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Intravitreal conbercept plus traditional Chinese medicine for diabetic macular edema: A systematic review and meta-analysis

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Abstract: **Background**: Despite the established role of anti-vascular endothelial growth factor (anti-VEGF) agents as first-line therapy for diabetic macular edema (DME), their therapeutic effect may be incomplete or unsustained in a proportion of patients. **Objectives**: This study aimed to evaluate the efficacy and safety of intravitreal conbercept (IVC) combined with traditional Chinese medicine (TCM) for the treatment of DME. **Methods**: A systematic search was conducted in PubMed, EMBASE, Web of Science, the Cochrane Library, Scopus, and CNKI from database inception to June 2025. Eligible randomized controlled trials (RCTs) comparing IVC combined with TCM versus IVC monotherapy were included. **Results**: A total of 14 studies involving 979 patients met the inclusion criteria. Compared with IVC monotherapy, IVC combined with TCM resulted in a greater reduction in central macular thickness (CMT) and significantly improved best-corrected visual acuity (BCVA) at both 3 and 6 months. However, no significant difference in BCVA was observed at 1 month (MD = -0.03; 95% CI -0.08 to 0.03; p = 0.34). The combination therapy was also associated with a significantly lower ineffectiveness rate (RR = 0.32; 95% CI 0.22-0.47; $p < 0.05$) and fewer adverse events (AEs) (RR = 0.67; 95% CI 0.45-1.00; $p < 0.05$). **Conclusion**: IVC combined with TCM may provide additional therapeutic benefits for patients with DME without increasing safety risks. Nevertheless, high-quality, large-scale, multicenter RCTs are still required to further confirm these findings.

Keywords: Conbercept; Diabetic macular edema; Meta-analysis; Traditional Chinese medicine

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INTRODUCTION

Diabetic macular edema (DME) is a common complication of diabetic retinopathy (DR) and one of the leading causes of vision loss in patients with diabetes (Urbancic *et al*., 2021). The pathogenesis of DME is complex and multifactorial. Recent studies have indicated that it is closely associated with the overexpression of vascular endothelial growth factor (VEGF), oxidative stress imbalance, activation of inflammatory cytokines, endothelial dysfunction, disruption of the blood-retinal barrier (BRB) and microcirculatory impairment (Petkova-Parlapanska *et al*., 2025; Peng *et al*., 2025). Hyperglycemia can activate intercellular adhesion molecule-1 (ICAM-1)-mediated inflammatory adhesion, leading to retinal microvascular endothelial injury and breakdown of the BRB, thereby accelerating the onset and progression of DME (Li *et al*., 2022). Epidemiological investigations have shown that approximately one-third of diabetic patients develop DR, of whom around 7% progress to DME (Sepahi *et al*., 2021). Patients with DME typically experience progressive visual impairment, foveal degeneration and metamorphopsia, which significantly reduce their quality of life (Xiang *et al*., 2022).

Intravitreal injection of anti-VEGF agents is the primary treatment option for DME (Donthula and Daigavane, 2024). Clinical studies have demonstrated that conbercept can significantly reduce CMT and improve BCVA. As a recombinant humanized fusion protein, conbercept binds VEGF-A, VEGF-B and PlGF simultaneously, exerting broad anti-angiogenic effects (Zhu *et al*., 2024; Yao *et al*., 2024). However, some patients exhibit suboptimal response to conbercept monotherapy and long-term repeated intravitreal injections may increase the risk of ocular adverse events such as intraocular hemorrhage, endophthalmitis, retinal detachment and corneal scarring (Zhao *et al*., 2025; Qi *et al*., 2024; Qi *et al*., 2023). With advances in medical technology, the diagnosis and treatment of DME are gradually moving toward precision and intelligence. Artificial intelligence has been applied in the early screening and grading of DR, improving the efficiency of identifying high-risk patients with DME (Zhu *et al*., 2025). Meanwhile, glucose monitoring systems based on nanozymes have demonstrated higher sensitivity and stability in evaluating glucose metabolism (Li *et al*., 2024a). These strategies currently focus mainly on diagnostic enhancement and metabolic regulation, with limited effectiveness in addressing the inflammatory and angiogenic pathological processes of DME. Therefore, exploring comprehensive therapeutic strategies, such as those incorporating traditional Chinese medicine (TCM), holds important clinical value.

TCM is increasingly employed as an adjuvant therapy for fundus disorders, leveraging its recognized mechanisms in ameliorating microcirculatory dysfunction, mitigating inflammatory responses and oxidative burden. (Nijat *et al*., 2025; Li *et al*., 2024c; Chen *et al*., 2024; Bi and Shi, 2025). TCM can modulate the pathological microenvironment of

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diabetes through multi-target mechanisms, such as inhibiting the VEGF/VEGFR2 signaling pathway (Song *et al*., 2024), activating the Nrf2/HO-1 antioxidant pathway (Liu *et al*., 2024) and regulating immune responses. Furthermore, Su *et al*., (2023) attributed the anti-inflammatory and antioxidant effects of TCM in DME to gut microbiota regulation, corroborating the rationale for its adjunctive use. Current clinical evaluations of intravitreal conbercept (IVC) integrated with TCM for diabetic macular edema face several methodological challenges, such as restricted cohort dimensions and variability in endpoint assessments. Moreover, a comprehensive appraisal of the risk-benefit profile of this therapeutic approach remains underexplored. To bridge this knowledge gap, we conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) examining the comparative effectiveness of IVC combined with TCM versus IVC alone. This research seeks to consolidate existing clinical data and establish a reliable foundation for treatment protocol refinement.

MATERIALS AND METHODS

Study design

The present investigation was structured in accordance with the PRISMA framework, ensuring standardized methodology for evidence synthesis and reporting (Sohrabi *et al*., 2021). The protocol was prospectively registered in INPLASY (INPLASY202560097; 25 June 2025) (Canellas *et al*., 2023).The detailed PRISMA 2020 checklist is provided in supplementary material 1.

Inclusion and exclusion criteria

Study eligibility was determined based on the following predefined criteria: (1) enrollment of adults (≥18 years) with a confirmed DME diagnosis; (2) comparison between IVC combined with TCM (experimental group) and IVC monotherapy (control group); (3) reporting of at least one relevant endpoint, such as BCVA, CMT, inefficacy rate, or adverse events; (4) implementation of a randomized controlled design; and (5) accessibility of the complete publication.

Studies were excluded for any of the following reasons: employment of non-randomized methodologies; redundant or overlapping patient cohorts; non-empirical publication types (e.g., reviews, case reports, or conference abstracts); or inability to retrieve the complete manuscript.

Literature search

The following electronic databases were systematically searched: PubMed (https://pubmed.ncbi.nlm.nih.gov/), Web of Science (WOS, https://www.webofscience.com), EMBASE (https://www.embase.com/), Cochrane Library (https://www.cochranelibrary.com), Scopus (https://www.scopus.com) and China National Knowledge Infrastructure (CNKI, https://www.cnki.net). Articles published from database inception to 1 June 2025 were retrieved. A search strategy combining Medical Subject Headings (MeSH) terms and free-text terms was used, with the following main keywords: "Conbercept" OR "KH902", "Traditional Chinese Medicine", "intravitreal injection" and "diabetic macular edema". These terms were combined using Boolean operators "AND" and "OR" as appropriate. In addition, the reference lists of relevant reviews were scrutinized for additional eligible studies

Data extraction

Duplicate records were removed and literature management was performed using EndNote X9 software (Clarivate Analytics, Philadelphia, PA, USA). Literature selection and data extraction were independently performed by two authors and any disagreements were resolved through discussion with a third author. The extracted data included the first author's name, year of publication, sample size, sex distribution and intervention details for both the experimental and control groups.

Risk of bias assessment

The methodological quality of the incorporated RCTs was evaluated with the Cochrane Risk of Bias 2.0 (ROB 2.0) toolkit (Higgins *et al*., 2011). The risk of bias was assessed across five domains: randomization process, deviations from intended interventions, completeness of outcome data, measurement of outcomes and selective reporting. Two authors independently assessed the risk of bias and any disagreements were resolved through consultation with a third author. Since fewer than 10 studies were included for each outcome, quantitative assessment of publication bias using Egger's test and Begg's test was not performed due to the limited statistical power under small-sample conditions.

Outcomes

The primary outcomes were BCVA and CMT measured at 1, 3 and 6 months after IVC intervention. Secondary outcomes included the proportion of patients with treatment inefficacy and the incidence of AEs related to the intervention. Treatment inefficacy was defined as: (1) <50% absorption of fluorescein leakage in the macular area with no improvement in BCVA, or (2) no change or worsening of visual acuity after treatment accompanied by fundus hemorrhage or edema. AEs were defined as ocular events occurring within 6 months after treatment, mainly including conjunctival hemorrhage, dry eye, vitreous hemorrhage, elevated intraocular pressure, endophthalmitis, cataract and acute retinal artery occlusion. Systemic adverse reactions judged by clinicians to be related to IVC or TCM treatment were also recorded as AEs.

Data transformation

BCVA values were standardized using the logarithm of the minimum angle of resolution (logMAR). If BCVA was reported using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score, the ETDRS scores were converted to logMAR values for statistical analysis. A

score of 85 letters was considered equivalent to normal visual acuity (0 logMAR) and a decrease of one line corresponded to an increase of 0.1 logMAR. The conversion formulas for logMAR and SD_{logMAR} were as follows:

$$\text{logMAR}=\frac{\text{85-ETDRS letters}}{50}$$

$$SD_{\text{logMAR}}=\frac{SD_{\text{letters}}}{50}$$

For studies that reported continuous variables as median and interquartile range (IQR; Q1–Q3), we converted these data into mean and standard deviation using the statistical methods proposed by Wan *et al*. (2014) and Luo *et al*. (2018) to ensure comparability across studies. When the sample size nnn, median mmm and interquartile range (Q1, Q3) were provided. The calculation of the mean and standard deviation employed the following:

$$\bar{x}=\frac{Q1+m+Q3}{3}$$

$$SD=\frac{Q3-Q1}{1.35}$$

Subgroup analysis

The included studies were categorized according to the primary therapeutic mechanisms and pharmacodynamic profiles of the Chinese herbal formulations. The included TCM interventions were classified into four categories: (A) Blood-activating and stasis-resolving formulas, including Huayu Xiaozhong Decoction, Xuefu Zhuyu Decoction and Buyang Huanwu Decoction; (B) Qi-invigorating and Yin-nourishing formulas, including Qiming Granules, Yijing Decoction, Yiqi Yangyin Huoxue Decoction and Yiqi Yangyin Huoxue Lishui Formula; (C) Spleen-strengthening and dampness-resolving formulas, including Modified Wuling San, Lishui Xiaozhong Granules, Jianpi Lishui Decoction and Yiqi Jianpi Xiaoshui Decoction; and (D) Neizhang formulas and self-prescribed formulas, in which the primary therapeutic principles could not be clearly classified or the prescription composition was highly heterogeneous.

Statistical analysis

Continuous variables were summarized as mean ± standard deviation (SD) and categorical variables were analyzed using risk ratio (RR) with corresponding 95% confidence intervals (CI). Statistical heterogeneity across studies was assessed using the I^2 statistic. A random-effects model was applied to pool the effect sizes, given the clinical and methodological heterogeneity across studies. Sensitivity analysis was performed by sequentially removing individual studies to evaluate the robustness of the pooled results. All statistical analyses were conducted using R software (version 4.3.2; R Foundation for Statistical Computing, Vienna, Austria). Meta-analyses were performed using the meta package (Balduzzi *et al*., 2019) and metafor package (Lortie and Filazzola, 2020).

RESULTS

Study selection and characteristics

A total of 14 studies involving 979 patients with DME were included in the analysis. Among the participants, 490 patients received IVC combined with TCM and 489 patients received IVC monotherapy. There were 254 males in the combination group and 255 males in the monotherapy group. In both groups, IVC was administered as a monthly intravitreal injection, with treatment duration ranging from 1 to 4 months. The duration of TCM intervention ranged from 1 to 6 months. The characteristics are summarized in table 1. The flow diagram is showed in fig. 1.

Risk of bias

The results of the risk of bias assessment based on the ROB 2.0 tool were presented in Fig. 2. Two studies were rated as having a high risk of bias, eight studies were rated as low risk and the remaining four studies were judged to have unclear risk of bias.

BCVA at 1, 3 and 6 months after IVC treatment

At the 1-month follow-up, BCVA outcomes from 6 clinical trials (n=369) demonstrated comparable efficacy between combination therapy and monotherapy. The pooled analysis showed a non-significant mean difference of -0.03 (95% CI: -0.08 to 0.03; p=0.34), with prediction intervals spanning -0.17 to 0.11. Heterogeneity was substantial (I^2=89%; Tau^2=0.004), supported by a significant Q statistic (Q=45.75, df=5, p<0.05). Eight studies involving 497 patients reported BCVA outcomes at 3 months and the combination therapy showed a trend toward greater improvement compared with IVC monotherapy (MD = −0.08; 95% CI [−0.09, −0.06]; 95% PI [−0.14, −0.02]; p < 0.05; Tau^2 = 0.001; Q = 13.45, df = 7, p = 0.06; I^2 = 48%). At 6 months, five studies including 398 patients indicated that the IVC combined with TCM group achieved a statistically significant improvement in BCVA compared with the IVC monotherapy group (MD = −0.10; 95% CI [−0.16, −0.05]; 95% PI [−0.22, 0.02]; p < 0.05; Tau^2 = 0.003; Q = 32.17, df = 4, p < 0.05; I^2 = 88%) (Fig. 3).

Sensitivity analysis for BCVA

After omitting Study 4, the pooled effect for BCVA at 1 month changed from non-significant to statistically significant (MD = −0.06; 95% CI [−0.09, −0.02]; p < 0.05) and the heterogeneity decreased from 89% to 66%, indicating that this study had a considerable influence on the overall effect size and heterogeneity at 1 month (Fig. 4). In contrast, sequential exclusion of each individual study at 3 and 6 months resulted in stable MD estimates, suggesting good robustness of the pooled results.

CMT at 1, 3 and 6 months after IVC treatment

Seven studies involving 453 patients reported CMT outcomes at 1 month after treatment. The IVC combined with TCM group showed a greater reduction in CMT compared with the IVC monotherapy group (MD = −44.76; 95% CI [−67.34, −22.17]; 95% PI [−89.80, 0.28]; p < 0.05; Tau^2 = 525.78; Q = 42.80, df = 6, p < 0.05; I^2 = 86%).

Nine studies involving 577 patients reported CMT outcomes at 3 months, again favoring the combination therapy (MD = −28.97; 95% CI [−46.03, −11.91]; 95% PI [−71.97, 14.03]; $p < 0.05$; $Tau^2 = 483.23$; $Q = 284.46$, df = 8, $p < 0.05$; $I^2 = 97\%$). At 6 months, five studies with 398 patients demonstrated a sustained advantage of IVC combined with TCM (MD = −31.64; 95% CI [−44.25, −19.03]; 95% PI [−51.20, −12.08]; $p < 0.05$; $Tau^2 = 99.69$; $Q = 10.57$, df = 4, $p = 0.03$; $I^2 = 62\%$) (Fig. 5).

Exclusion of study 9 reduced heterogeneity from 86% to 17% at 1 month, suggesting that this study was a major source of heterogeneity for CMT at this time point. Similarly, exclusion of study 3 decreased heterogeneity from 97% to 16% at 3 months and exclusion of study 1 reduced heterogeneity from 62% to 10% at 6 months, indicating that these studies substantially contributed to variability in the pooled results. However, none of these exclusions materially altered the direction or statistical significance of the overall effect estimates, demonstrating the robustness of the findings (Fig. 6).

Ineffectiveness rate and safety

Eight studies involving 652 patients reported treatment ineffectiveness outcomes. The IVC combined with TCM group showed a significantly lower ineffectiveness rate compared with the IVC monotherapy group (RR = 0.32; 95% CI [0.22, 0.47]; $p < 0.05$; $Tau^2 = 0.00$; $Q = 3.58$, df = 7, $p = 0.90$; $I^2 = 0\%$). Nine studies involving 686 patients reported AEs. The incidence of AEs was also lower in the IVC combined with TCM group (RR = 0.67; 95% CI [0.45, 1.00]; $p < 0.05$; $Tau^2 = 0.00$; $Q = 1.97$, df = 7, $p = 0.96$; $I^2 = 0\%$) (Fig. 7).

DISCUSSION

The primary objective of this study was to evaluate the efficacy and safety of IVC combined with TCM compared with IVC monotherapy. The findings of this meta-analysis demonstrated that, except for BCVA at 1 month, the combination therapy significantly improved BCVA at 3 and 6 months. In addition, IVC combined with TCM resulted in greater reduction in CMT compared with IVC alone, without increasing the risk of AEs.This analysis provides supportive evidence for the therapeutic potential of the IVC-TCM combination in DME care.

Recent studies have reported that combining TCM with anti-VEGF therapy exerts a synergistic effect in DME, improving both visual function and macular morphology (Zhou *et al*., 2025b). Our findings are consistent with these results, showing that IVC combined with TCM provided greater long-term improvement than IVC monotherapy, possibly due to the sustained regulatory effects of TCM (Li *et al*., 2024c; Chen *et al*., 2024). Emerging evidence suggests that TCM may exert therapeutic benefits by modulating the gut microbiota and improving microcirculation (Zhou *et al*., 2025a; Xue *et al*., 2023; Wu *et al*., 2024; Tong *et al*., 2024), which may help explain its additional value in DME management.

The lack of significant BCVA improvement at 1 month in the IVC combined with TCM group may be due to the delayed functional recovery of retinal neurons. Visual improvement does not immediately follow macular edema reduction and is influenced by photoreceptor integrity and macular ischemia (Yozgat *et al*., 2021). This explains why short-term functional gains were limited, while BCVA benefits became evident at 3–6 months in this study. Sensitivity analysis showed that heterogeneity at 1 month was mainly driven by study 4, in which the self-made TCM prescription may have had limited therapeutic effect.

At the 1-month follow-up, blood-activating formulas showed greater CMT reduction than Qi-invigorating and Yin-nourishing or spleen-strengthening formulas. This is likely because blood-activating therapy improves retinal microcirculation more rapidly (Huang *et al*., 2021), while Qi-invigorating and Yin-nourishing therapy acts more gradually through metabolic support (Shi *et al*., 2023). Spleen-strengthening formulas also have a slower onset of action. Even so, both showed modest early effects, suggesting potential cumulative benefits over time.

At the 3-month follow-up, all TCM subgroups showed significant structural improvement in CMT compared with IVC monotherapy. The greatest reduction was observed in studies using self-made prescriptions, which may reflect their individualized formulation and stronger targeted intervention. In contrast, spleen-strengthening formulas, which primarily reduce retinal exudation through fluid metabolism regulation, had a milder effect. These findings suggest that the efficacy of combination therapy may be influenced not only by herb selection but also by therapeutic strategy and prescription design.

Compared to IVC monotherapy, the integrated regimen showed marked reductions in both therapeutic failure rates and the frequency of AEs. Reported AEs of IVC are mostly related to intravitreal injection, such as elevated intraocular pressure, conjunctival hemorrhage and mild endophthalmitis and the addition of TCM did not increase these risks. TCM may also provide systemic regulatory effects that improve treatment tolerance and patient adherence. However, most included studies were single-center trials with short follow-up durations and inconsistent AE reporting standards, making it difficult to evaluate long-term safety. Therefore, the safety profile of this combination therapy should be further validated in future well-designed multicenter RCTs.

This study has several limitations. First, only RCTs published in Chinese databases were included, which may introduce language and publication bias, as studies with positive results are more likely to be published locally while negative or inconclusive findings may remain unpublished.

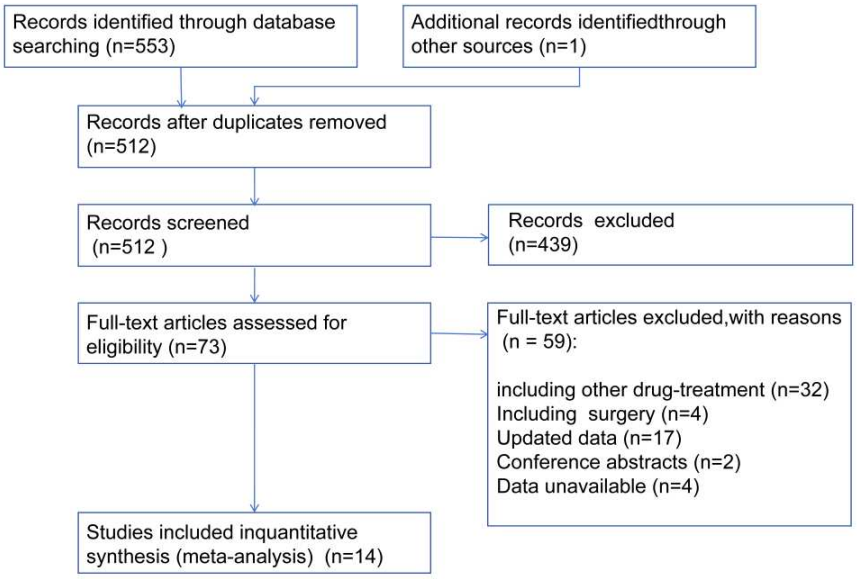

Fig. 1: Flow diagram

Table 1: Summary of study characteristics

Study ID	Author (Year)	Sample size (T/C)	Male (T/C)	Intervention (IVC + TCM)	Control (IVC alone)
Study 1	Feng *et al*. (2025)	74/68	40/33	IVC, 1 injection/month × 3 months + Huayu Xiaozhong Formula (oral) × 6 months	IVC, 1 injection/month × 3 months
Study 2	Chen *et al*. (2025)	42/42	24/22	IVC, 1 injection/month × 1 month + Neizhang Formula (oral) × 1 month	IVC, 1 injection/month × 1 month
Study 3	Zhou *et al*. (2024)	43/43	20/21	IVC, 1 injection/month × 3 months + Modified Wuling San (oral) × 3 months	IVC, 1 injection/month × 3 months
Study 4	Ju *et al*. (2024)	39/39	21/22	IVC, 1 injection/month × 2 months + Self-made Formula (oral) × 2 months	IVC, 1 injection/month × 2 months
Study 5	Shuai *et al*. (2024)	40/40	23/21	IVC, 1 injection/month × 3 months + Qiming Granules (oral) × 3 months	IVC, 1 injection/month × 3 months
Study 6	Ke *et al*. (2022)	30/30	13/16	IVC, 1 injection/month × 3 months + Yijing Decoction (oral) × 3 months	IVC, 1 injection/month × 3 months
Study 7	Liang *et al*. (2025)	31/31	13/14	IVC, 1 injection/month × 1 month + Xuefu Zhuyu Decoction (oral) × 2 months	IVC, 1 injection/month × 1 month
Study 8	Ye *et al*. (2021)	30/30	15/18	IVC, 1 injection/month × 1 month + Buyang Huanwu Decoction (oral) × 1 month	IVC, 1 injection/month × 1 month
Study 9	Yang *et al*. (2025)	23/23	11/12	IVC, 1 injection/month × 3 months + Lishui Xiaozhong Granules (oral) × 3 months	IVC, 1 injection/month × 3 months
Study 10	Wang *et al*. (2024)	29/35	18/15	IVC, 1 injection/month × 1 month + Yiqi Yangyin Huoxue Decoction (oral) × 3 months	IVC, 1 injection/month × 1 month
Study 11	Chen *et al*. (2020)	30/30	17/19	IVC, 1 injection/month × 4 months + Lishui Xiaozhong Granules (oral) × 3 months	IVC, 1 injection/month × 4 months
Study 12	Sun *et al*. (2021)	30/30	12/14	IVC, 1 injection/month × 3 months + Yiqi Yangyin Huoxue Decoction (oral) × 3 months	IVC, 1 injection/month × 3 months
Study 13	Nong *et al*. (2022)	19/18	8/11	IVC, 1 injection/month × 3 months + Yiqi Jianpi Xiaoshui Decoction (oral) × 3 months	IVC, 1 injection/month × 3 months
Study 14	Zhang *et al*. (2017)	30/30	19/17	IVC, 1 injection/month × 1 month + Jianpi Lishui Decoction (oral) × 2 months	IVC, 1 injection/month × 1 month

IVC, intravitreal Conbercept; TCM, Traditional Chinese Medicine; T, treatment group; C, control group.

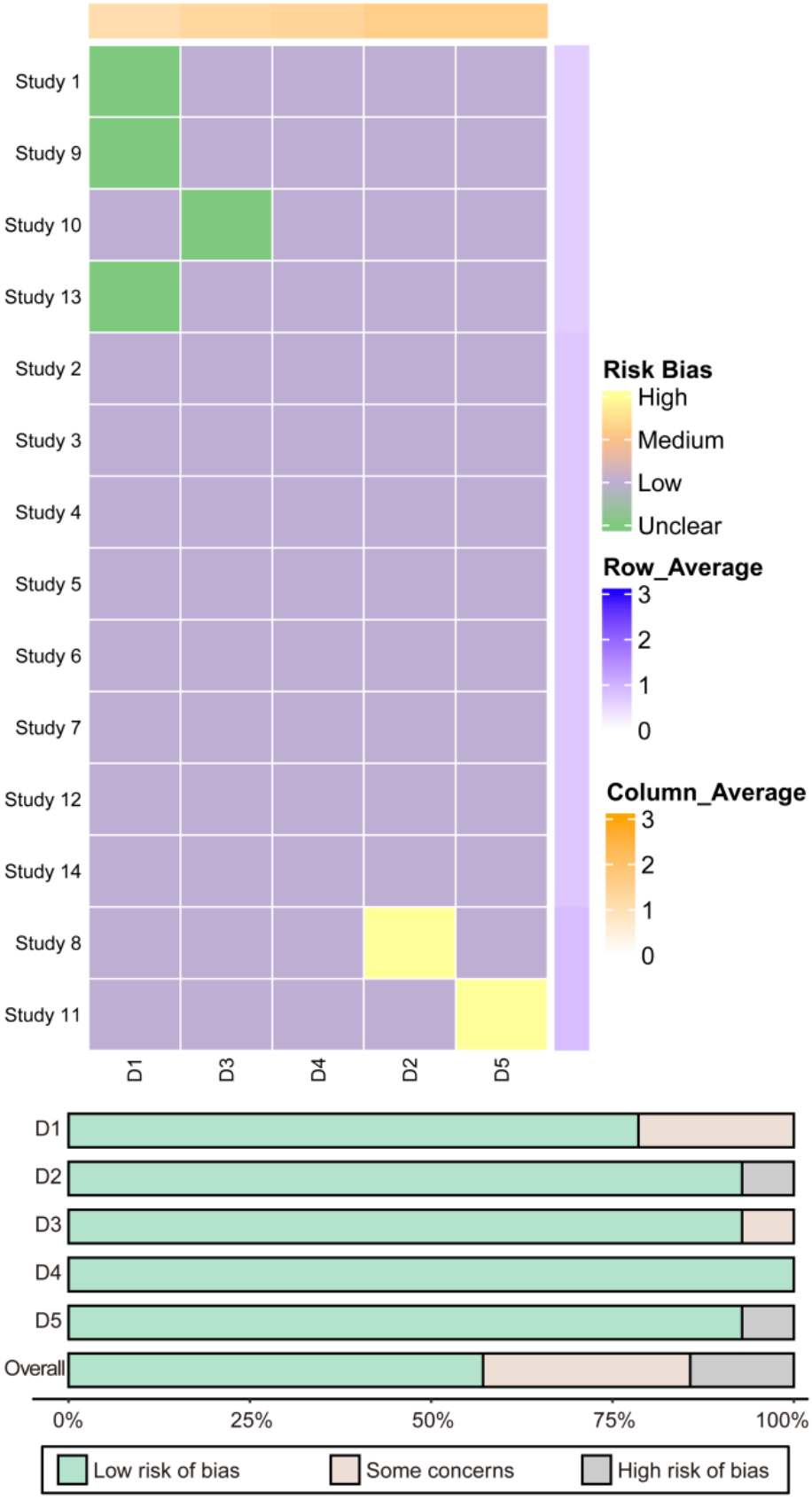

Fig. 2: Risk of bias assessment.

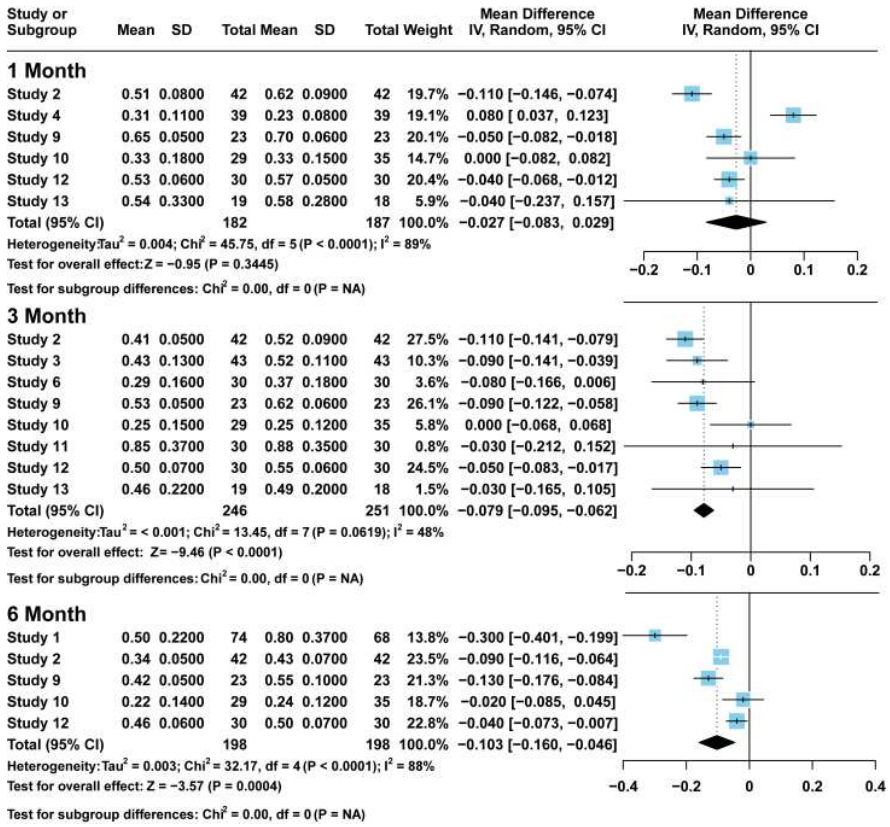

Fig. 3: ICV plus TCM versus IVC Monotherapy for DME at 1, 3 and 6 Months.

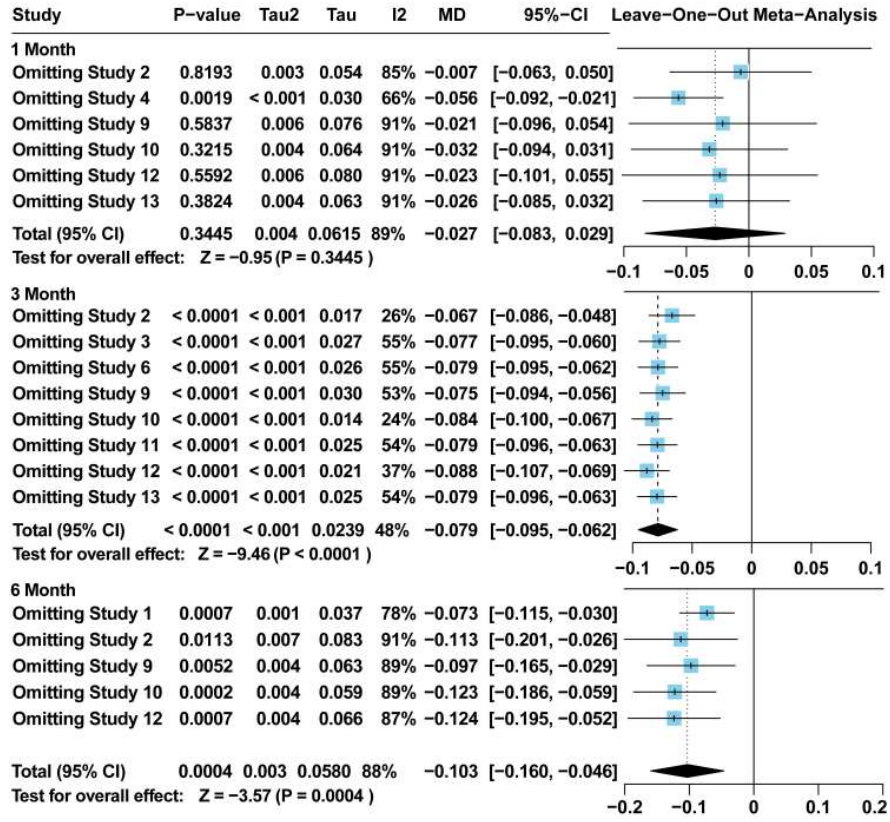

Fig. 4: Sensitivity analysis of BCVA at 1, 3 and 6 months

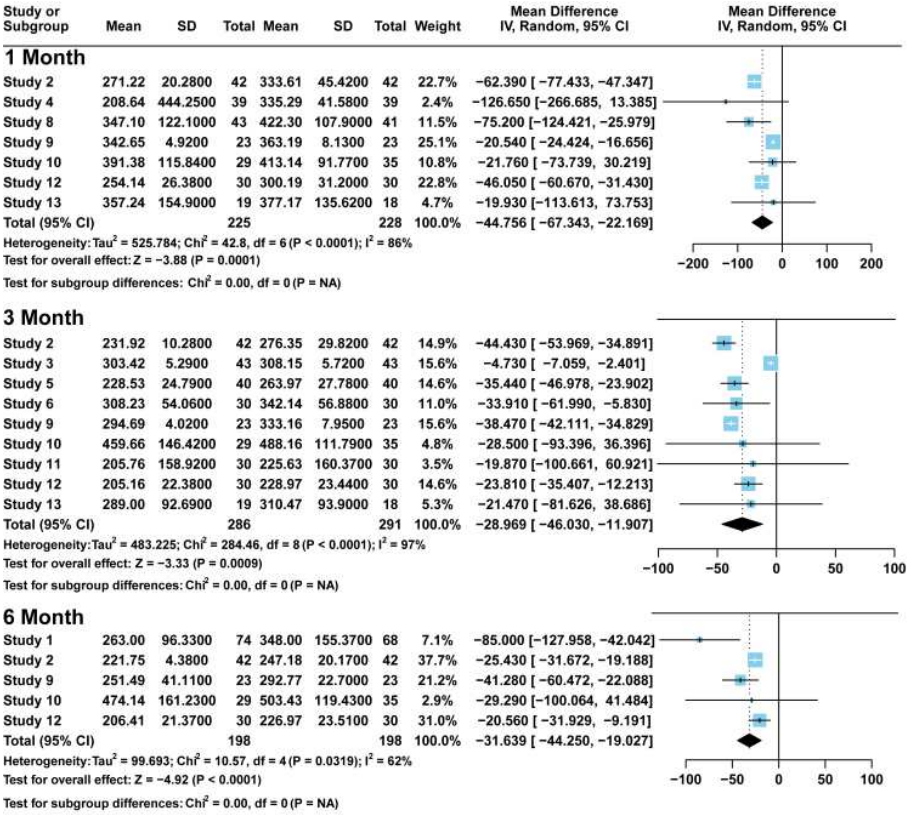

Fig. 5: Meta-analysis of CMT at 1, 3 and 6 months comparing IVC combined with TCM versus IVC monotherapy in patients with DME

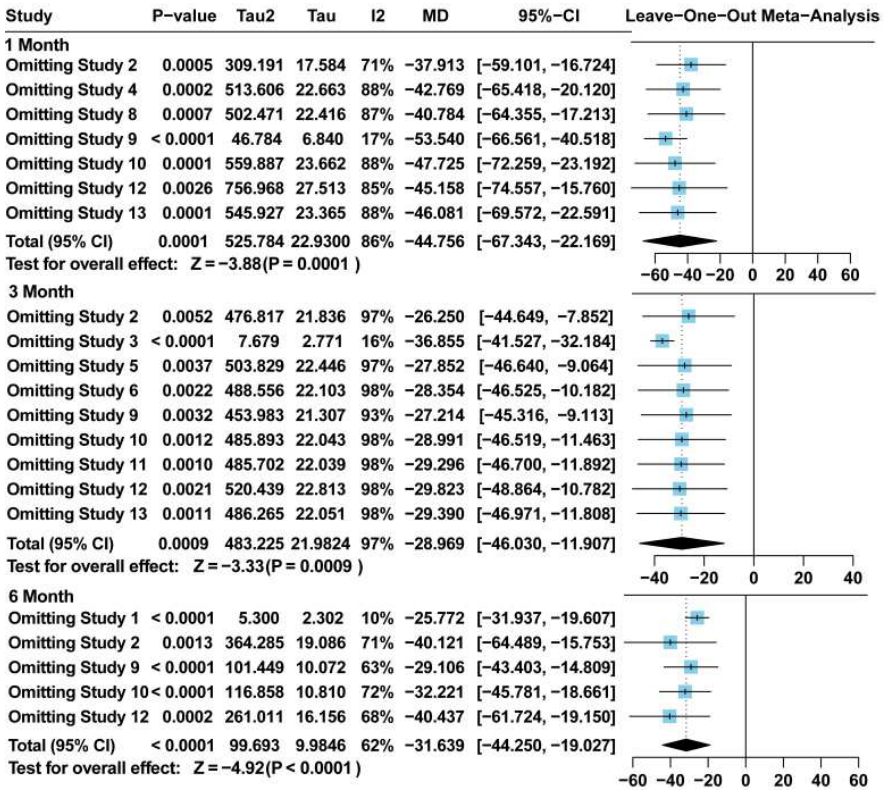

Fig. 6: Sensitivity analysis of CMT at 1, 3 and 6 months

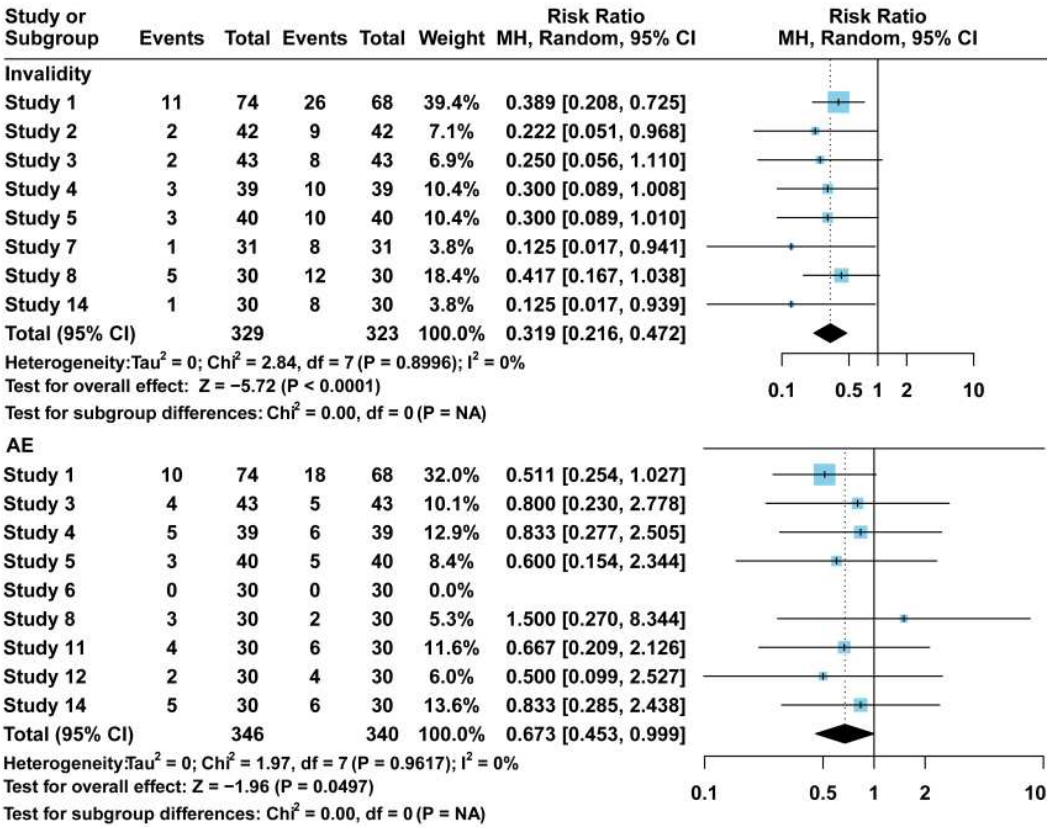

Fig. 7: Meta-analysis of treatment ineffectiveness and AEs comparing IVC combined with TCM versus IVC monotherapy in patients with DME

Second, all included studies were conducted in China, which may limit the generalizability of our findings to other populations. Third, heterogeneity could not be completely avoided due to variations in TCM prescriptions, treatment duration and follow-up periods among the included trials. In addition, the follow-up durations were generally short, preventing evaluation of long-term outcomes and safety. Future research should adopt standardized safety reporting, include longer follow-up and incorporate high-quality multicenter RCTs to enhance the evidence base for TCM as an adjunctive therapy in DME.

CONCLUSION

IVC combined with TCM may represent a promising therapeutic option for patients with DME. However, substantial heterogeneity was observed among studies. The considerable heterogeneity could be potentially explained by the considerable variations in the specific composition of TCM interventions, treatment course lengths of enrolled patients. Large-scale, multicenter and well-designed randomized controlled trials are warranted to further validate the long-term efficacy and safety of IVC combined with TCM in the management of DME.

Acknowledgements
Not applicable.

Authors' contributions
Zhenjun Fang contributed to the study conceptualization, literature search, data extraction, methodology development and drafting of the manuscript. Zhongyue Zhang, as the corresponding author, designed and supervised the study, provided critical revisions and approved the final version of the manuscript. Duxin Dong performed data analysis, statistical validation and assisted in the preparation of figures and tables. Xincheng Du was responsible for quality assessment and validation of the extracted data. Wenyi Li participated in data management, investigation and manuscript editing. Yu Zan contributed to resource support, project coordination and review of the final manuscript. All authors read and approved the final manuscript.

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Data availability statement
All data generated or analysed during this study are included in this published article and its supplementary information files.

Ethical approval
Ethical approval was not applicable for this study because it synthesized data from published literature without

involving any individual patient data or new clinical interventions. The study protocol was registered with INPLASY under Registration No. INPLASY202560097.

Conflict of interest

The authors declare that they have no competing interests.

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