central fovea of macula thickness; ④Adverse event rate.

AC = acupuncture, AI = acupoint injections, C = control group, CD = calcium dobesilate, EA = electroacupuncture, NR = not report, T = treatment group, TCM = traditional Chinese medicine.

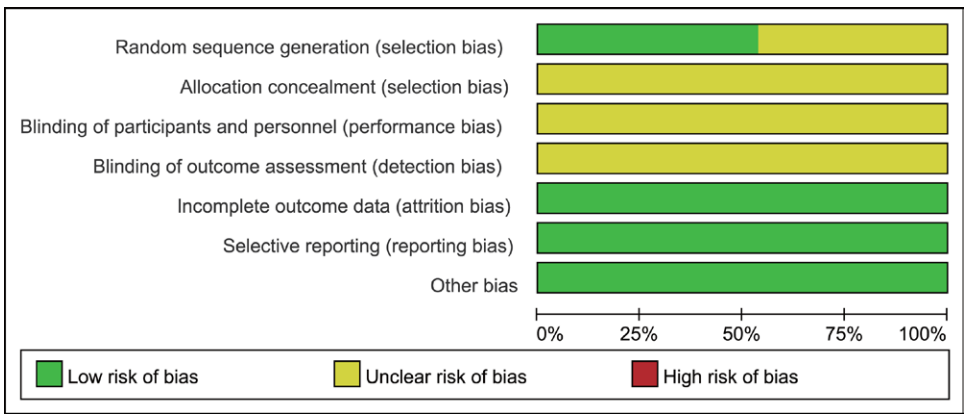

Figure 2. Potential risk of bias of included studies.

Chains (MCMC) were integrated with consistency modeling for NMA within the framework of Bayesian theory.[22] A 4 chains model of MCMC was built with 30,000 annealing times and 50,000 times of iterations, and the convergence effect of the NMA results was judged according to the Potential Scale Reduction Factor potential scale contraction factor. Two-by-two comparison tables were created to show the results of the final comparisons, using the surface under the cumulative ranking (SUCRA) value to assess the interventions. The larger the SUCRA value, the greater the likelihood that the intervention was the best, and a cumulative probability line graph was plotted to visualize the ranking of the interventions.[23] Finally, corrected funnel plots were generated using Stata 12.0 software to evaluate for the publication bias as well as the small sample effects.

2.7. Ethical approval

This study was a NMA based on published studies of RCTs and did not require ethical approval. Informed consent was obtained from the included patients for the RCTs included in this study and the data were anonymised. This study relied on the analysis of published data and therefore did not require ethical approval or informed consent.

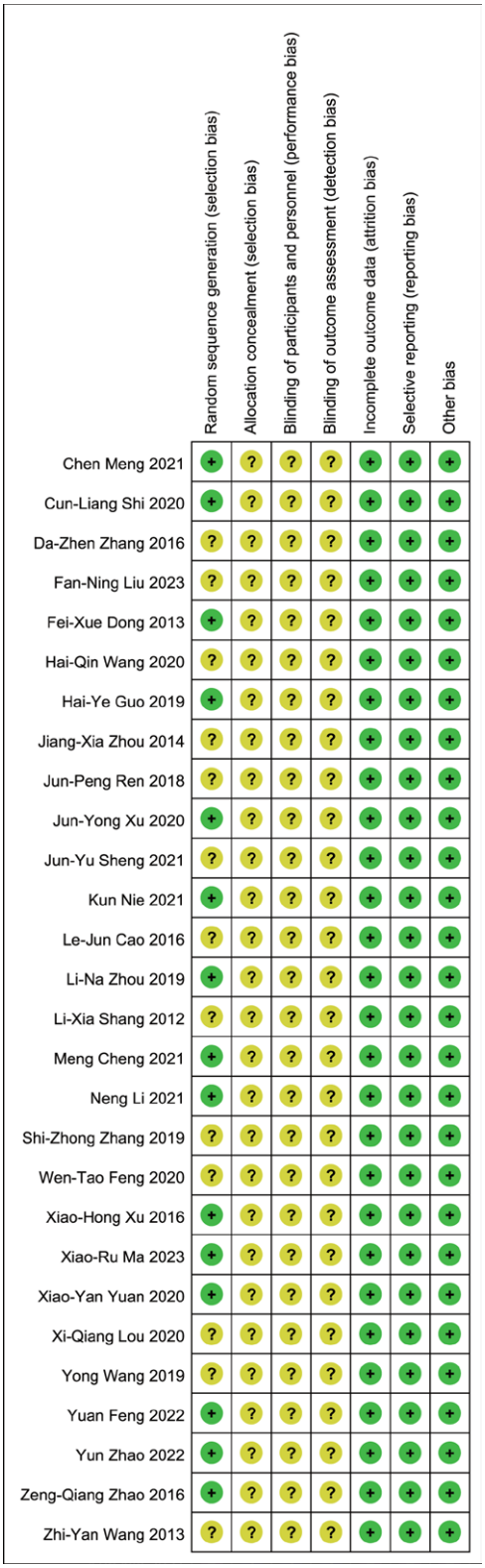

Figure 3. Risk of bias graph.

3. Result

3.1. Literature search

Based on the predefined search strategy, an overall of 1561 literature were retrieved and 28 RCTs[24–51] were finally included. The detailed inclusion and the procedure of screening is shown in Figure 1.

3.2. Characteristics of the included studies

The basic characteristics of the 28 literature are shown in Table 1. After meticulous reading and screening, a total of 28 RCTs were included, which were published between 2012 and 2023. All research were carried out in China and included an overall of 2801 patients with DR. All participants received different interventions on top of the basal treatment (defined as control of blood glucose, blood pressure, and serum lipids). The treatment group obtained interventions such as AC, EA, AI, and TCM; interventions in the control group included CD (the basic treatment regimen for DR), TCM, and AC-related therapies. The above treatments could be used alone or in combination. Excluding 2 studies that did not report the mean age,[28,46] the average age of the included patients ranged from 46 to 69 years. The 28 studies included sample sizes ranging from 30 to 94. One study was a 3-armed trial[25] and the remaining 27 studies were 2-armed. The intervention period in these trials varied from 0.3 to 4 months.

3.3. Risk of bias for research quality evaluation

The detailed quality assessment results of the 28 included literature are presented in Figure 2. Fifteen studies mentioned the use of a randomized table of numbers, while the remaining 13 mentioned only "random" without specifying the method of allocation. All studies mentioned completeness and nonselectivity of outcome data reporting were assessed as having a low risk, but did not mention allocation concealment were assessed as unclear risk. None of the studies mentioned whether participants and outcome assessors were blinded and were classified as having an unclear risk. The literature was assessed for whether they had funding source bias, publication bias, duplicate publication bias, baseline imbalance bias, design bias, and analytical bias, and 15 studies were assessed as being at low risk for other bias. In general, all the included investigations were determined to have a low risk of bias. The risk of bias summary results are shown in Figure 3. The quality of the included literature was assessed with the Jadad scale, and 14 studies were classified as having a low quality (1–2 points), 12 studies were classified as having a medium quality (3 points), and 1 study was classified as having a high-quality (4–5 points; Table 1).

3.4. Pairwise meta-analysis results

There were 26 studies that examined the overall effective rate among AC and related therapies combined with TCM and control groups. We performed 11 pairwise meta-analyses, and detailed comparative results are presented in the Supplementary Material S5, Supplemental Digital Content, https://links.lww.com/MD/O886. Compared with CD, AC + TCM (3 RCTs, RR = 1.25, 95% CI = 1.12–1.39, I^2 = 33%, P < .001) and AC + CD (4 RCTs, RR = 1.20, 95% CI = 1.10–1.30, I^2 = 0%, P < .001) were more effective in increasing the overall effectiveness rate. Compared with TCM, AC + TCM (9 RCTs, RR = 1.29, 95% CI = 1.21–1.37, I^2 = 4%, P < .001) and AI + TCM (2 RCTs, RR = 1.32, 95% CI = 1.15–1.51, I^2 = 21%, P < .001) were more effective in increasing the total effective rate. AI + TCM (2 RCTs, RR = 1.22, 95% CI = 1.07–1.40, I^2 = 0%, P = .003) and AI + AC (1 RCTs, RR = 1.36, 95% CI = 1.03–1.80, P = .03) can better increase the effective rate than treatment with AI alone. There was no significant statistical difference in pairwise meta-analysis among several treatments of AC + TCM, AC, EA + AC + TCM, TCM, EA, and EA + TCM. In general, AC-related integrative therapies were superior to single treatments in improving the overall effective rate.

In improving the best corrected visual acuity, the efficacy of AC + TCM (4 RCTs, MD = 0.13, 95% CI = 0.10–0.17, I^2 = 0%, P < .001), AI + TCM (1 RCTs, MD = 0.21, 95% CI = 0.13–0.29, P < .001), and EA + TCM (1 RCTs, MD = 0.11, 95%

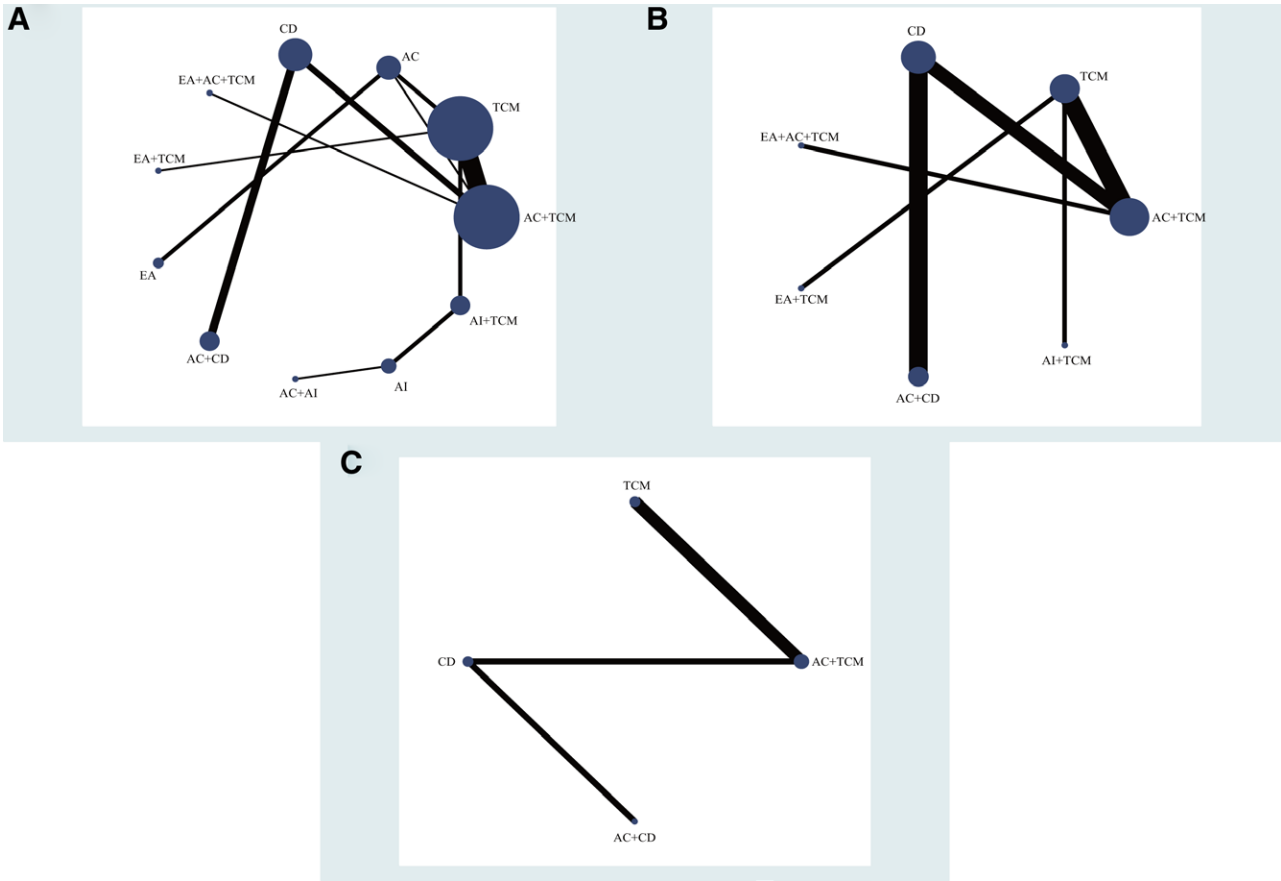

Figure 4. Network plot for different outcome events. (A) Overall effective rate; (B) best corrected visual acuity; (C) central fovea of macula thickness. AC = acupuncture, AI = acupoint injections, CD = calcium dobesilate, EA = electroacupuncture, TCM = traditional Chinese medicine.

CI = 0.01–0.21, I^2 = 0%, P = .04) was more effective than the use of TCM alone. The efficacy of AC + TCM (3 RCTs, MD = 0.15, 95% CI = 0.10–0.20, I^2 = 65%, P < .001) was superior to that of CD alone. There was no statistically significant difference when comparing AC + TCM with EA + AC + TCM, AC + CD with CD (Supplementary Material S6, Supplemental Digital Content, https://links.lww.com/MD/O886).

For reducing the thickness of the central fovea of macula, AC + TCM (2 RCTs, MD = −28.51, 95% CI = −50.52 to −6.49, I^2 = 86%, P = .01) was more effective than TCM. AC + TCM (1 RCTs, MD = −17.26, 95% CI = −23.37 to −11.15, P < .001) and AC + CD (1 RCTs, MD = −14.72, 95% CI = −23.60 to −5.84, P = .001) were more effective than CD (Supplementary Material S7, Supplemental Digital Content, https://links.lww.com/MD/O886).

3.5. Network evidence plot

This study comprised 28 studies of AC and related treatments for DR, of which 26 reported overall effective rate and involved 11 interventions. Sixteen studies reported posttreatment best-corrected visual acuity, and 4 studies reported posttreatment thickness of central fovea of macula. The network diagram of the 3 outcome events is displayed in Figure 4. The dimensions of the blue circle are directly proportional to the sample size, while the thickness of the black line is directly proportional to the quantity of 2-by-2 comparisons.

3.6. Convergence diagnosis

The NMA was conducted using the MCMC algorithm and consistency modeling. Convergence diagnostic plots are shown in the Supplementary Material S8, Supplemental Digital Content, https://links.lww.com/MD/O886, where the median and 97.5% values of the reduction factor stabilize after 50,000 iterations, and the parameter potential scale reduction factor move close to 1, indicating good convergence of the model.

3.7. Network meta-analysis of overall effective rate

The NMA results indicated the overall effective rate of AC + TCM, EA + AC + TCM, and AC + CD were superior to CD. Several combined treatment regimens, AC + TCM, EA + AC + TCM, EA, AC + CD, and AI + TCM had better overall effective rate than the application of TCM or CD treatment alone. Detailed results are presented in Table 2.

We ranked the different interventions according to their SUCRA values, with a larger SUCRA suggesting a more effective intervention. The results showed that the 11 interventions were ranked, in descending order, as EA + AC + TCM, AC + AI, AI + TCM, AC + CD, AC + TCM, EA, EA + TCM, AC, CD, and TCM. The SUCRA line graph is displayed in Figure 5A.

3.8. Network meta-analysis of best corrected visual acuity

The NMA results for best corrected visual acuity are presented in Table 3, with no statistically significant differences in comparisons between the various interventions.

The SUCRA results showed that AI + TCM was the best intervention to improve best-corrected visual acuity, and the probability ranking line graph is shown in Figure 5B.

Table 2

Results of network meta-analysis for total effective rate.

AC + TCM										
4.48 (3.03, 6.81)	TCM									
2.65 (1.08, 6.52)	0.59 (0.25, 1.34)	AC								
2.69 (1.58, 4.68)	0.6 (0.31, 1.18)	1.02 (0.35, 2.91)	CD							
0.33 (0.05, 1.49)	**0.07 (0.01, 0.34)**	**0.13 (0.02, 0.72)**	**0.12 (0.02, 0.59)**	EA + AC + TCM						
2.81 (0.68, 11.93)	0.63 (0.16, 2.46)	1.06 (0.22, 5.12)	1.04 (0.23, 4.61)	**8.62 (1.09, 88.79)**	EA + TCM					
1.46 (0.47, 4.46)	**0.33 (0.11, 0.92)**	0.55 (0.29, 1.05)	0.54 (0.16, 1.9)	4.43 (0.69, 36.61)	0.52 (0.1, 2.9)	EA				
1.04 (0.51, 2.15)	**0.23 (0.1, 0.53)**	0.4 (0.12, 1.3)	**0.39 (0.24, 0.62)**	3.2 (0.61, 21.95)	0.37 (0.08, 1.79)	0.71 (0.18, 2.79)	AC + CD			
0.74 (0.11, 4.31)	**0.17 (0.02, 0.93)**	0.28 (0.04, 1.89)	0.28 (0.04, 1.72)	2.29 (0.18, 25.97)	0.27 (0.03, 2.42)	0.5 (0.06, 3.9)	0.71 (0.09, 4.68)	AC + AI		
3.29 (0.98, 11.59)	0.73 (0.24, 2.42)	1.26 (0.29, 5.29)	1.22 (0.33, 4.73)	**10.29 (1.38, 85.99)**	1.17 (0.2, 7.3)	2.26 (0.46, 10.92)	3.15 (0.79, 13.36)	**4.38 (1.3, 20.04)**	AI	
0.97 (0.37, 2.44)	**0.22 (0.09, 0.48)**	0.37 (0.11, 1.18)	0.36 (0.12, 1)	2.97 (0.48, 21.83)	0.34 (0.07, 1.64)	0.65 (0.17, 2.48)	0.92 (0.28, 2.94)	1.27 (0.28, 7.22)	**0.29 (0.12, 0.65)**	AI + TCM

Bold values indicate statistically significant differences ($P < .05$).

AC = acupuncture, AI = acupoint injections, CD = calcium dobesilate, EA = electroacupuncture, TCM = traditional Chinese medicine.

3.9. Network meta-analysis of central fovea of macula thickness

The NMA results for macular central foveal thickness are displayed in Table 4, and comparisons between several interventions were not statistically different.

The SUCRA results suggested that AC + TCM is the best intervention to reduce the thickness of the macular central fovea, and the detailed SUCRA rankings are displayed in Figure 5C.

3.10. Adverse events

Out of the 28 studies, 8 recorded the occurrence of adverse events. Liu[24] reported an adverse event, localized hematoma, with an incidence rate of 6.3%. Li et al[28] reported gastric distension as an adverse event with an adverse event rate of 2.4%. Ren[33] reported 2 adverse events, nausea and vomiting and loss of appetite, with an adverse event rate of 20%. Meng[41] reported an adverse event of subcutaneous hematoma with an adverse event rate of 5%. The most common adverse effects we found were localized hematomas after AC and gastrointestinal symptoms after oral medication. According to the present investigation, there have been no additional serious adverse event occurrences observed at this moment.

3.11. Inconsistency and heterogeneity test

We examined the inconsistency of closed loops in network evidence plots using the node splitting method, and the forest plots examining the inconsistency are displayed in the Supplementary Material S9, Supplemental Digital Content, https://links.lww.com/MD/O886. There is consistency of results between direct and indirect comparisons of overall effective rate, as shown in the Supplementary Material S9 ($P > .05$), Supplemental Digital Content, https://links.lww.com/MD/O886. Forest plots for the heterogeneity test are shown in the Supplementary Material S10, Supplemental Digital Content, https://links.lww.com/MD/O886. Different courses of treatment may be a source of clinical heterogeneity, and we performed subgroup analyses of different disease courses. After excluding the literature 1 by 1, the original results remained unchanged, indicating that the sensitivity analysis was negative and the results were robust.

3.12. Publication bias assessment

The bias of publication was evaluated with a corrected funnel plot, which is displayed in Figure 6. The funnel plot of overall effective rate showed several symmetrical distributions of points in the mid and upper ranges, suggesting a sufficient sample size and no evidence of significant publication bias (Fig. 6A). All the data points fell inside the bounds of the diagonal line, indicating no evidence of heterogeneity. The corrected funnel plot of the best corrected visual acuity showed several symmetrical distributions of points in the upper mid segment, but there were data points that were conveniently beyond the diagonal, suggesting that there may be some heterogeneity (Fig. 6B). Regarding the central fovea of macula thickness, the corrected funnel plot was asymmetrically distributed due to the limited sample size, which impeded the full representativeness of the results, indicating the potential presence of some risk of bias and a small sample effect (Fig. 6C).

4. Discussion

Many previous research have described the effectiveness and safety of AC in treating DR. However, AC-related therapies are diverse, and there is no evidence-based medical evidence to guide the treatment of DR with AC and related treatments. In this NMA, by comparing the effectiveness of

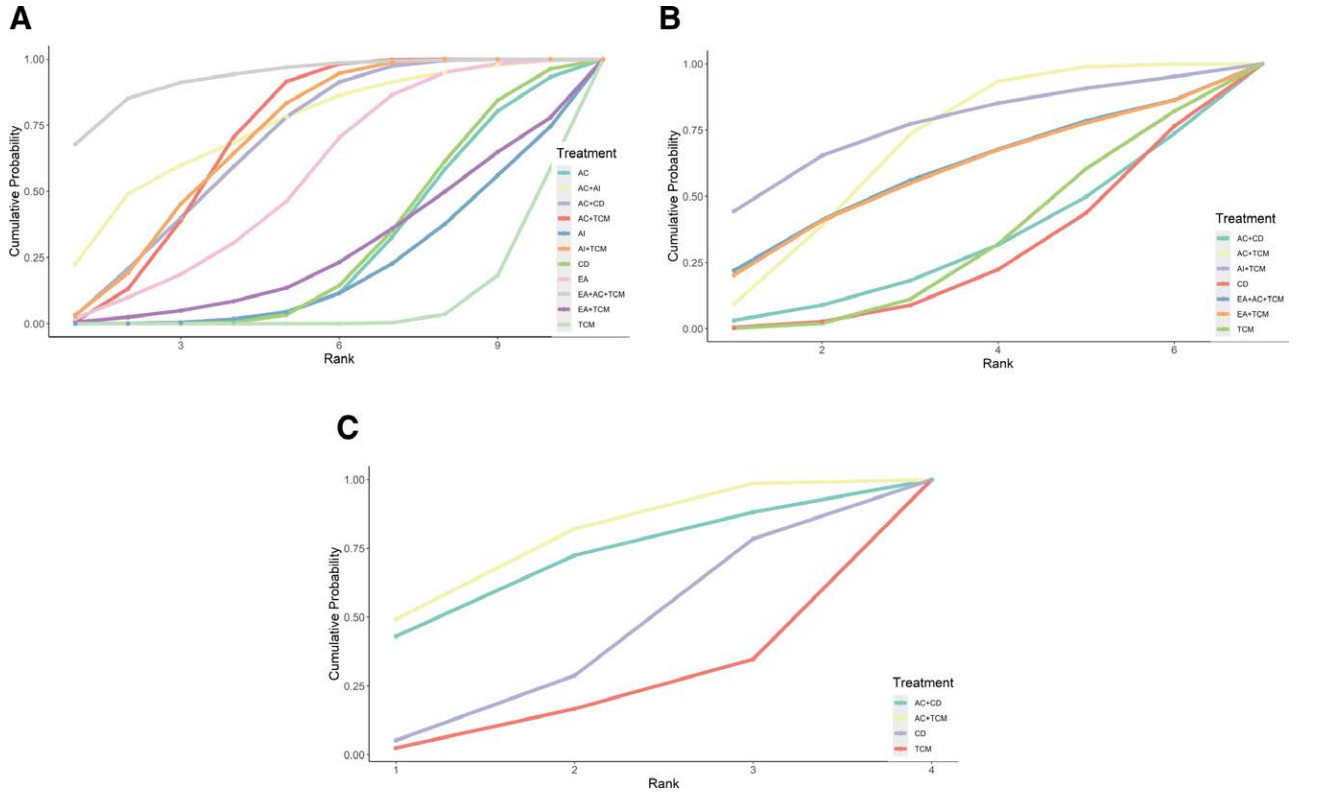

Figure 5. SUCRA line for different outcome events. (A) Overall effective rate; (B) best corrected visual acuity; (C) central fovea of macula thickness. AC = acupuncture, AI = acupoint injections, CD = calcium dobesilate, EA = electroacupuncture, SUCRA = surface under the cumulative ranking, TCM = traditional Chinese medicine.

Table 3

Results of network meta-analysis for the best corrected visual acuity.

AC + TCM						
0.12 (–0.05, 0.31)	TCM					
0.16 (–0.05, 0.36)	0.03 (–0.24, 0.3)	CD				
0.02 (–0.36, 0.39)	–0.11 (–0.52, 0.3)	–0.14 (–0.56, 0.28)	EA + AC + TCM			
0.02 (–0.4, 0.42)	–0.11 (–0.48, 0.25)	–0.14 (–0.6, 0.31)	0 (–0.56, 0.55)	EA + TCM		
0.15 (–0.12, 0.42)	0.02 (–0.3, 0.35)	–0.01 (–0.19, 0.17)	0.13 (–0.33, 0.59)	0.13 (–0.36, 0.62)	AC + CD	
–0.08 (–0.49, 0.31)	–0.21 (–0.57, 0.15)	–0.24 (–0.7, 0.21)	–0.1 (–0.64, 0.45)	–0.1 (–0.61, 0.42)	–0.23 (–0.72, 0.24)	AI + TCM

AC = acupuncture, AI = acupoint injections, CD = calcium dobesilate, EA = electroacupuncture, TCM = traditional Chinese medicine.

Table 4

Results of network meta-analysis for central fovea of macula thickness.

AC + TCM			
–27.97 (–65.55, 7.42)	TCM		
–17.02 (–68.19, 32.44)	10.82 (–50.29, 72.94)	CD	
–2.36 (–74.47, 67.82)	25.3 (–53.29, 104.95)	14.89 (–36.62, 64.52)	AC + CD

AC = acupuncture, CD = calcium dobesilate, TCM = traditional Chinese medicine.

different AC-related interventions for DR, we derived reliable results. This NMA comparing 11 AC and related treatments for DR found that EA + AC + TCM may be the most effective intervention for the treatment of DR. AI + TCM may be the optimal intervention to improve the best corrected visual acuity, and AC + TCM may be the optimal intervention to improve the central fovea of macula thickness. Pairwise meta-analysis found that an integrative treatment option that combines AC and multiple therapies can be more effective than a single treatment, and acupoint therapies such as AC are more effective than oral medication therapies. Common adverse effects of AC and related treatments for DR are local hematomas and gastrointestinal reactions, which are acceptable. The overall quality of evidence in the included literature according to the Jadad scale was mostly of low and medium quality, thus further well-designed RCTs are needed. These findings provided valuable insights into potential therapeutic options for treating and slowing the progression of DR.

DR has attracted much attention as one of the major causes of blindness in people of working age. The pathogenesis of DR is still unclear, and there are no specific treatment options and limitations of the existing treatment options. The long-term hyperglycemic state of diabetic patients triggers ischemia and hypoxia in the retina, which evolves into retinal neovascularization in response to a combination of factors, ultimately affecting vision. Inflammatory responses, oxidative stress, increased advanced glycation end products (AGEs), and dysregulated vascular regeneration play important roles in this process.[52–57] AC and its related therapies are an important part of TCM and are complementary and alternative treatments with clear efficacy. It has a variety of effects on degenerative disorders involving the brain or peripheral ischemia, and AC stimulation can increase

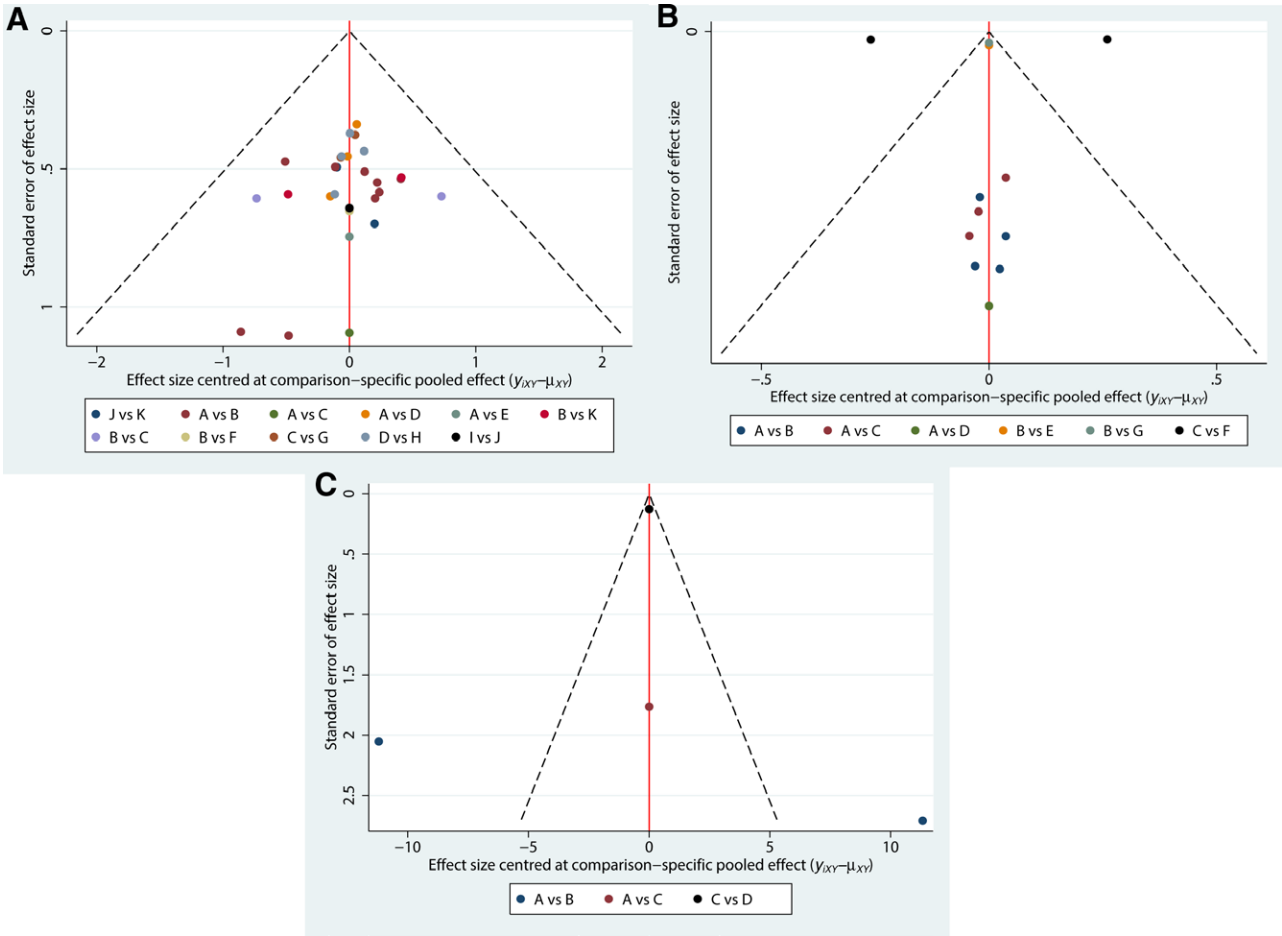

Figure 6. The corrected funnel plots for different outcome events. (A) Overall effective rate; (B) best corrected visual acuity; (C) central fovea of macula thickness.

blood flow to tissues by modulating dysfunction in the central circulatory and autonomic nervous systems.[58] Animal experiments demonstrated that AC increased blood flow to mouse ocular vessels and tissues by increasing the release of the vasodilator nitric oxide in the skin.[58] Clinical studies have found a significant increase in central retinal artery and central retinal vein blood flow rates in patients treated with 10 days of AC.[59] The early stages of DR may drive disease progression by affecting retinal blood velocity and flow.[60] AC work by locally stimulating tissues to stop the progression of DR by improving retinal blood flow. Similarly, animal study have shown that EA can alleviate metabolic disturbances in a sustained high-glucose environment by decreasing pro-inflammatory cytokines and reducing the production of AGEs and receptor for advanced glycation end products.[61] EA also alleviated insulin resistance, lowered fasting blood glucose and improved insulin sensitivity in diabetic rats.[62,63] The mechanism of EA in the treatment of DR is not clear, but it may prevent the progression of DR in terms of reducing the inflammatory response, decreasing the production of AGEs, and alleviating insulin resistance.[64–67] AI are an important part of AC and its related therapies, where stimulation is produced by injecting small amounts of medication at specific points to treat disease. The therapeutic mechanism of AI is unclear, and available studies have shown that AI therapy is effective in relieving pain, stimulating local nerves, and regulating blood flow rates.[12,68] AC and its related therapies may prevent the occurrence of DR in terms of regulating blood flow rate, reducing inflammatory response, decreasing the production of AGEs, and improving insulin resistance, which provided an explanation for our discoveries and a reference for future investigations.

Overall, our findings suggested that integrative therapies combining AC, EA, and other therapies have a positive impact on DR. Similar to our findings, Ang et al[69] found that AC in combination with standard medications or AC alone may be more effective than standard medications alone in the treatment of DR. The therapeutic approach of Chinese traditional medicine should follow the principle of syndrome differentiation in Chinese medicine, and different treatment plans should be given to patients with different types of evidence in order to maximize the therapeutic effect. The lack of a harmonized protocol for selecting acupoints is a major issue affecting the promotion of AC and its related therapies, and further efforts as well as evidence on the optimal acupoints for DR treatment are needed.

There are some limitations to this study. First, all experiments were conducted in China, and the language of publication was restricted to Chinese and English, which could lead to bias. Second, AC and its related therapies operate at different treatment frequencies, depths, and durations, and these factors may contribute to differences in outcomes and be a source of heterogeneity. Third, the evaluation of the quality of the included literature suggested that the overall quality of the literature was medium and there was some publication bias, and more well-designed, high-quality, large-sample RCTs are needed in the future.

5. Conclusion

This NMA study confirmed that AC, EA, AI, TCM, and CD are several effective therapies for the treatment of DR. EA + AC + TCM is the most effective therapeutic regimen for DR. AI + TCM and AC + TCM are effective in improving the

best corrected visual acuity and reducing macular edema. A combination of multiple treatments of AC and its related therapies is more effective than a single treatment. However, there is a lack of sufficient evidence to guide optimal point selection, frequency and depth of AC. At the same time, the overall quality of the included RCTs was medium, and a large number of high-quality RCTs are required to verify our findings.

Author contributions

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