Systematic Review and Meta-Analysis

Medicine

OPEN

Clinical efficacy of subthreshold micropulse laser combined with anti-VEGF drugs in the treatment of diabetic macular edema

A meta-analysis

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Abstract

Background: To systematically evaluate the efficacy and safety of subthreshold micropulse laser (SML) combined with anti-vascular endothelial growth factor (VEGF) drugs for the treatment of diabetic macular edema (DME).

Methods: The randomized controlled trials on SML combined with anti-VEGF drugs for DME were retrieved from China National Knowledge Infrastructure, Wan Fang Data, VIP Data, Sino Med (China Biomedical Literature Database), PubMed, Web of Science, The Cochrane Library, and Embase by computer from inception to April 19, 2022. The observation group was treated with SML combined with anti-VEGF drugs, while the control group was treated with anti-VEGF agents alone or SML. And the references of the included literature were manually searched. The Meta-analysis was performed using Revman 5.4 and STATA SE 15.

Results: This study finally included 15 randomized controlled trials involving 891 eyes for Meta-analysis. The results showed that there was no statistically significant difference between the 2 groups in best-corrected visual acuity at 1, 3, 6, 9, and 12 months after treatment. There was no statistical difference between the 2 groups in central macular thickness (CMT) at 1, 3, and 6 months after treatment ($P > .05$). CMT in the observation group was lower than that in the control group at 9 and 12 months ($P < .05$). There was no statistical difference between the 2 groups in total macular volume at 3, 6, 9, and 12 months in CMT ($P > .05$). The number of anti-VEGF drugs injections in the observation was lower than that in the control group ($P < .05$). The occurrence of complications between the 2 groups was not statistically significant difference ($P > .05$).

Conclusion: SML in combination with anti-VEGF drugs in patients with DME are comparable in reducing the number of anti-VEGF drugs injections and CMT, thereby reducing the financial burden on patients. It does not differ in best-corrected visual acuity and total macular volume.

Abbreviations: BCVA = best-corrected visual acuity, CI = confidence interval, CMT = central macular thickness, DM = diabetes mellitus, DME = diabetic macular edema, DR = diabetic retinopathy, RCTs = randomized controlled trials, RPE = retinal pigment epithelium, SML = subthreshold micropulse laser, TMV = total macular volume, VEGF = vascular endothelial growth factor.

Keywords: anti-VEGF drugs, diabetic macular edema, meta-analysis, subthreshold micropulse laser

1. Introduction

The latest epidemiological results show that the prevalence of diabetes mellitus (DM) was as high as 11.2% in people over 18 years of age in China, exceeding the global level. And the incidence of diabetic complications in China remain the highest among the world.[1] It has been reported that 1 out of fifteen diabetic patients has diabetic macular edema (DME), which will have profound clinical and public health implications.[2] Diabetes mellitus can cause a variety of complications, including diabetic cataracts, neovascular glaucoma, diabetic optic neuropathy, diabetic retinopathy (DR), and so on. Among them, DR is the most common ocular microvascular complication and the leading cause of vision loss in working-age people.[2] DR includes 3 forms: non-proliferative diabetic retinopathy, proliferative diabetic retinopathy, and

DX and TZ contributed equally to this work.

This study has been supported by the Chongqing Science and Health Technology Innovation and Application Development Project of Traditional Chinese Medicine (NO.2020ZY024098).

The authors have no 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.

This study is a meta-analysis, so no ethics committee approval is required for this study.

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How to cite this article: Xu D, Zhu T, Huang L, Wang X, Chen M. Clinical efficacy of subthreshold micropulse laser combined with anti-VEGF drugs in the treatment of diabetic macular edema: A meta-analysis. Medicine 2024;103:5(e34583).

Received: 26 April 2023 / Received in final form: 12 July 2023 / Accepted: 13 July 2023

http://dx.doi.org/10.1097/MD.0000000000034583

DME.[2] DME is also the most common cause of vision loss in patients with DM.[3] There are various clinical treatments for DME,[4] among which anti-vascular endothelial growth factor (VEGF) drugs remain the first-line treatment for DME.[5] Previous studies have shown that anti-VEGF drugs can improve clinical symptoms and signs in patients with DME. However, anti-VEGF drugs require frequent injections to maintain the therapeutic effect. That increases the financial burden on patients and the occurrence of complications, such as subconjunctival hemorrhage, infection, and cerebrovascular accidents.[6,7]

Although the conventional laser can reduce macular edema, it destroys the target tissue by thermal damage, resulting in dark vision loss, visual field defects, laser spot enlargement, and secondary choroidal neovascularization in some patients. With continuous technological advances, there has been an evolution from conventional laser to subthreshold micropulse laser (SML). Unlike conventional continuous lasers, SML is a new laser that consists of large repetitive pulse lasers. SML selectively acts on retinal pigment epithelium (RPE) cells to exert modulatory effects and reduce inflammatory responses and macular edema.[8,9] The subthreshold micropulse laser includes 4 types according to wavelength: 810 nm, 532 nm, 577 nm, and 670 nm.[8]

Recently, many scholars have used SML in combination with anti-VEGF drugs in the treatment of DME, but the results remain controversial.[10–13] Most of the results showed that the combination therapy can significantly improve patients visual acuity and reduce the number of drug injections, but some scholars came to the opposite conclusion.[10,14–24] And there is no relevant evidence-based medical literature to confirm effect of the combination therapy. Therefore, in this study, we conducted a meta-analysis by searching randomized controlled trials (RCTs) of SML combined with anti-VEGF drugs in the treatment of DME published in China and English. This study will offer more evidence to support the clinical efficacy of SML combined with anti-VEGF drugs for the treatment of DME.

2. Materials and methods

2.1. Search strategy

This research was registered at PROSPERO (https://www.crd.york.ac.uk/prospero/, registration number CRD42022359632). This systematic review and meta-analysis were conducted according to the PRISMA guidelines (http://prisma-statement.org/?AspxAutoDetectCookieSupport=1).

The source of China National Knowledge Infrastructure, Wan Fang Database, VIP Database, China Biomedical Literature Database, PubMed, Web of Science, The Cochrane Library, and Embase, was conducted by computer. The search period was from the establishment of the database to April 19,2022. The search language was limited to Chinese and English. Search terms include: "diabetic macular edema," "randomized," "subthreshold micropulse laser," "bevacizumab," "ranibizumab ", "conbercept," "aflibercept," "anti-VEGF drug."

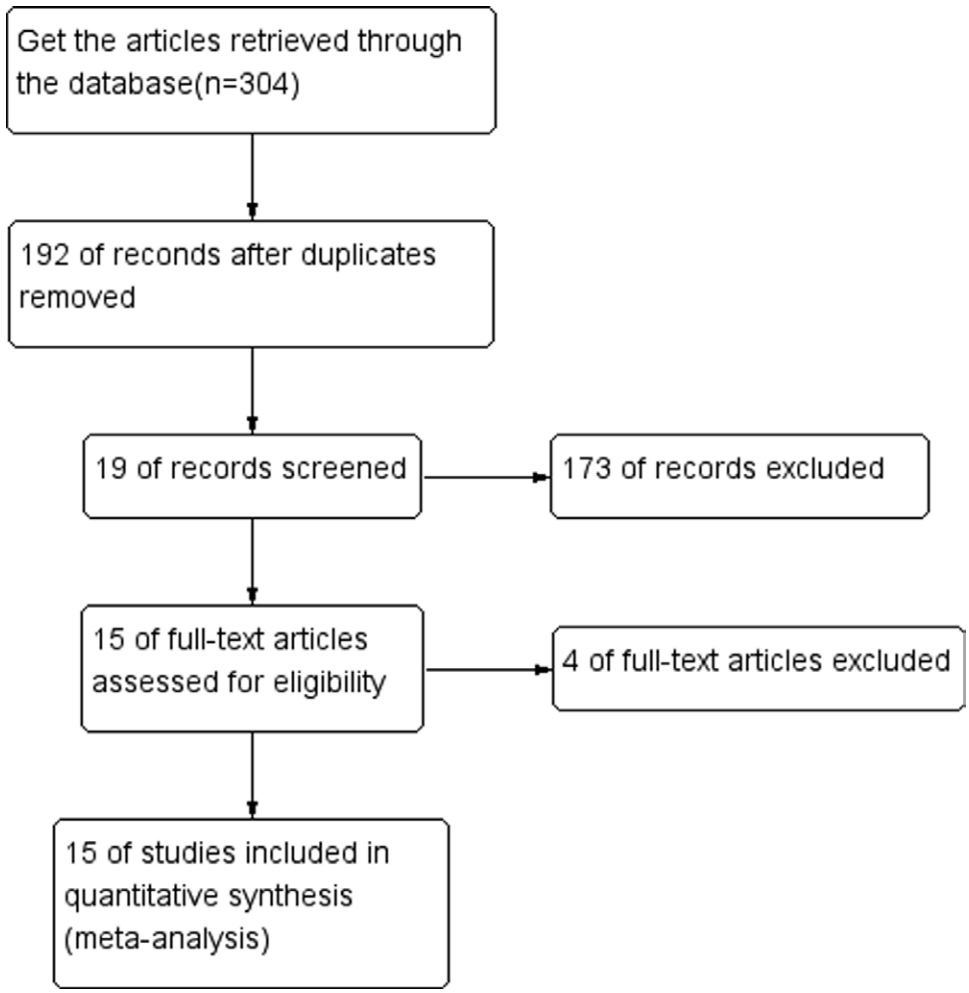

Figure 1. Literature screening process.

2.2. Inclusion criteria

Study type: only RCTs were included; Study subjects: age > 18 years, diagnosed with diabetes, regardless of gender, race, and nationality; Interventions: the observation group was treated with SML combined with anti-VEGF drugs, and the control group was treated with anti-VEGF drugs or SML alone; The reported outcome indicators included at least one of the following: best-corrected visual acuity (BCVA), central macular thickness (CMT), total macular volume (TMV), the number of anti-VEGF drug injections, and complications.

2.3. Exclusion criteria

Non-RCTs; Studies with nondiabetic macular edema; Interventions that do not meet the requirements, such as traditional laser combined with anti-VEGF drugs; Animal experiments, case reports, conference papers, reviews; Duplicate publications; Literature for which the full text is not available or for which the original data cannot be extracted.

2.4. Literature screening and data extraction

All retrieved literature was imported into Endnote X9, and 2 evaluators independently completed literature screening, data extraction, and literature quality assessment according to inclusion and exclusion criteria. If any disagreement existed, then 2 evaluators would negotiate to solve the problem. If there were still disagreements after negotiation, the third evaluator would solve the problem. The basic information included: year of publication, first author, number of cases, age, duration of diabetes, interventions (including observation and control groups), and outcome indicators.

2.5. Quality evaluation of the literature

A quality evaluation of all included RCTs was completed independently by 2 researchers with reference to the Cochrane Handbook Risk of Bias Assessment Tool,[25] which including the generation of random sequences, allocation concealment, blinding of investigators and subjects, blinding of study outcome assessment, completeness of outcome data, selective reporting of outcome bias, and other biases. The results of the bias evaluation for each article were divided into 3 grades: "high risk of bias," "low risk of bias," and "unclear risk of bias."

2.6. Statistical methods

Revman 5.4 (https://training.cochrane.org/online-learning/core-software/revman) and Stata SE15 software (https://bbs.pinggu.org/thread-7307635-1-1.html) provided by the Cochrane Collaboration Network were used to complete the Meta-analysis. The weighted mean difference and its 95% confidence interval (CI) were used as the effect analysis statistic for measurement data, while the relative risk ratio or the ratio of ratios and its 95% CI were used for count data. I^2 test was used for the heterogeneity test, and $I^2 \geq 50\%$ indicated large homogeneity between studies, and Meta-analysis was performed using the random-effects mode. $I^2 < 50\%$ suggests low homogeneity, and Meta-analysis was performed using the fixed-effect model. Differences were considered statistically

Table 1

Basic characteristics of RCTs.

Author	Year	Number of cases T/C (eyes)	Age	Duration of diabetes	Interventions (T/C)	The course of treatment (mo)	Outcome
Sun GL[15]	2017	15/15	58.27 ± 6.85 57.69 ± 6.39	NA	SML + ranibizumab/ Ranibizumab	12–17 13–20	①②④⑤
Li WQ[16]	2019	36/32	57.2 ± 10.1 60.6 ± 12.3	NA	SML + conbercept/ Conbercept	12	① ②③ ④
Huang KQ[13]	2022	26/26	62.31 ± 5.48 63.77 ± 5.37	62.81 ± 20.01/ 64.04 ± 20.44 (mo)	SML + ranibizumab/ Ranibizumab	9	① ② ④
Mao YJ[18]	2022	34/34	50.35 ± 10.14 51.47 ± 11.23	6.74 ± 2.03/ 6.80 ± 2.11 (yr)	SML + aflibercept/ Aflibercept	12	① ② ④⑤⑧
Zhang Q[14]	2021	35/35	56.0 ± 7.7/ 53.3 ± 9.1	13.5 ± 4.2/ 12.9 ± 4.1 (yr)	SML + aflibercept/ Aflibercept	12	① ② ④
Chen SN[25]	2020	30/28	56.17 ± 5.44/ 58.68 ± 5.92	NA	SML + ranibizumab/ Ranibizumab	12	① ②③ ④⑦
Yan LJ[21]	2019	40/38	59.7 ± 4.5/ 56.9 ± 4.4	12.7 ± 3.3/ 13.4 ± 3.7 (yr)	SML + ranibizumab/ Ranibizumab	NA	① ② ④
Wu Q[20]	2021	36/36	56.8 ± 10.2 56.3 ± 9.5	NA	SML + ranibizumab/ Ranibizumab	9	① ②③ ④⑥
Liu HX[26]	2021	44/44	69.57 ± 5.31 68.16 ± 3.28	6.72 ± 1.31/ 6.72 ± 1.31 (yr)	SML + ranibizumab/ SML	1	① ②⑤⑧
Akhlaghi[10]	2019	42/42	60.86 ± 8.57 60.86 ± 8.57	NA	SML + bevacizumab/ Bevacizumab	4	① ②
Tatsumi[9]	2020	22/21	NA	NA	SML + aflibercept/ Aflibercept	24	① ② ④⑤
Abouhussein[17]	2020	20/20	60.4 ± 4.2/ 59.5 ± 4.3	NA	SML + aflibercept/ Aflibercept	12	① ② ④⑤
Khattab[11]	2019	27/27	59.4 ± 4.3/ 55.7 ± 3.4	17.8 ± 3.4/ 17.4 ± 4.2 (yr)	SML + aflibercept/ Aflibercept	18	① ② ⑤
Kanar[19]	2019	28/28	63.43 ± 10.14/ 62.64 ± 9.03	18.76 ± 2.08/ 18.28 ± 2.24 (yr)	SML + aflibercept/ Aflibercept	12	① ②③ ④⑥
Koushan[22]	2022	15/15	59.8 ± 9.47/ 58.8 ± 9.28	NA	SML + aflibercept/ Aflibercept + sham SML	12	① ②③ ④

①BCVA; ②CMT; ③TMV; ④The number of anti-VEGF drugs; ⑤Complications.

RCTs = randomized controlled trials, SML = subthreshold micropulse laser.

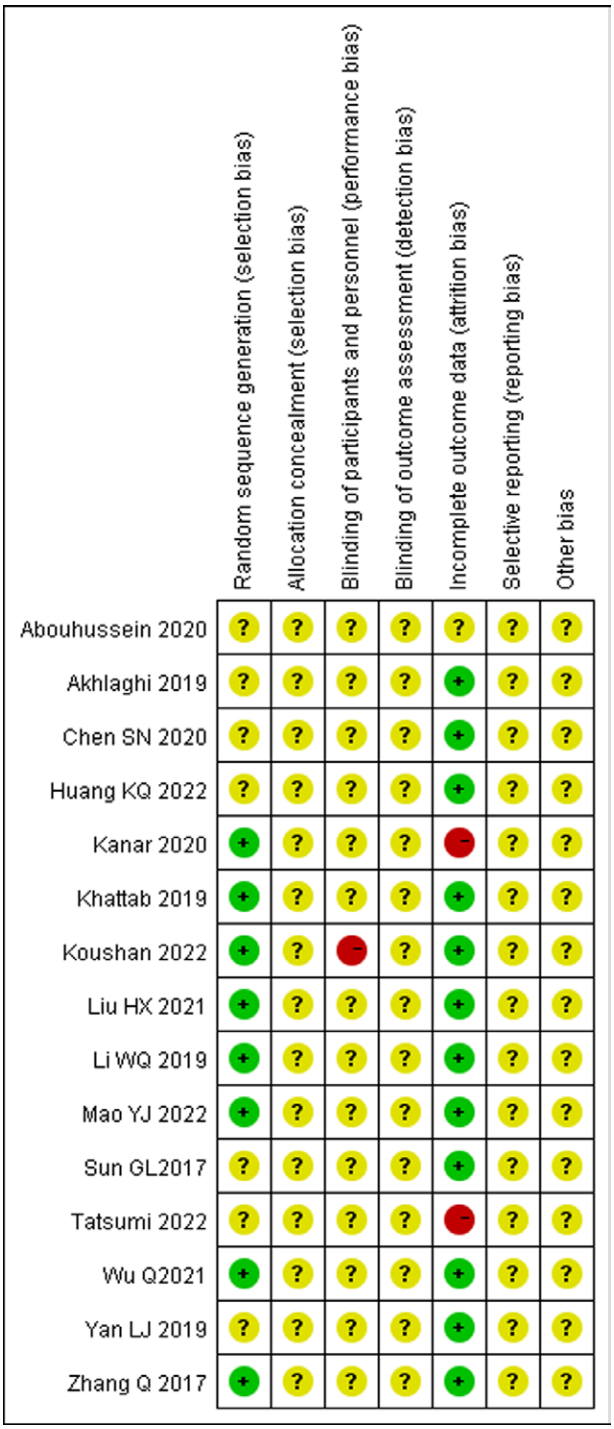

Figure 2. The assessment of risk of bias for include RCTs. RCTs = randomized controlled trials.

significant at $P < .05$. Sensitivity analysis was performed using 1-by-1 exclusion. Publication bias analysis was performed by Egger test using STATA 15, and $P < .05$ showed the presence of publication bias.

3. Results

3.1. Literature screening process and results

Based on the above search strategy, a total of 304 papers were collected. After eliminating duplicates, 192 papers were obtained. One hundred seventy-three papers were removed after reading the titles and abstracts of the papers. The remaining 19 papers were left after reading carefully for the full text. A total of 15 RCTs were finally included in this Meta-analysis, and all RCTs were single-center studies. (Fig. 1)

3.2. Basic information for inclusion in the literature (Table 1)

3.3. Evaluation of the quality of the literature on RCTs included in the literature (Fig. 2)

3.4. Results of efficacy analysis

3.4.1. BCVA. LogMAR visual acuity and ETDRS visual acuity were included and analyzed separately.

3.4.1.1. LogMAR visual acuity Nine studies reported BCVA (LogMAR) after treatment, and subgroup analyses of BCVA were performed according to different follow-up times (1, 3, 6, 9, and 12 months). The results existed large heterogeneity ($P < .001$, $I^2 = 88\%$), using a random-effects model combined with effect size analysis. There was no statistical difference in BCVA at 1 month between the 2 groups (MD = 0.04, 95% CI: −0.04 to 0.12, $P = .30$). Four studies reported BCVA at 3 months after treatment and there was no statistically significant difference in BCVA between the 2 groups (MD = −0.11,95% CI: −0.41 to 0.18, $P = .46$). Five papers reported BCVA at 6 months after treatment and there was no statistically significant difference in BCVA between the 2 groups (MD = −0.03, 95% CI: −0.07 to 0.00, $P = .08$). Two papers reported BCVA at 9 months after treatment and there was no statistically significant difference in BCVA between the 2 groups (MD = −0.03, 95% CI: −0.07 to 0.00, $P = .08$). Two papers reported BCVA at 9 months after treatment and there was no statistically significant difference in BCVA between the 2 groups (MD = −0.03, 95% CI: −0.11 to 0.05, $P = .44$). Eight studies reported BCVA at 12 months after treatment and there was no statistically significant difference in BCVA between the 2 groups (MD = 0.03, 95% CI: −0.05 to 0.10, $P = .50$).(Fig. 3)

3.4.1.2. ETDRS visual acuity Four of the included analyses reported BCVA (ETDRS) after treatment, and subgroup analyses of BCVA were performed according to different follow-up times (3, 6, 9, and 12 months), and the combined results showed low heterogeneity ($P = .70$, $I^2 = 0\%$), using a fixed-effects model combined with effect size analysis. Four studies reported BCVA at 3 months after treatment and there was no statistically significant difference in BCVA between the 2 groups (MD = 0.03, 95% CI: −1.16 to 1.22, $P = .96$). Four studies reported BCVA at 6 months after treatment and there was no statistical difference in BCVA between the 2 groups (MD = 0.51, 95% CI: −0.42 to 1.79, $P = .23$). Three studies reported BCVA at 9 months after treatment and there was no statistical difference between the 2 groups (MD = 0.68, 95% CI: −0.42 to 1.79, $P = .23$). Two papers reported BCVA at 12 months after treatment and there was no statistically significant difference between the 2 groups (MD = 2.55, 95% CI: −1.73 to 6.82, $P = .24$). (Fig. 4)

3.4.2. CMT. Fourteen papers reported CMT after treatment, and CMT was analyzed in subgroups according to different follow-up times (1, 3, 6, 9, and 12 months), and the results showed large heterogeneity ($P < .001$, $I^2 = 78\%$), using a random-effects model combined with effect size analysis. Five papers reported CMT at 1 month after treatment and there was no statistically significant difference in CMT between the 2 groups (MD = −18.12, 95% CI: −49.21 to 12.97, $P = .25$). Eight papers reported CMT at 3 months after treatment and there was no statistical difference in CMT between the 2 groups (MD = −6.03,95% CI: −24.55 to 12.50, $P = .52$). Nine papers reported CMT at 6 months after treatment and there

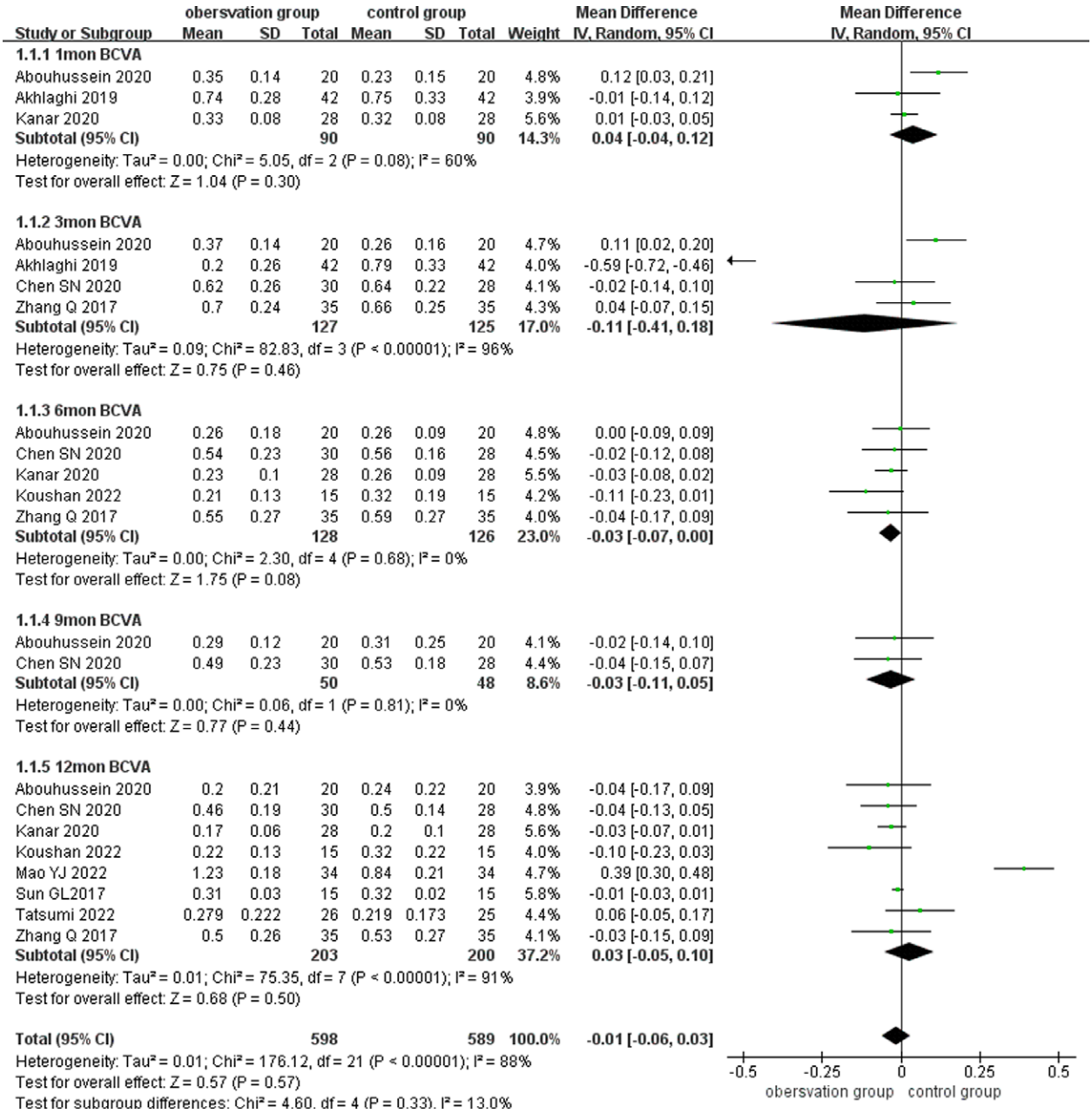

Figure 3. Forest plots comparing BCVA subgroups at different times after treatment in the observation and control groups. BCVA = best-corrected visual acuity.

was no statistically significant difference in CMT between the 2 groups (MD = −20.55, 95% CI: −39.12 to −1.98, P = .18). Four studies reported CMT at 9 months after treatment and there was a statistically significant difference between the 2 groups (MD = −6.03, 95% CI: −24.55 to 12.50, P = .03). Ten papers reported CMT at 12 months after treatment and result showed that CMT at 12 months after treatment was lower than that of the control group (MD = −17.50, 95% CI: −30.50 to −4.51, P = .008). (Fig. 5)

3.4.3. TMV. Four studies reported TMV after treatment, and subgroup analyses of TMV after treatment were performed according to different follow-up times (3, 6, 9, and 12 months), and the results existed large heterogeneity between studies (P = .005, I^2 = 61%), using a random-effects model. Three studies reported TMV at 3 months after treatment and there was no statistically significant difference between the 2 groups (MD = −0.23,95% CI: −0.80 to 0.33, P = .42). Three studies reported TMV at 6 months after treatment and there was no statistical difference between the 2 groups (MD = −0.27,95% CI: −0.72 to 0.19, P = .25). Three studies reported TMV at 9 months after treatment and there was no statistical difference between the 2 groups (MD = −0.01, 95% CI: −0.39 to 0.37, P = .96). Two studies reported TMV at 12 months after treatment and there was no statistical difference between the 2 groups (MD = −0.48, 95% CI: −1.64 to 0.69, P = .42). (Fig. 6)

3.4.4. Number of anti-VEGF drug injections. Eleven studies compared the complications of SML combined with anti-VEGF drugs for DME, and there was large heterogeneity (I^2 = 93%, P < .001) and were analyzed using a random-effects model. Meta-analysis showed that the number of vitreous cavity injections of anti-VEGF drugs was lower in the observation group than in the control group (MD = −1.85, 95% CI: −2.61 to −1.08, P < .001). (Fig. 7)

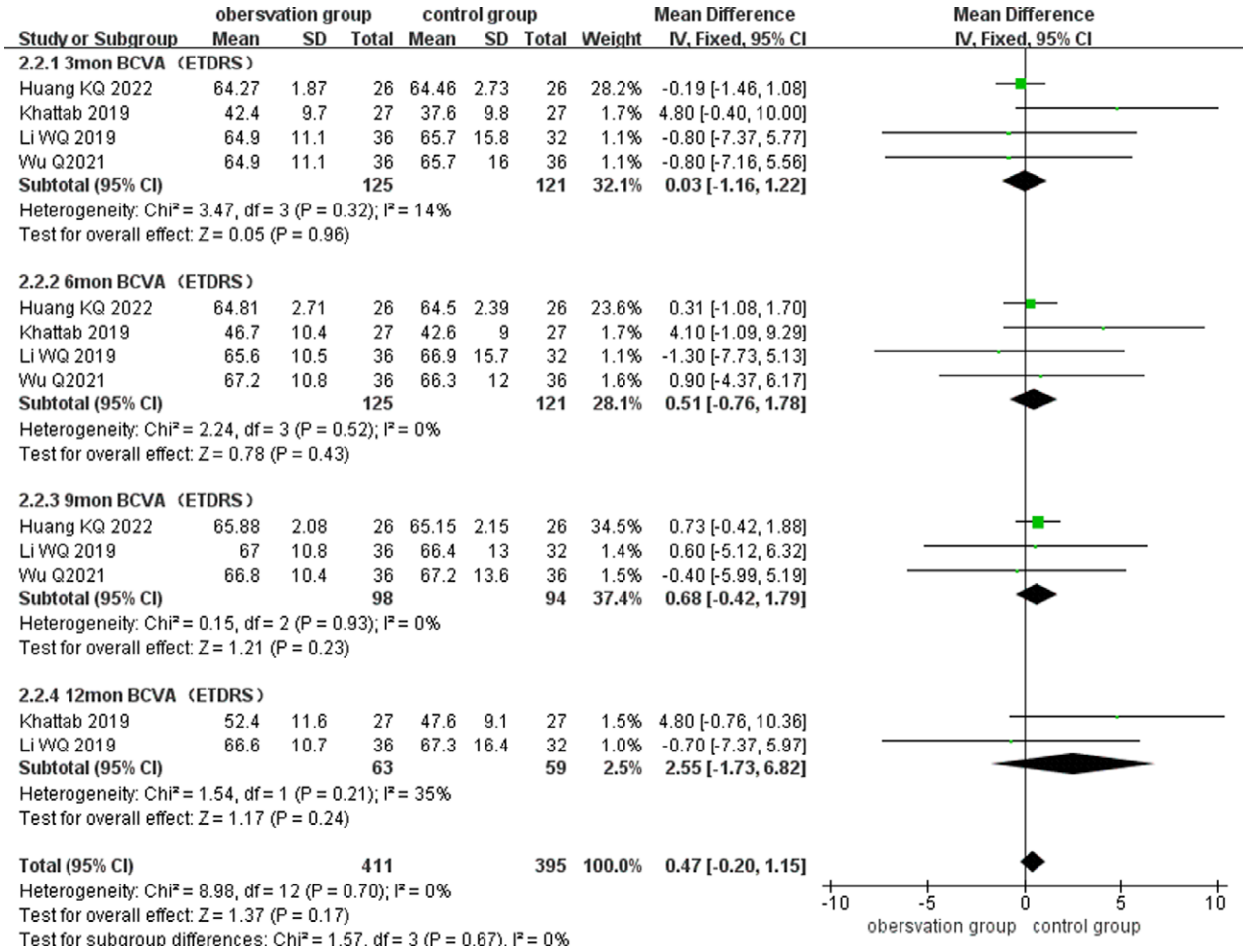

Figure 4. Forest plots comparing BCVA subgroups at different times after treatment in the observation and control groups. BCVA = best-corrected visual acuity.

3.4.5. Complications. Three studies compared the complications of SML combined with anti-VEGF drugs for DME, and results existed low heterogeneity (I^2 = 0%, P = .57), indicating no heterogeneity between studies, and were analyzed using a fixed-effects model. There was no statistically significant difference in occurrence of adverse events between 2 groups (ratio of ratios = 1.28. 95% CI: 0.61–2.66, P = .51). (Fig. 8)

3.5. Sensitivity analysis

Sensitivity analysis was performed for each of the 5 outcome indicators of BCVA, CMT, TMV, the number of anti-VEGF drugs, and complications. The result showed that changing the model had no significant effect on the combined results. By removing every literature, there was no statistically significantly reduced ieterogeneity, suggesting stable and reliable results.

3.6. Analysis of publication bias

Publication bias was detected for the combined results when the included literature over 3 papers. Egger test was performed by STATA 15. The results showed that there was a publication bias in BCVA (ETDRS) and CMT 9 months after treatment (P = .039, P = .013, respectively). The remaining outcome indicators had no publication bias. (Table 2)

4. Discussion

DME is the leading cause of vision loss in patients with DM.[2,3] The pathogenesis of diabetic macular edema is complex and not fully understood, mainly due to a series of inflammatory responses secondary to ischemia and hypoxia, in which multiple inflammatory factors are involved. VEGF is one of them.[28]VEGF has been shown to be one of the most important inflammatory factors in the pathogenesis of DME, and the expression of VEGF in the vitreous of DM patients is 10-fold higher than that of non-DM patients. The upregulation of VEGF leads to the breakdown of the blood-retinal barrier, disrupts vascular permeability, promotes neovascularization, and ultimately leads to the formation of DME. The current treatment modalities for DME are diverse and include vitreous cavity injections of anti-VEGF drugs, glucocorticoids (Triamcinolone acetonide, dexamethasone implant, and fluorescence implant), photocoagulation (conventional retinal laser, subthreshold micropulse laser), surgical treatment, herbal medicine, and combination therapy, among which anti-VEGF drugs are currently the first choice.[29,30]

Common anti-VEGF drugs include the following: nucleic acid aptamers (Pegaptanib), VEGF antibodies (Bevacizumab), VEGF antibody fragments (Ranibizumab), and fusion proteins (Aflibercept, Conbercept).[31] Anti-VEGF drugs alleviate DME by reducing the inflammatory response and inhibiting neovascularization.[32] Although anti-VEGF is effective in treating DME, it requires repeated multiple injections, which not only increases the financial burden but also the potential risks such as infection.[6] In recent years, many scholars have used SML combined with anti-VEGF drugs for the treatment of DME. Subthreshold micropulse laser is a conventional laser split into multiple short, repetitive pulsed lasers, with a single pulsed laser time including ON and OFF period. During the ON period, the laser energy is

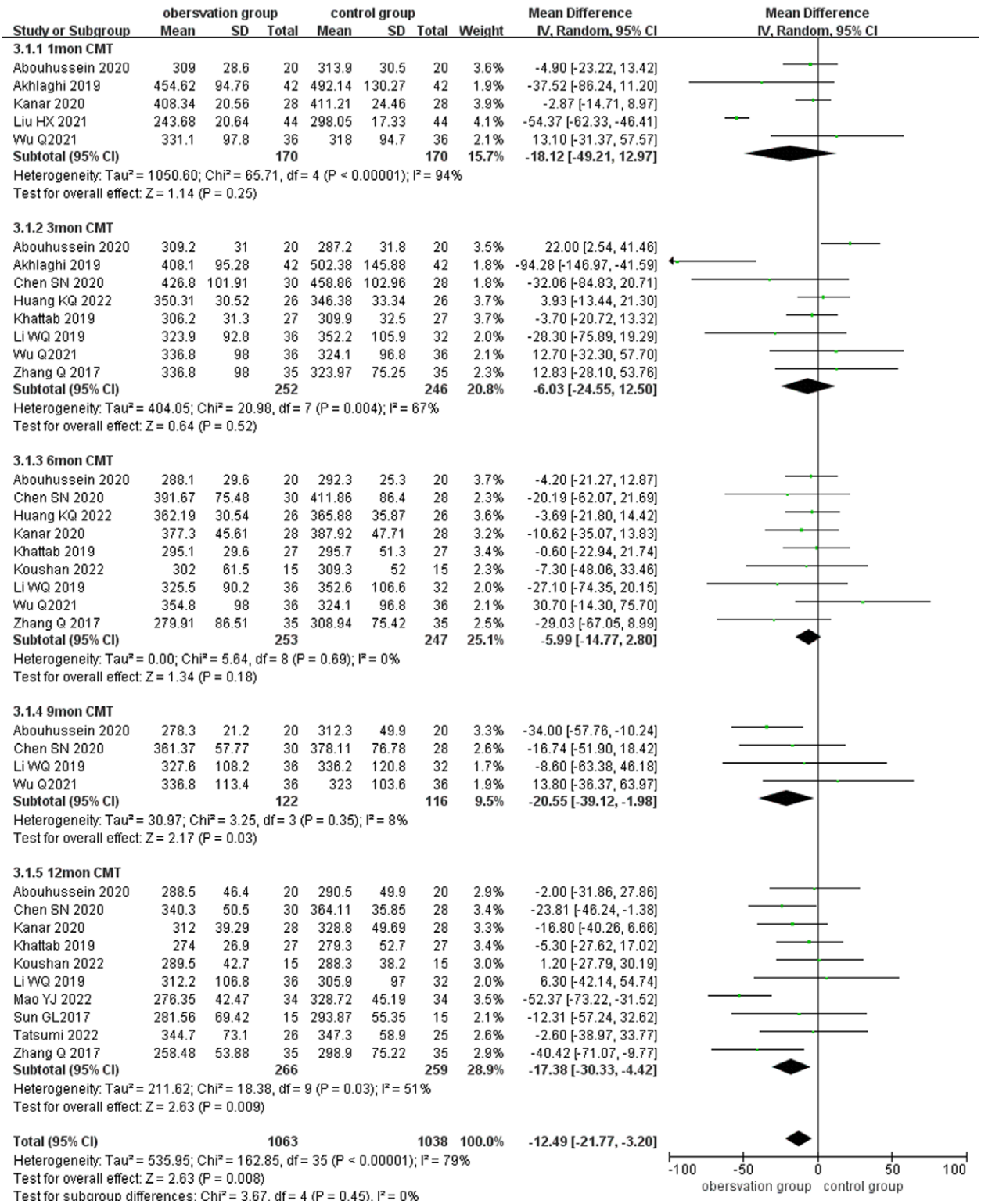

Figure 5. Forest plot comparing CMT subgroups at different times after treatment in the observation and control groups. CMT = central macular thickness.

converted into heat energy in the RPE cells, but the RPE cells start to cool during OFF period to avoid thermal damage to the RPE cells and finally prevent the laser energy from spreading to the surrounding area. The mechanism of action of subthreshold micropulse laser is not fully well understood, and it is speculated that it may be related to the promotion of RPE cell proliferation, tight junctions between RPE cells, restoration of RPE cell function, promotion of subretinal and intraretinal fluid uptake. What's more, SML could upregulate heat shock protein 70 and pigment epithelium-derived factor, downregulation of VEGF.[33]

Recently, scholars have used SML combined with anti-VEGF drugs for the treatment of DME, but the results are controversial. Several studies have found that SML combined with anti-VEGF drugs can reduce the number of vitreous injections of anti-VEGF drugs.[14–22] However, some scholars believe that combination therapy cannot reduce the number of anti-VEGF drug injections,

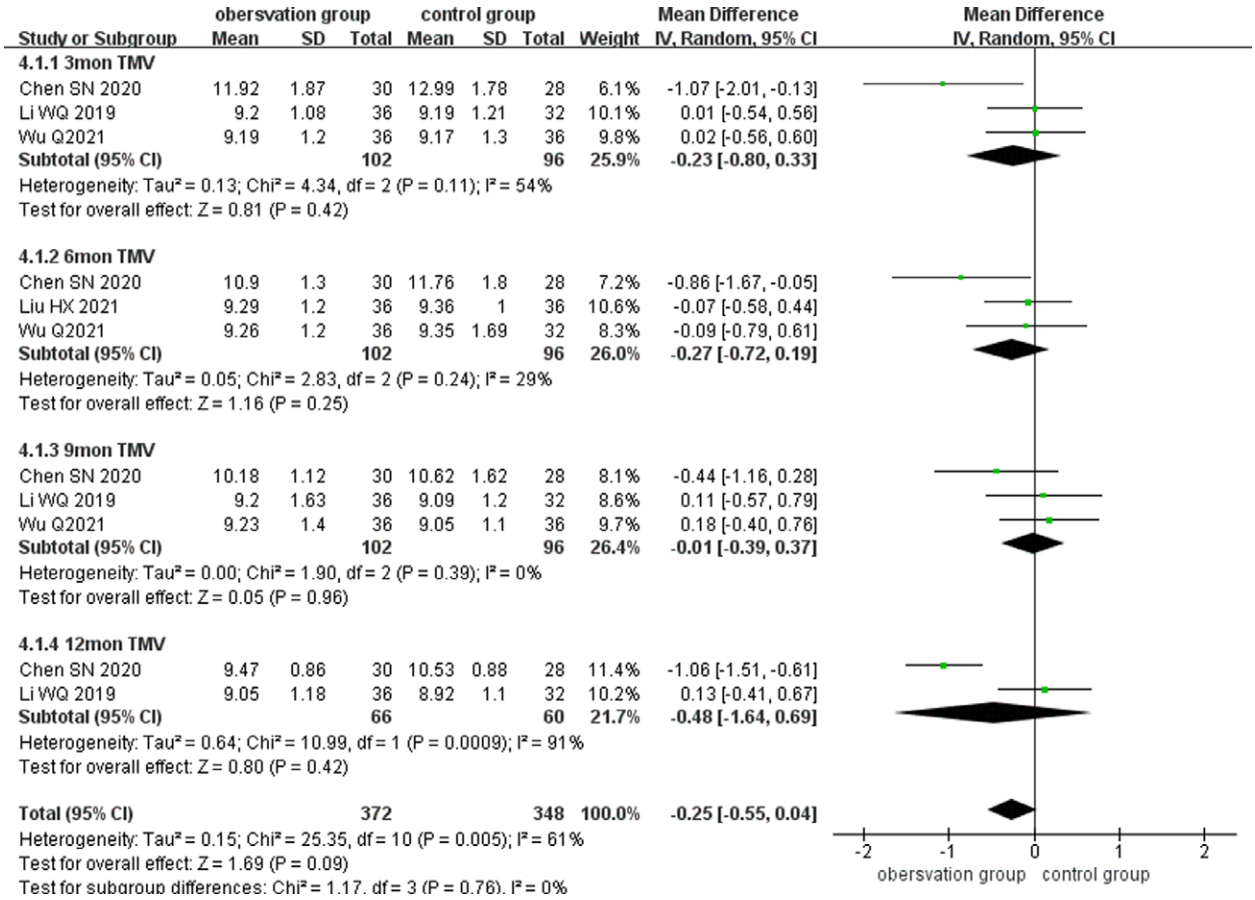

Figure 6. Forest plot comparing TMV subgroups at different times after treatment in the observation and control groups. TMV = total macular volume.

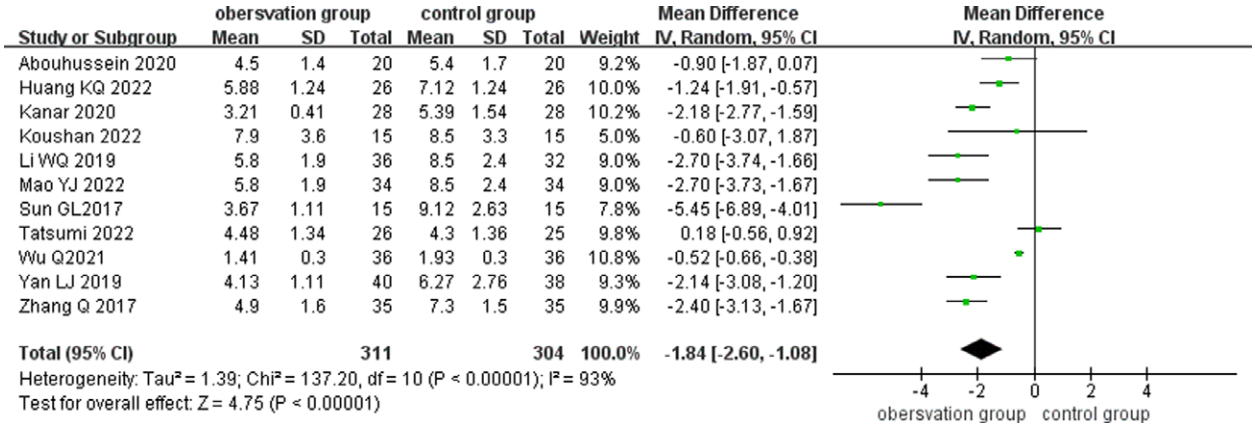

Figure 7. Forest plot comparing the number of anti-VEGF drugs injected into the vitreous cavity in the observation and control groups. VEGF = vascular endothelial growth factor.

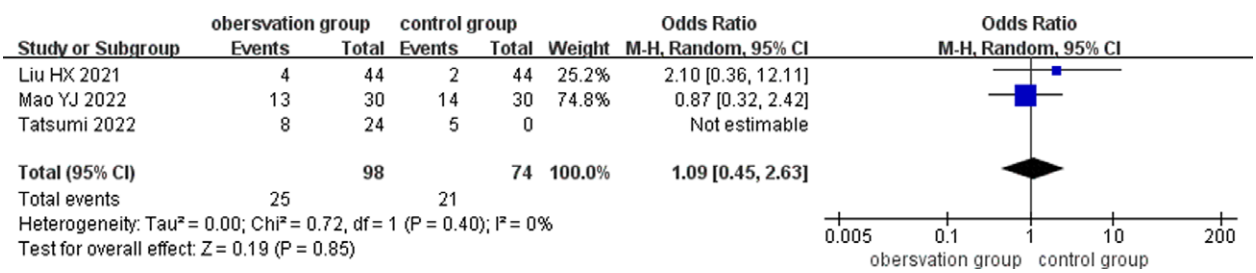

Figure 8. Forest plot comparing complications during treatment in the observation and control groups.

Table 2

Analysis of publication bias.

Research content	Inclusion of literature (article)	The *P* value of Egger test
BCVA (LogMAR)		
1 mo	3	*P* = .19
3 mo		
6 mo	5	*P* = .315
12 mo	8	*P* = .903
BCVA (ETDRS)		
3 mo	4	*P* = .488
6 mo	4	*P* = .327
9 mo	3	*P* = .039
CMT		
1 mo	5	*P* = .388
3 mo	8	*P* = .083
6 mo	9	*P* = .825
9 mo	4	*P* = .013
12 mo	10	*P* = .382
TMV		
3 mo	3	*P* = .138
6 mo	3	*P* = .150
9 mo	3	*P* = .071
Number of injections	11	*P* = .545
Adverse reactions	3	*P* = .207

BCVA = best-corrected visual acuity, CMT = central macular thickness, TMV = total macular volume.

but increases the financial burden of patients.[10,23] Therefore, in this paper, we conducted this meta-analysis, aiming to compare the clinical efficacy of SML combined with anti-VEGF drugs and provide more reliable evidence for the application of SML combined with anti-VEGF drugs in the treatment of DME.

15 RCTs were included for Meta-analysis. There was not statistically significant difference between 2 groups in BCVA after treatment at 1, 3, 6, 9, and 12 months. The CMT in the observation group was lower than that in the control group at 9 and 12 months after treatment ($P < .05$). There was no statistically significant difference between 2 groups in TMV at 3, 6, 9, and 12 months. The number of anti-VEGF injections was lower in the observation group than that in the control group, and the difference was statistically significant ($P < .05$). The occurrence of complications in the 2 groups was no statistical difference between the 2 groups.

This Meta-analysis has some limitations: First, only the literature published in the journal were included, which may lead to some bias; The number of included studies is small and follow-up periods are inconsistent. The duration of diabetes mellitus patients is inconsistent. The above differences may have led to variability in the study results; The time points for observation of outcome indicators were inconsistent. The wavelength and protocol of SML in different studies were inconsistent. The above difference may lead to some bias; The types of anti-VEGF drugs are inconsistent, which may lead to differences in the results. Hence, because of the above limitations of this study, more high-quality, multicenter, large-sample randomized controlled trials are needed in the future to provide more clinical evidence for the clinical use of SML in combination with anti-VEGF drugs in the treatment of DME.

5. Conclusion

In summary, this study shows that SML combined with anti-VEGF drugs does not improve BCVA and TMV well in patients with DME, but it improves macular edema and reduces the number of injections of anti-VEGF drugs, thereby reducing the financial burden on patients. And the combination never increases the risk of ocular or systemic complications.

Author contributions

Conceptualization: Dahua Xu, Mei Chen.
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Formal analysis: Dahua Xu, Ting Zhu, Lin Huang, Xiaolin Wang.
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