Systematic Review and Meta-Analysis

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Impact of antimalarial (AM) on serum lipids in systemic lupus erythematosus (SLE) patients

A systematic review and meta-analysis

Chen-Yang Tao, MM[a], Jin Shang, MD[a], Tao Chen, MD[a,b], Dahai Yu, MD[a,c], Yu-Min Jiang, MD[d], Dong Liu, MD[a], Gen-Yang Cheng, MD[a], Jing Xiao, MD[a], Zhan-Zheng Zhao, MD[a,*]

Abstract

Background: Dyslipidemia is a common disorder in systemic lupus erythematosus (SLE) patients. It is still inconclusive whether antimalarial drugs could affect the serum lipids in SLE patients, therefore we conducted a systematic review and meta-analysis of available data to address this issue.

Methods: We comprehensively searched the databases of PubMed, EMBASE and Cochrane Library from date of inception to Sep 2018 for both randomized controlled trials (RCTs) and observational studies. Review Manager 5.3 software was used for analysis. We performed meta-analysis using random-effects model and weighted the mean difference (WMD) and its 95% confidence interval (CI). The *Q* test was used to assess the presence of heterogeneity and the I^2 index was used to quantify the extent of heterogeneity.

Results: In total, 8 studies met our selection criteria including 2 RCTs, 2 cohort studies, and 4 case-control studies. There were 717 patients (336 patients in CQ (chloroquine) or HCQ (hydroxychloroquine) group, and 381 patients in control group (SLE patients without the therapy of AM)). Compared with the control group, TC, TG, LDL-C, VLDL-C were associated with a significant decrease, respectively (WMD = −21.40 mg/dL, 95% CI −27.62 to −15.18, $P < .00001$), (WMD = −29.07 mg/dL, 95% CI −45.28 to −12.86, $P = .0004$), (WMD = −16.25 mg/dL, 95% CI −28.82 to −3.68, $P = .01$), (WMD = −6.41 mg/dL, 95% CI −12.39 to 0.44, $P = .04$), however the change of HDL-C did not reach statistically significance (WMD = 4.42 mg/dL, 95% CI −1.21 to 10.06, $P = .12$).

Conclusions: CQ or HCQ can infect the serum lipids in SLE patients. However, these results should be interpreted with cautions since lacking sufficient RCTs.

Abbreviations: CI = confidence interval, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, RCTs = randomised controlled trials, SLE = systemic lupus erythematosus, TC = cholesterol, TG = triglyceride, VLDL-C = very low-density lipoprotein cholesterol, WMD = weighted the mean difference.

Keywords: antimalarial, meta-analysis, serum lipids, systemic lupus erythematosus

1. Introduction

SLE is a chronic autoimmune disease with multiple system impairments that can be severe and threaten patients' life.[1–3] The morbidity of SLE was 8.3/100,000/year for females and 1.4/100,000/year for males.[4] Premature atherosclerosis and subsequent progressions have become the leading cause of death in patients with SLE.[5–7] Dyslipidemia is one of the traditional risk factors for atherosclerosis,[8,9] and it is a very frequent comorbidity in SLE patients with negative effects in the long term,[10,11] which not only increases the risk of cardiovascular disease but also affects other clinical symptoms of SLE patients, such as accelerating chronic kidney disease process and damaging brain function. There are also some conditions which influence

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C-YT and JS contributed equally to this work.

We retrieved all data for the meta-analyses from published material. Therefore, the data are available in the respective articles.

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[a] Department of Nephrology, the First Affiliated Hospital of Zhengzhou University, Zhengzhou, China, [b] Tropical Clinical Trials Unit, Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, [c] Arthritis Research UK Primary Care Centre, Research Institute for Primary Care & Health Sciences, Keele University, Keele, UK, [d] Department of Emergency, the First Affiliated Hospital of Zhengzhou University, Zhengzhou, China.

[*] Correspondence: Zhan-Zheng Zhao, Department of Nephrology, the First Affiliated Hospital of Zhengzhou University, Zhengzhou, China (e-mail: zhanzhengzhao@zzu.edu.cn).

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dyslipidemia prevalence, such as auto-antibody in lipoprotein metabolism, renal involvement, disease activity and increased lipid level due to drugs.[6,12,13] Tselios et al reported that the prevalence of dyslipidemia was 36% among newly diagnosed SLE patients, and 60% or even higher after 3 years.[14]

Antimalarials are the old drugs used in clinics. CQ and HCQ are common antimalarials, CQ was introduced in 1953, and HCQ in 1955.[15] These 2 kinds of drugs are both 4-amino-quinolines, HCQ is an analog of CQ. These 2 compounds have many similarities in pharmacological function and biological mechanism.[16] Nowadays, CQ and HCQ are widely used in SLE patients.[17–20]

The use of CQ or HCQ may be associated with lower levels of serum lipid in SLE patients, especially among those who were on steroids. In 1990, Wallace et al had suggested that HCQ therapy had a significantly statistical association with serum lipids reduction in SLE patient.[21] However, Tam et al had reported that HCQ has no significant effect on lipid in Chinese lupus patients in 2000.[22] Since then, there were some studies on this, but the evidences are insufficient and inconclusive. We, therefore, performed a systematic review and meta-analysis to evaluate the impact of CQ or HCQ on serum lipids in SLE patients.

2. Methods

2.1. Search strategy

In order to identify all available studies, the study was performed according to PRISMA (preferred reporting items for systematic review and meta-analysis) guidelines.[23] We searched all literatures in PubMed, Cochrane Databases and EMBASE (up to September 2018). There were no limitations on language or publication date. Literature search was performed using the following search terms in all possible combinations: systemic lupus erythematosus (SLE), lupus erythematosus disseminatus, lupus, SLE, Antimalarials, Hydroxychloroquine, chloroquine, lipid (see search strategy for PubMed in online supplementary file, http://links.lww.com/MD/C902). In addition, all the references in the retrieved literatures were manually reviewed to identify other potentially relevant articles.

2.2. Study selection

The following inclusive selection criteria were applied:

1. study design: RCTs, cohort or case-control studies with detailed data,
2. study population: the diagnosis of patients was fulfilled the American College of Rheumatology (ACR) criteria for SLE, without diseases caused by dyslipidemia and the current taking lipid-lowering drugs,
3. comparison intervention: with and without CQ or HCQ,
4. outcome measure: serum lipids (TC, TG, LDL-C, HDL-C, and VLDL-C). In the case of duplicate data publication (several studies with overlapping samples), we only included the most informative article or complete study to avoid duplication of information.

2.3. Date extraction and quality assessment

In each study, the following data items were extracted:

(1) first author's name,
(2) year of publication,
(3) study design,
(4) population,
(5) number of participants in the CQ or HCQ and control groups,
(6) age, weight of study participants,
(7) duration of SLE,
(8) mean dose of drug,
(9) level of serum lipids.

A systematic assessment of bias in the included RCTs' studies was performed using the Cochrane criteria.[24] We assessed the authenticity and quality of the included observational studies by Newcastle-Ottawa scales (NOS).[25] The scoring system encompasses a resulting score range between 0 and 9 with a higher score representing a better methodological quality.[26] Two investigators (Chen Yang Tao and Jin Shang) carried out the literature search, study selection, data extraction and quality assessment independently. Any discrepancies were resolved by consensus.

2.4. Statistical analysis and risk of bias assessment

All statistical analysis was conducted by Review Manager 5.3 software. Differences between cases and controls were calculated by using the WMD for continuous variables and were illustrated by a forest plot. Random-effects model was employed to obtain an average effect size and to study heterogeneity. Statistical heterogeneity between studies was assessed with Chi-square heterogeneity statistic Q and then quantified with I^2. $P < .1$ or $I^2 > 50\%$ revealed significant heterogeneity among studies.[27,28] When standard error of the mean (SEM) was only reported, standard deviation (SD) was estimated using the following formula: $SD = SEM \times \text{sqrt}(n)$, where n is the number of subjects. A P value less than .05 was considered significant for all statistical tests.

2.5. Sensitivity analyses

Our sensitivity analysis was performed by leave-one-out approach.[29]

2.6. Patient and public involvement

No patients or the public were involved in this study.

3. Results

3.1. Characteristics of included studies

Three hundred twenty-five publications were found during the initial literature search. Of which, 47 were excluded for duplicate studies and 245 papers were excluded by reading their title and abstract (see the detail in Fig. 1). The remaining 8 studies were included in the final review.[21,30–36] The main characteristics of the 8 included studies are shown in Table 1. These studies were published between 1990 and 2017. In the 8 studies, 717 SLE patients were included (336 cases in CQ or HCQ group and 381 cases in control group). Of which, 2 experimental of studies used CQ,[33,34] 2 experimental of studies used HCQ or CQ while there was not detailed statement,[31,32] 4 experimental of studies used HCQ.[21,30,35,36] The overall patients were unbalanced in gender composition with more females than males.

3.2. Quality assessment

Figure 2 and Table 1 show a risk-of-bias made for the studies included. There are some unclear items in 2 RCTs. No observational studies obtain the score of 9 stars, 2 studies scored 7, 3 scored 6, 1 scored 4. Therefore, the methodological quality of studies included here was not satisfied.

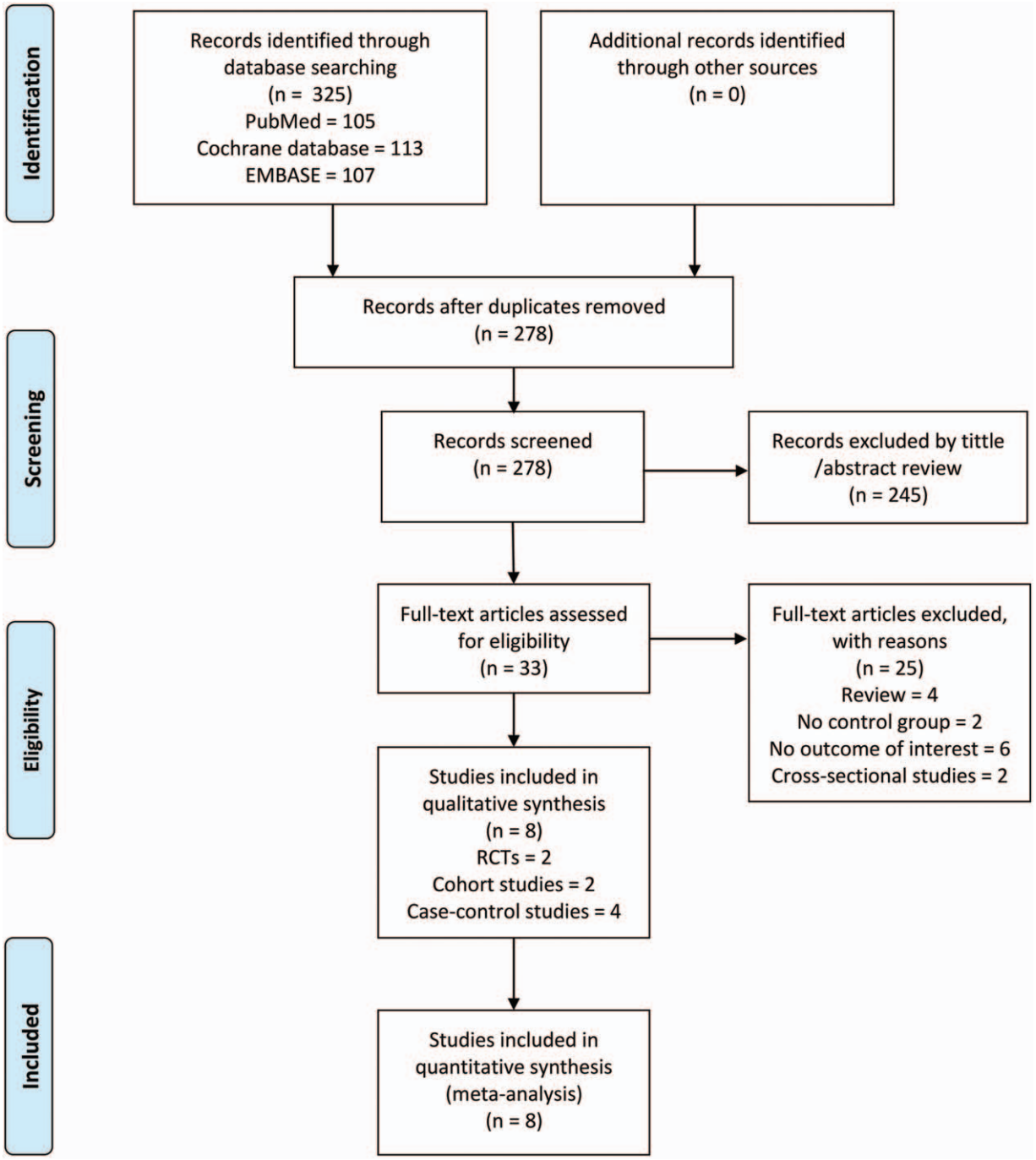

Figure 1. Schematic representation of the literature identification and selection process.

3.3. Meta-analysis results

Figure 3 shows the pooled results from the random-effects model combing the WMD for serum lipids. CQ or HCQ's effect on SLE serum lipids was reported in 2 RCTs, 2 cohort studies and 4 case-control studies. Among them, 8 of the studies assessed TC, 7 of the studies assessed TG, LDL-C, HDL-C and 5 of the studies assessed VLDL-C.

The systematic review and meta-analysis suggested that the CQ or HCQ therapy reduce the level of serum TC (WMD = −21.40 mg/dL, 95% CI −27.62 to −15.18, $P < .00001$; $I^2 = 0\%$, $P = .71$). TG (WMD = −29.07 mg/dL, 95% CI −45.28 to −12.86, $P = .0004$; $I^2 = 48\%$, $P = .07$). LDL-C (WMD = −16.25 mg/dL, 95%CI −28.82 to −3.68, $P = .01$; $I^2 = 73\%$, $P = .001$), HDL-C (WMD = 4.42 mg/dL, 95% CI −1.21 to 10.06, $P = .12$; $I^2 = 70\%$, $P = .003$). VLDL-C (WMD = −6.41 mg/dL, 95% CI −12.39 to 0.44, $P = .04$; $I^2 = 67\%$, $P = .02$).

3.4. Subgroup and sensitivity analysis

We repeated the primary analyses among subgroups defined by: drugs (RCTs or observational studies). Table 2 shows the results

Table 1

Characteristics of included studies.

				HCQ or CQ group				Control group					
First author/yr	Number (n)	Study design	Population	Number of patients	Mean age (yr)	Mean weight (kg)	Dose	Duration (yr)	Number of patients	Mean age (yr)	Mean weight (kg)	Dose	Duration (yr)	NOS score
Wallace, DJ (1990)	53	Cohort study	≥16 years, 100% females	HCQ and steroids (18)	46.4	62.3	Mean dose HCQ 400 mg/d Mean dose steroids 8 mg/d	–	Steroids alone (35)	46.3	63.6	Mean dose steroids 10.83 mg/d	–	6
Kavanaugh, A (1997)	11	RCT	100% female	HCQ (6)	–	–	Mean dose HCQ 400 mg/d	–	Placebo (5)	–	–	–	–	–
Rahman, P (1999)	382	Cohort study	–	Prednisone and Anti-malarials (181)	–	–	Maximum HCQ was 400 mg/d, or Maximum CQ was 250 mg/d, Mean dose Prednisone 10.4 mg/d	–	Prednisone (201)	–	–	Mean dose Prednisone 10.1 mg/d	–	6
Tam, LS (2000)	123	Case control study	89.4% female	Antimalarials (59)	–	–	Mean dose HCQ 355 mg/d Or Mean dose CQ 205 mg/d	–	Non-AMs (64)	–	–	–	–	7
Borba, EF (2001)	29	Case control study	100% consecutive female patients	CDP+ Prednisone (14)	32.2	–	CDP 250 mg /d Prednisone 12.5 mg/d	8.5	Prednisone (15)	34.6	–	Prednisone 10.0 mg/d	7.0	7
Sachet, JC (2007)	20	Case control study	100% consecutive female patients	CDP (10)	35.4	60.2	CDP 250 mg /d	9.5 ± 4.6	Non-therapy (10)	36.5	63	–	8.2 ± 6.6	6
Meng, J (2014)	72 (lost 11)	RCT	87.5% female	HCQ (31)	40	BMI 25	HCQ 400 mg/d Prednisone 5–10 mg/d	2.3 ± 1.0	No-HCQ (30)	39	BMI 25	Prednisone 5–10 mg/d	2.1 ± 1.1	–
Ali Abdalla, M (2017)	38	Case control study	100% female SLE patients	HCQ (17)	–	–	HCQ 400 mg/d	–	No-HCQ (21)	–	–	–	–	4

AM = Antimalarial, BMI = body mass index, CDP = chloroquine diphosphate, CQ = chloroquine, HCQ = hydroxychloroquine, Non-AMs = non-antimalarial, RCT = randomized controlled trial.

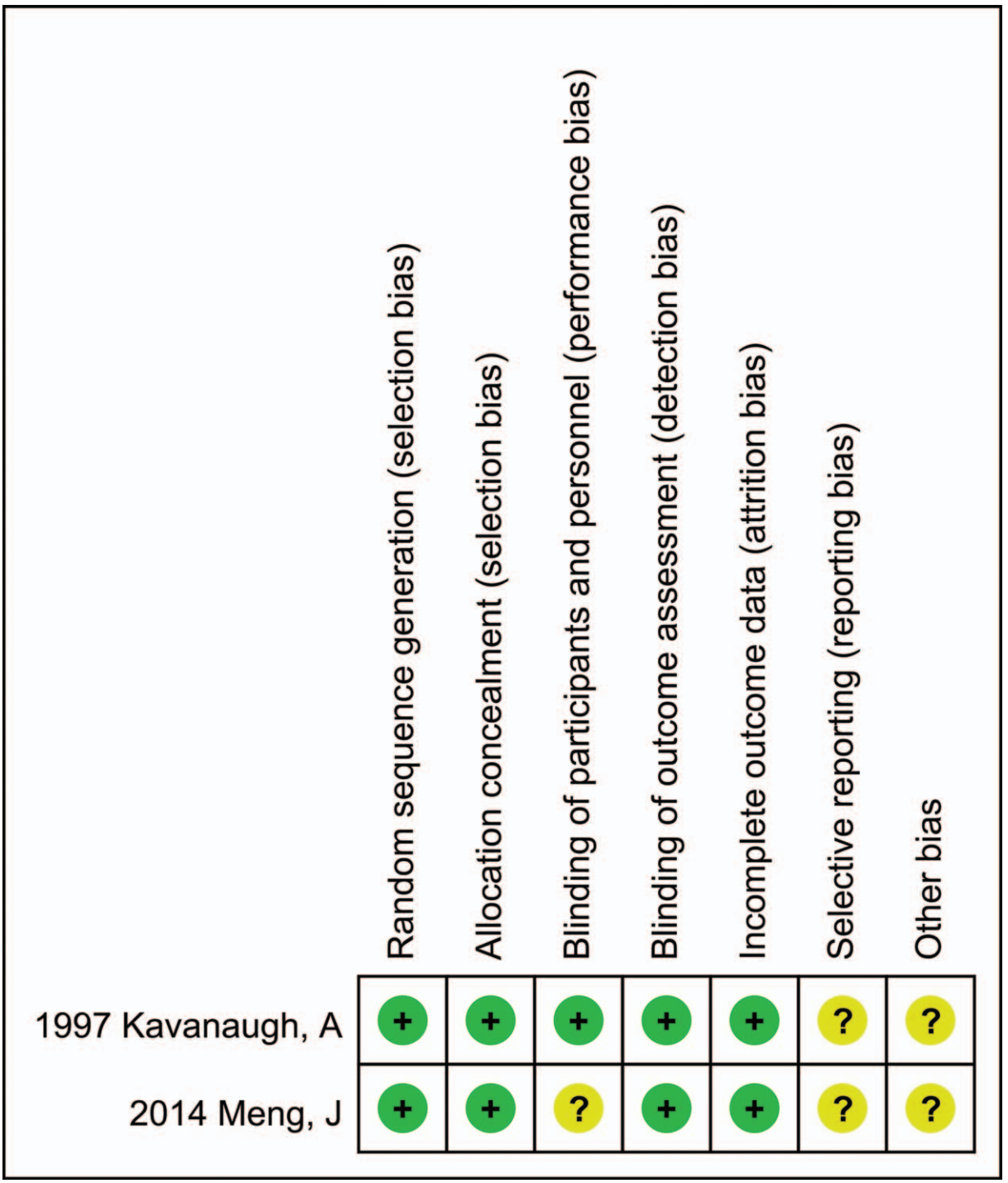

Figure 2. Quality assessment of the included RCTs. RCTs = randomised controlled trials.

of subgroup analysis for serum lipids. The finding of antimalarials decreased serum lipids (TC, TG, LDL-C, VLDL-C) in SLE patients was consistently found in most subgroup analysis.

Our sensitivity analysis indicates that excluding one study at a time does not make a significant difference on TC, TG, LDL-C, HDL-C. None of the results was significantly altered, confirming that the result was robust.

3.5. Publication bias

There was significant asymmetry in the funnel plot for the effect of CQ or HCQ on TG, LDL-C, HDL-C, VLDL-C, which may be due to publication bias and other causes and no publication bias was found for the effect of CQ or HCQ on TC (Fig. 4).

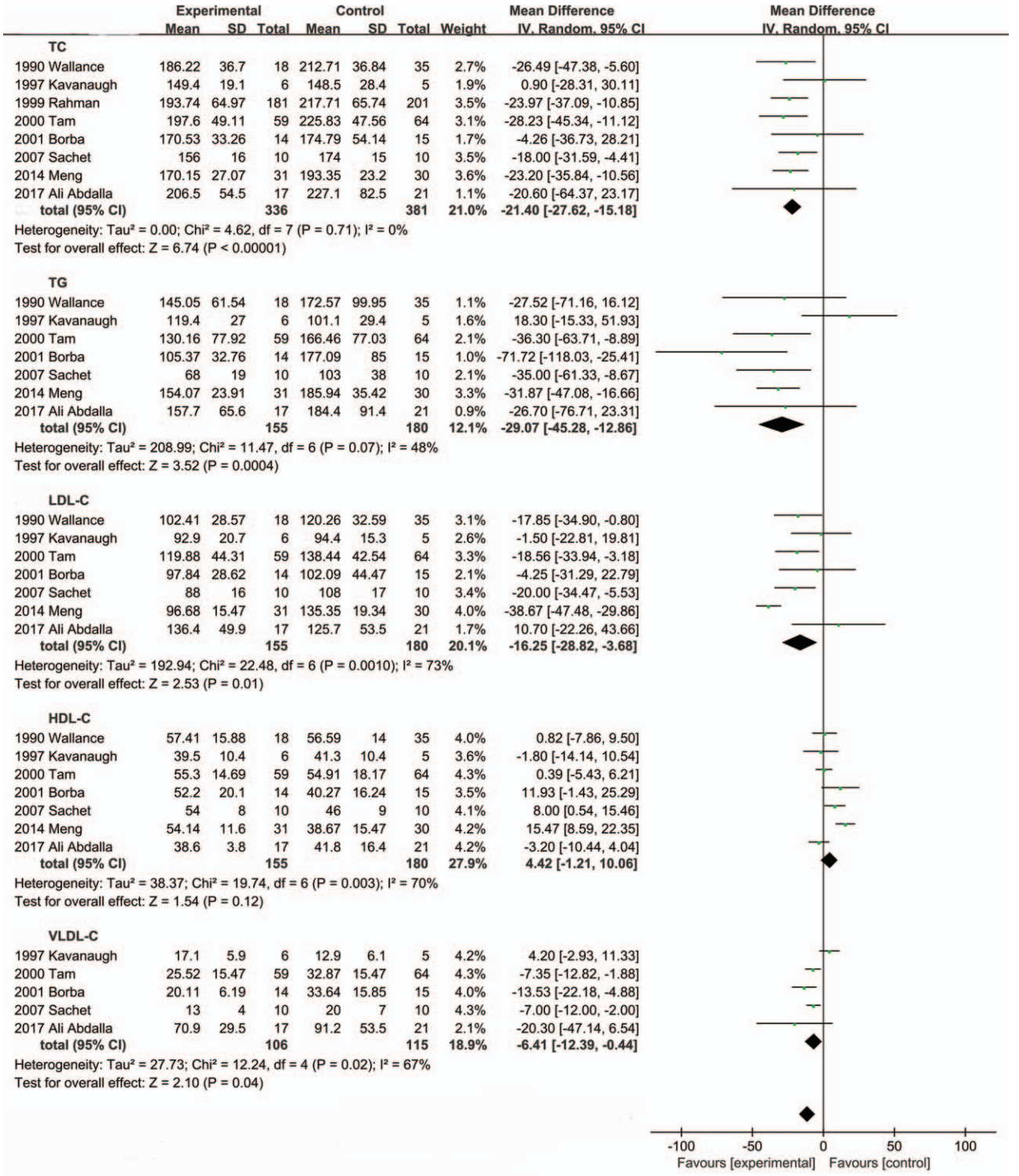

Figure 3. Meta-analysis of the results.

4. Discussion

To the best of our knowledge, this is the first meta-analysis to explore the effect of CQ or HCQ on TC, TG, LDL-C, HDL-C and VLDL-C in SLE patients. A total of 8 studies, predominantly reporting low level of evidence (2 RCTs, 2 cohort studies, 4 case-control studies) were included in this study. Overall, we quantitatively summarize all the available evidences and find that HCQ or CQ therapy could significantly decrease the serum TC, TG, LDL-C, VLDL-C by 21.40 mg/dL, 29.07 mg/dL, 16.25 mg/dL, 6.41 mg/dL, respectively, but not HDL-C in comparison of control group. We found that the trend varied a little in subgroup analyses.

Although the treatments of SLE vary, antimalarials were still considered as the basic drugs in SLE patients.[37,38] Some

Table 2

The results of subgroup analyses.

Studies	No. of studies	Total sample size	WMD (mg/dL)	95% CI (mg/dL)	Heterogeneity I^2
1. Subgroup outcomes of TC (different drugs)					
CQ	2	49	−15.95	−28.49 to −3.41	0
HCQ	4	163	−21.05	−30.93 to −11.17	0
AM (CQ or HCQ)	2	505	−25.55	−35.96 to −15.13	0
2. Subgroup outcomes of TG (different drugs)					
CQ	2	49	−48.22	−82.76 to −13.67	45%
HCQ	4	163	−17.50	−42.96 to 7.95	58%
AM (CQ or HCQ)	1	123	−36.30	−63.71 to −8.89	–
3. Subgroup outcomes of LDL-C (different drugs)					
CQ	2	49	−16.44	−29.35 to −3.52	1%
HCQ	4	163	−14.85	−36.84 to 7.14	84%
AM (CQ or HCQ)	1	123	−18.56	−33.94 to −3.18	–
4. Subgroup outcomes of HDL-C (different drugs)					
CQ	2	49	8.94	2.42 to 15.45	0
HCQ	4	163	3.18	−6.52 to 12.88	81%
AM (CQ or HCQ)	1	123	0.39	−5.43 to 6.21	–
5. Subgroup outcomes of VLDL-C (different drugs)					
CQ	2	49	−9.27	−15.37 to −3.18	39%
HCQ	2	49	−4.49	−27.47 to 18.48	67%
AM (CQ or HCQ)	1	123	−7.35	−12.82 to 1.88	–

relevant studies have reported the influence of CQ or HCQ on serum lipids in SLE patients. In 1997, Arthur Kavanaugh et al reported a double-blind, randomized, placebo-controlled, pilot study on 17 patients with SLE, the results showed a significant decrease in TC among patients receiving 400 mg/day HCQ (MD = 11.6 mg/dL, $P = .03$).[30] A recent meta-analysis also reported the decrease of LDL-C after using HCQ, but this study did not include other serum lipids in terms of TC, TG, HDL-C, and VLDL-C, and could not give people a complete acknowledge of the impact of AM on serum lipids in SLE patients. In 2017, Ali Abdalla et al reported a case-control study about the impact of HCQ on serum lipids, this study showed that there was no significant difference between the HCQ group and the control group.[36]

The mechanism of HCQ or CQ decreasing the serum lipid among SLE patients remains unclear. In 1983, Sewell et al reported that after chloroquine administration, the hepatic activities of lysosomal enzymes (N-acetyl-beta-glucosaminidase, beta-glucuronidase, and beta-galactosidase) were increased and cholesterol saturation of bile decreased by 22% in rat.[39] In 1984, Chen et al reported that CQ treatment of rat cells in culture results in the increase of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase activity,[40] HMG-CoA reductase was a rate limiting enzyme in the process of cholesterol synthetize in hepatocytes. In 2007, Sachet et al reported that CQ can up-regulation LDL-receptor, this is a very efficient mechanism for LDL reduction in SLE.[34] This up-regulation in LDL receptors may be due to the CQ-mediated decrease in cholesterol

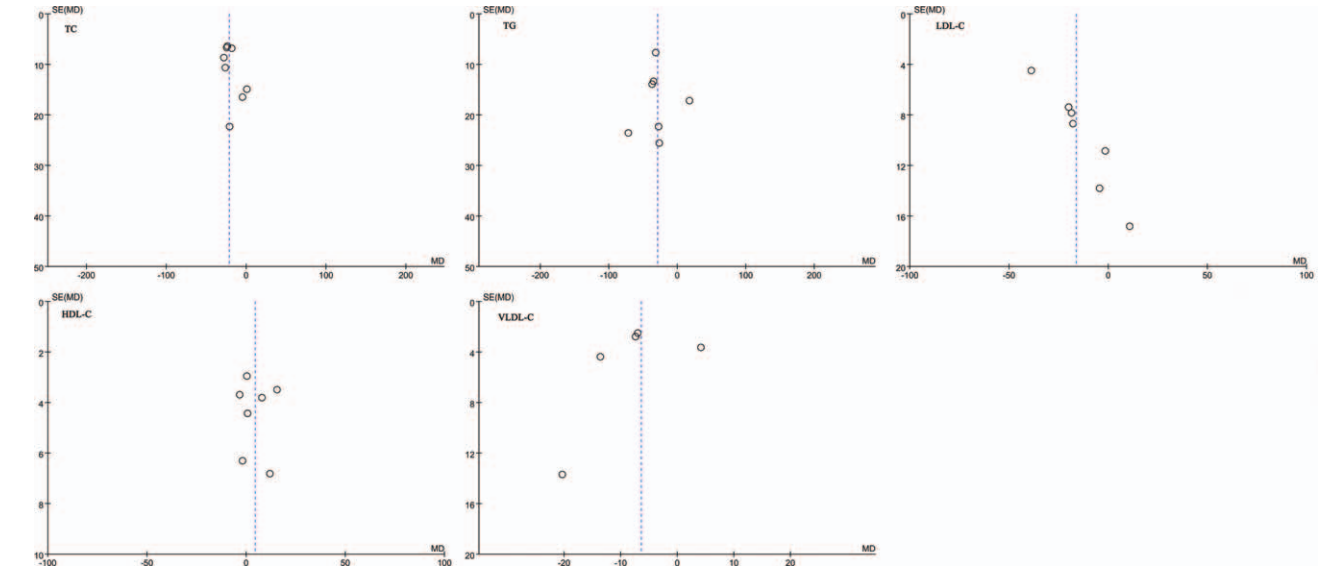

Figure 4. Funnel plots for the effect of CQ or HCQ on serum lipids in SLE patients. CQ = chloroquine, HCQ = hydroxychloroquine, SLE = systemic lupus erythematosus.

synthesis.[41] More studies are needed to determine the mechanism of CQ or HCQ decrease serum lipid.

Different studies had different results and conclusions, we conducted a meta-analysis of relevant studies to further confirm the impact. The results showed that CQ or HCQ can decrease the TC, TG, LDL-C, VLDL-C in SLE patients, and our findings are of clinical significance to some extent. CQ or HCQ can decrease the serum lipids, which was the most risk factor results in atherosclerosis and coronary heart disease (CAD). In 2014, Meng et al reported that after 24 months' using of HCQ, the level of serum lipids reduced, and the left ventricular end diastolic diameter and left ventricular posterior wall thickness decreased as well.[35] We proposed that CQ or HCQ might be a beneficial choice in the prevention of CAD in lupus patients. To our best knowledge, SLE patients have a more prevalent about atherosclerosis and CAD. Once diagnosed with CAD, patients were probably to take several drugs lifelong. HCQ is a multifunctional drug that contains the both benefits of therapy SLE and prevents CAD. In China, SLE patients from the onset to the use of HCQ is still relatively interval a long time, we think that should shorten the time. SLE patients may be more popular to promote the use of HCQ.

Strengths of this meta-analysis included its exhaustive search without language restrictions and validated systematic review methods following the PRISMA guidelines. Several limitations of this meta-analysis merit consideration. First, the characteristics of populations, and the adjusted confounding factor were not strictly described in some studies; however, these factors may result in heterogeneity and have a potential impact on our results. Second, since there were not enough RCTs for this meta-analysis, the conclusion remains questionable for all the SLE population.

5. Strength and limitations

5.1. Strength

This study exhaustive searched without language restrictions and validated systematic review methods following the PRISMA guidelines.

5.2. Limitations

(1) The characteristics of populations and the adjusted confounding factor were not strictly described in some studies. However, these factors may result in heterogeneity and have a potential impact on our results.
(2) There were not enough RCTs for this meta-analysis, the conclusion remains questionable for all the SLE population.

6. Conclusions

Our results suggest that CQ or HCQ has the effect on reducing the serum lipids in patients with SLE; however, these results should be interpreted with cautions due to the significant heterogeneity in the study and limited RCTs. Further RCTs are needed to confirm this conclusion.

Author contributions

Conceptualization: Chen-Yang Tao, Jin Shang.
Data curation: Chen-Yang Tao, Jin Shang, Tao Chen.
Formal analysis: Chen-Yang Tao, Jin Shang, Dahai Yu.
Funding acquisition: Jin Shang, Zhan-Zheng Zhao.
Investigation: Chen-Yang Tao, Jin Shang, Yu-Min Jiang
Methodology: Chen-Yang Tao, Jin Shang, Yu-Min Jiang
Project administration: Chen-Yang Tao, Jin Shang, Gen-Yang Cheng.
Resources: Chen-Yang Tao, Jin Shang, Zhan-Zheng Zhao.
Software: Chen-Yang Tao, Jin Shang, Tao Chen.
Supervision: Dong Liu, Gen-Yang Cheng, Jing Xiao.
Validation: Chen-Yang Tao, Jin Shang, Dong Liu.
Visualization: Chen-Yang Tao, Jin Shang, Jing Xiao.
Writing – Original Draft: Chen-Yang Tao, Jin Shang.
Writing – Review and Editing: Chen-Yang Tao, Jin Shang.

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