Systematic Review and Meta-Analysis

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The efficacy and safety of acupuncture in nonalcoholic fatty liver disease

A systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: The aim of this study was to determine the efficacy and safety of acupuncture treatment (AT) or acupuncture plus conventional medicine (CM) versus CM alone using a meta-analysis of all published randomized controlled trials (RCTs) for nonalcoholic fatty liver disease (NAFLD).

Methods: Eight databases were searched independently from inception to April 30, 2020. RCTs were included if they contained reports on the use acupuncture or the use of acupuncture combined with CM and compared with the use of CM. Summary odds ratio (OR) and 95% confidence intervals (CIs) were used to calculate the overall clinical efficacy. Secondary outcomes, namely aspartate aminotransferase, alanine aminotransferase, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and body mass index, were calculated by mean difference with 95% CIs.

Results: After the final screening, 8 RCTs with 939 patients were included. This meta-analysis showed that AT was superior to CM in improving overall clinical efficacy (OR = 3.19, 95% CI: 2.06–4.92, $P < .00001$). In addition, AT plus CM could significantly improve overall clinical efficacy compared to treatment with CM alone (OR = 5.11, 95% CI: 2.43–10.75, $P < .0001$). Moreover, the benefits were also demonstrated in other outcomes, including alanine aminotransferase, aspartate aminotransferase, total cholesterol, triglyceride, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol indexes. However, AT plus CM could not decrease body mass index levels in comparison with CM. The safety profile of Acupuncture therapy was satisfactory. Taichong, Zusanli, Fenglong, and Sanyinjiao were major acupoints on NAFLD treatment.

Conclusion: Acupuncture may be effective and safe for treatment of NAFLD. However, due to insufficient methodological quality and sample size, further high-quality studies are needed.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, AT = acupuncture treatment, BMI = body mass index, CI = confidence interval, CM = conventional medicine, DGEC = diammonium glycyrrhizinate enteric capsule, EA = electroacupuncture, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, LR3 = Taichong acupoint, MA = manual acupuncture, MD = mean difference, NAFLD = nonalcoholic fatty liver disease, OR = odds ratio, PPC = polyene phosphatidylcholine capsule, RCTs = randomized controlled trials, SIL = silybin capsules, SP6 = Sanyinjiao acupoint, ST36 = Zusanli acupoint, ST40 = Fenglong acupoint, TC = total cholesterol, TET = thread embedding therapy, TG = triglyceride.

Keywords: acupuncture, meta-analysis, nonalcoholic fatty liver disease, randomized controlled trial, systematic review

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PC and ZZ contributed equally to this work.

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1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is a clinical and pathological syndrome characterized by fat degeneration and lipid storage in hepatocytes in the absence of significant alcohol consumption.[1] The pathological changes include simple fatty liver, fatty hepatitis, fatty liver fibrosis and liver cirrhosis.[2] In the past 20 years, NAFLD has evolved from a relatively unknown disease to the most common cause of chronic liver disease in the world, with a worldwide prevalence of 25%.[3] In addition, NAFLD is closely related to the occurrence and development of metabolic diseases and cardiovascular diseases, such as obesity, type 2 diabetes and hepatic complications such as liver fibrosis, cirrhosis, and end-stage liver disease.[4–6] Therefore, NAFLD is emerging as a major threat to general health.

Lifestyle changes, such as diet management, physical exercise, and weight loss, are regarded as the best treatments for NAFLD so far. However, these changes are not easy for many people to implement.[7,8] If patients fail to effectively change their lifestyle, some adjuvant conventional drugs may be recommended according to China's clinical guidelines, such as Statins, polyene phosphatidylcholine capsule (PPC), diammonium glycyrrhizinate enteric capsule (DGEC), and silybin capsule (SIL), are also known to ameliorate NAFLD.[9–11] However, these drugs are generally associated with adverse effects, including manifestations due to hepatotoxicity, increased risk of death, heart failure.[9] As a result, a convenient and effective adjunctive therapy with minimal side effect is needed.

Acupuncture treatment (AT) has a long history in treating diseases and it is well-accepted by many patients because of its convenience and good curative effect.[12] Nowadays, an increasing number of patients from different countries receive AT to treat diseases.[13,14] Acupuncture is a kind of therapy that uses needles to stimulate acupuncture points. The selection of acupoints or treatment frequency may vary from person to person according to the theory of traditional Chinese medicine.[15] Techniques include electroacupuncture (EA), (mild electric stimulation of acupuncture needles), manual acupuncture (MA) (acupuncture stimulation by hand), and thread embedding therapy (TET) (stimulation by inserting a thread into meridian points).[16]

AT has been used to treat NAFLD in China for many years. Previous studies indicated that acupuncture could reduce blood lipids, improve liver function and improve insulin resistance.[17–23] Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) concentrations are clinically known as markers of liver function, and blood lipids parameters (total cholesterol [TC], triglyceride [TG], high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C]) and body mass index (BMI) are defined as the important evaluation indexes of NAFLD[24]. One meta-analysis[25] reported that TET alone or TET plus Chinese herbal medicines was superior to conventional medications on ALT, AST, TC, TG, and overall clinical efficacy on NAFLD treatment. However, the Chinese herbal medicine were used in some studies in their review, which cannot reflect the exact effect of TET on NAFLD treatment. Therefore, we carried out a systematic review and meta-analysis to assess the relative efficacy of acupuncture (MA, EA, TET) or acupuncture plus conventional medicine (CM) in the treatment and management of NAFLD. The meta-analysis showed that acupuncture or acupuncture plus CM was superior to CM in improving overall clinical efficacy, and ALT, AST, TC, TG, HDL-C, LDL-C levels on NAFLD treatment. In addition, LR3 (Taichong), ST36 (Zusanli), ST40 (Fenglong), and SP6 (Sanyinjiao) may be considered as important therapeutic acupoints for NAFLD treatment according to our review.

2. Materials and methods

2.1. Eligibility criteria

The studies included were randomized controlled trials (RCTs) in humans written in Chinese and English reporting on acupuncture for NAFLD. Cells or animal research, case reports, observational studies, academic conferences, duplicated publications, or non-RCTs were excluded.

2.2. Patients

Pregnant women, juveniles, and patients with autoimmune liver diseases, hereditary liver diseases, severe diabetes, malignant tumours or severe cardiovascular diseases were excluded.

2.3. Intervention

All included patients were required to change their lifestyles during treatment such as diet management, and physical exercise, and the way of life interventions adopted by the experimental groups were the same as that of the control groups. Patients in the experimental groups were treated with acupuncture or acupuncture combined with conventional drugs, while the control groups were treated with conventional drugs. All types of penetrating acupuncture were included, such as EA, auricular acupuncture, warm acupuncture, MA, and acupoint thread embedding.

2.4. Databases and search strategy

Eight electronic databases were researched from their inception to April 30, 2020 (PubMed, EMBASE, Cochrane Library, Springer Link, China National Knowledge Infrastructure, Chinese Scientific Journal Database, Wanfang database, and CBM). The search keywords were: "acupuncture", "electroacupuncture", "manual acupuncture", "thread embedding", "nonalcoholic fatty liver disease", "nonalcoholic steatohepatitis", "NALFD", "randomized controlled trial", and "RCTs". For example, the search terms used in PubMed were (((((“Acupuncture Therapy” [Mesh]) or (“Acupuncture” [Mesh])) or ((“acupuncture” [All Fields]) or (“acupuncture therapy” [All Fields]))) AND ((“Medicine” [Mesh]) or ((“medication” [All Fields]) or (“drug” [All Fields])))) AND ((“nonalcoholic Fatty Liver Disease” [Mesh])))) or ((((((((((“Non alcoholic Fatty Liver Disease” [All Fields]) or (“NAFLD” [All Fields])) or (“Nonalcoholic Fatty Liver Disease” [All Fields]))) or (“Fatty Liver, Nonalcoholic” [All Fields])))) or (“Fatty Livers, Nonalcoholic” [All Fields])))) or (“Liver, Nonalcoholic Fatty” [All Fields]))))) or (“Livers, Nonalcoholic Fatty” [All Fields])))))) or (“Nonalcoholic Fatty Liver” [All Fields])))))))) or (“Nonalcoholic Fatty Livers” [All Fields]))))))))) or (“Nonalcoholic Steatohepatitis” [All Fields])))))))))) or (“Nonalcoholic Steatohepatitides” [All Fields])))))))))))) or (“Steatohepatitides, Nonalcoholic” [All Fields])))))))))))) or (“Steatohepatitis, Nonalcoholic” [All Fields]))))))))))))) and (((randomized controlled Trial [Publication Type]) or (randomized [Title/Abstract])) or (placebo [Title/Abstract])))

2.5. Endpoint indicators

Overall clinical efficacy was the primary outcome. According to the appropriate guidelines,[26] it was graded into 4 categories: cure, remarkably effective, effective and ineffective, which was calculated according to the ratio of the total number of those who were effectively treated and the total number of people included. The secondary outcomes were the following: liver function indices: AST, ALT; serum lipid indices: TC, TG, HDL-C, LDL-C; BMI; and adverse events.

2.6. Study identification

Two investigators (Zunming Zhou and Peiwen Chen) reviewed the title and abstract of these studies independently. The full text was independently reviewed by the same authors when those studies could not be identified as an RCT by the title and abstract. Finally, investigators (Zunming Zhou and Peiwen Chen) independently extracted data from the included articles, including the first author's name, year, intervention type, points selected, intervention treatment frequency, course of the disease, duration, and main outcomes, etc. When disagreements occurred, a third author (Yunkai Dai) judged the decisions. Ethical approval and patient written informed consent are not required due to that this is a systematic review and meta-analysis of previously published studies.

2.7. Quality assessment

Two reviewers (Zunming Zhou and Peiwen Chen) used Cochrane Collaboration risk of bias[27] and Jadad score[28] independently to manage methodological quality evaluation. We judged whether all the included literature had bias from selection, performance, detection, attrition, reporting, other bias from randomization, double-blinding, and dropout. If the Jadad scores were ≥3, the article was considered as a high-quality one; otherwise, it was considered as a low-quality article.

2.8. Data synthesis and analysis

Review Manager 5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used for data analysis in this review. Summary odds ratio (OR) and 95% confidence interval (CI) were calculated for the primary outcome. Mean difference (MD) and 95% CI were reported for the secondary outcomes. Inconsistency index statistic I^2 was applied to evaluate heterogeneity.[29] If possible, heterogeneity was investigated and subgroup analysis was conducted. Sensitivity analysis was also performed to evaluate the influence of an individual study on the final effect. When $I^2 > 50\%$, the random-effects model was used, otherwise, the fixed-effects model was applied to analyze data ($I^2 < 50\%$). [30]$P < .05$ meant there was a statistical difference.

3. Results

3.1. Description of studies

A total of 784 records were identified. After further full-texts screening, 8 studies[31–38] were finally included. In addition, all included studies were published in Chinese between 2012 [38] and 2019.[35]Figure 1 shows the study selection details. Overall, 939 participants were enrolled (471 in the experiment groups versus 468 in the control groups). All participants were Chinese. Sample sizes ranged from 48[38] to 260,[34] and participants ages were from 18[34,38] to 68.[32] The disease duration ranged from 5 months[36] to 15.5 years.[34] However,3 studies[31,37,38] did not mention the disease duration. (Table 1).

All included patients were required to change their lifestyles during treatment. They were required to do moderate aerobic exercises, limit daily calories, and adjust their dietary structure. The experiment intervention in the included studies was done using acupuncture or acupuncture combined with CM. The therapeutic sessions ranged from 1 month[36] to 6 months.[33] The selection of acupoints and stimulation methods was different in the included studies. MA was used in 4 studies,[32,34,37,38] EA was used in 2 studies[31,36] and TET was used in 2 studies.[33,35] The most commonly used acupoints were LR3[31–34,36–38] and ST36[32–38], which were respectively used in 7 RCTs, followed by ST40,[32–37] SP6.[32–34,36–38] In the control groups, conventional supplementary drugs were SIL, silybin meglumine tablet, PPC, DGEC, and simvastatin tablet. The characteristics of interventions and comparators are shown in Table 2.

3.2. Risk of bias assessment

No differences were found between the baseline data of the 2 groups. All studies mentioned randomization. However, only 3 studies[32,33,35] used a random number of tables to allocate participants. Blinding of the acupuncturists was difficult to implement because of the characteristic of acupuncture. Only 1 trial[33] used a single-blind method. Moreover, all studies did not use allocation concealment. Three trials[32,33,35] reported some dropouts. The availability of this meta-analysis was considered as high risk due to the lack of specific information. The evaluation of methodological quality is shown in Table 3 and Figures 2 and 3.

3.3. Effects of acupuncture

As shown in Table 2, AT was compared with CM in 4 RCTs,[31,33–35] of which 1 contrasted EA with SIM + SILME,[31] 1 contrasted MA with SIL,[34] while another 2 compared TET with PPC.[33,35] AT plus CM was compared with CM alone in 4 RCTs,[32,36–38] of which 1 contrasted MA plus DGEC with DGEC,[32] 1 contrasted EA plus SIM with SIM,[36] 1 contrasted MA plus SIM with SIM,[37] while 1 contrasted MA plus PPC with PPC.[38]

3.3.1. Primary outcome. Four trials[31,33–35] reported overall clinical efficacy between AT and CM and another 4 trials [32,36–38] reported it between AT plus CM and CM. Significant heterogeneity was not found ($I^2 = 0\%$), therefore, fix-effects model was used. There was significant difference in overall clinical efficacy between AT and CM (n = 669, OR = 3.19, 95% CI: 2.06–4.92, $P < .00001$) (Fig. 4A). In addition, AT plus CM could significantly improve overall clinical efficacy compared with CM alone (n = 270, OR = 5.11, 95% CI: 2.43–10.75, $P < .0001$) with no statistical heterogeneity ($I^2 = 0\%$) (Fig. 4B).

3.3.2. Secondary outcomes

3.3.2.1. Liver function outcomes

3.3.2.1.1. Alanine aminotransferase. The effects of ALT between AT and CM were reported in 4 RCTs,[31,33–35] while another 4 RCTs reported[32,36–38] ALT between AT plus CM and CM. It showed favorable effects of AT on ALT compared with the CM

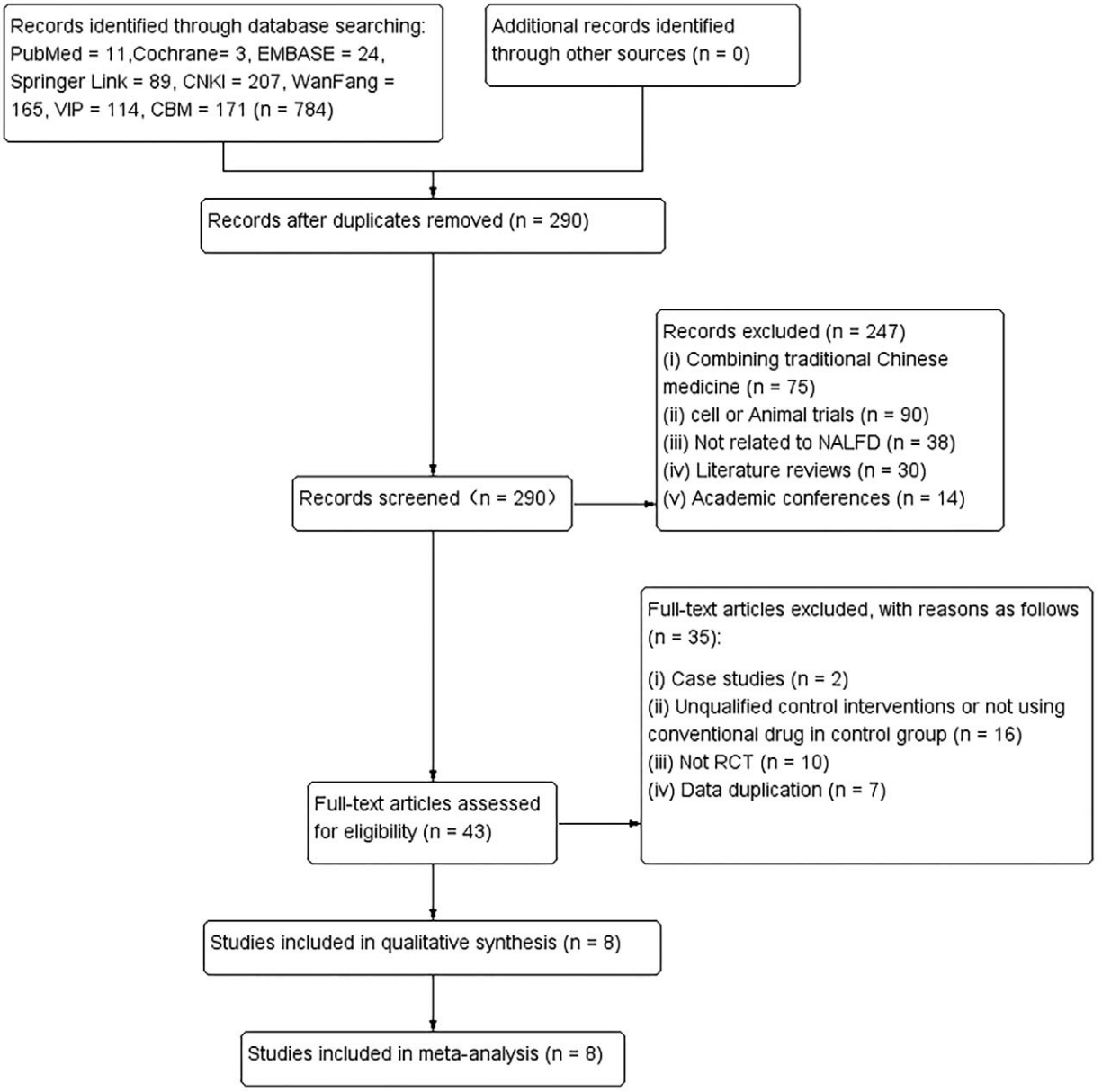

Figure 1. Flowchart of the trial selection process.

(n = 669, MD = −17.40, 95% CI: −25.17 to −9.62, $P < .0001$). Marked heterogeneity was found ($I^2 = 90\%$) in this mode, therefore, the subgroups were further analyzed. Compared with CM, results of Figure 5A showed that EA, MA, and TET could improve ALT levels (EA: n = 130, MD = −24.78, 95% CI: −26.62 to −22.94, $P < .00001$; MA: n = 260, MD = −8.47, 95% CI: −14.80 to −2.14, $P = .009$; TET: n = 279, MD = −17.47, 95% CI: −22.06 to −12.88, $P < .00001$) (Fig. 5A); In addition, AT plus CM could significantly improve ALT levels better than CM alone (n = 270, MD = −11.84, 95% CI: −14.60 to −9.08, $P < .00001$)) with no statistical heterogeneity ($I^2 = 40\%$) (Fig. 5B).

3.3.2.1.2. Aspartate aminotransferase. Two RCTs[33,35] involving 279 patients reported the result of AST between AT and CM. Marked heterogeneity was not found ($I^2 = 0$), therefore, a fix-effects model was used. The results of meta-analysis demonstrated that patients with AT had significantly lower level of AST than patients in the control group (n = 279, MD = −17.69, 95% CI: −20.58 to −14.80, $P < .00001$) (Fig. 6A). Four RCTs[32,36–38] reported the result of AST between AT plus CM and CM. Marked heterogeneity was found ($I^2 = 57$), the heterogeneity was decreased ($I^2 = 0\%$) when Zhang in 2017[37] was removed. It showed that AT plus CM could significantly improve AST levels compared with CM (n = 204, MD = −10.14, 95% CI: −12.34 to −7.95, $P < .00001$) (Fig. 6B).

3.3.2.2. Serum lipid

3.3.2.2.1. Total cholesterol. Four studies[31,33–35] with a total of 669 patients provided the data of TC levels between AT and CM. Marked heterogeneity was found ($I^2 = 95\%$), therefore, the

Table 1

Characteristics of the included studies.

Study ID (first author, year	Sample size EG (M/F)	CG (M/F)	Age (yr)	Course of disease	Duration	Diagnostic criteria	Reported endpoints of interest
Fei 2018[31]	65 (30/35)	65 (29/36)	EG:53.21 ± 3.98 CG:54.08 ± 4.09	NR	3 mo	Chinese NAFLD guideline, 2006 edition Radiologic evidence required	1, 2, 4, 5, 6, 7
Hou 2016[32]	34 (20/14)	37 (21/16)	EG:43.33 ± 25.56 CG:50.72 ± 19.33	E:14.65 ± 11.72 mo C:15.46 ± 10.03 mo	2 mo	Chinese NAFLD guideline, 2006 edition Radiologic evidence required	1, 2, 3, 4, 5, 8, 9
Huang 2016[33]	88 (37/51)	90 (36/54)	EG:46 ± 12 CG:43 ± 16	E:17.5 ± 3.2 mo C:16.8 ± 3.6 mo	6 mo	Internal medicine handbook, 2010 edition Radiologic evidence required	1, 2, 3, 4, 5, 9
Wang 2017[34]	130 (63/67)	130 (84/41)	EG:45.74 ± 3.40 CG:45.32 ± 3.28	E:5.09 ± 1.20 yr C:5.02 ± 1.12 yr	3 mo	Chinese NAFLD guideline, 2006 edition Radiologic evidence required	1, 2, 4, 5, 9
Yang 2019[35]	52 (34/18)	52 (31/21)	EG:43 ± 12 CG:41 ± 16	E:18.11 ± 3.24 mo C:16.96 ± 3.76 mo	3 mo	Chinese NAFLD guideline, 2018 edition Radiologic evidence required	1, 2, 3, 4, 5
Zhang 2016[36]	38 (31/7)	38 (30/8)	EG:46.5 ± 3.4 CG:46.8 ± 3.2	E:1.2 ± 0.4 yr C:1.1 + 0.2 yr	1 mo	Chinese NAFLD guideline, 2006 edition Radiologic evidence required	1, 2, 3, 4, 5
Zhang 2017[37]	33 (17/16)	33 (16/17)	EG:44.0 ± 13 CG:42.0 ± 15	NR	3 mo	Chinese NAFLD guideline, 2006 edition Radiologic evidence required	1, 2, 3, 4, 5
Zhang 2012[38]	24 (9/15)	24 (10/14)	EG:56.7 ± 3.5 CG:57.8 ± 7.2	NR	45 d	Chinese NAFLD guideline, 2006 edition Radiologic evidence required	1, 2, 3, 4, 5, 8

1 = overall clinical efficacy, 2 = alanine transaminase (ALT), 3 = aspartate aminotransferase (AST), 4 = triglyceride (TG), 5 = total cholesterol (TC), 6 = high-density lipoprotein cholesterol (HDL-C), 7 = low-density lipoprotein cholesterol (LDL-C), 8 = body mass index (BMI), 9 = adverse events, CG = control group, EG = experiment group, F = female, M = male, NAFLD = nonalcoholic fatty liver disease, NR = not reported.

Table 2

Interventions and comparators.

Study ID (first author, year	Intervention type	Points selected	Intervention treatment frequency (AT/CM)	Control details	Control treatment frequency (CM)
Fei 2018[31]	LC + EA	Taichong(LR3), Mingnen(GV4), Xuanshu (GV5), Guilai(ST29), Zhongzhu(KI15)	20 min, 5 times per wk	LC + SIM + SILME (oral)	20 mg qn/200 mg tid
Hou 2016[32]	LC + MA + DGEC (oral)	Taichong(LR3), Zusanli(ST36), Fenglong (ST40), Zhongwan(CV12), Sanyinjiao (SP6)	30 min,3 times per wk/ 150 mg tid	LC + DGEC (oral)	150 mg tid
Huang 2016[33]	LC + TET	Taichong(LR3), Zusanli(ST36), Fenglong (ST40), Sanyinjiao(SP6), Ganshu (BL18)	once a wk	LC + PPC (oral)	456 mg tid
Wang 2017[34]	LC + MA	Taichong(LR3), Zusanli(ST36), Fenglong (ST40), Zhongwan(CV12), Hegu(LI4), Neiguan(PC6), Guanyuan(CV4), Sanyinjiao(SP6), Yingnglingquan (SP9), Tianshu(ST26), Taixi(KI3), Fuliu(KI7), Shenshu(BL23)	30 min, 10 times per 2 wk	LC + SIL (oral)	70 mg tid
Yang 2019[35]	LC + TET	Ganshu(BL18), Zusanli(ST36), Fenglong (ST40), Tianshu(ST26), Zhongwan (CV12), Yingnglingquan(SP9), Pishu (BL20), Weishu(BL21), Daheng (SP15), Daimai(GB26), Shuifen(CV9)	once a wk	LC + PPC (oral)	232 mg tid
Zhang 2016[36]	LC + EA + SIM (oral)	Taichong(LR3), Zusanli(ST36), Sanyinjiao(SP6), Fenglong(ST40), Ganshu(BL18),Zhangmen(LR13), Yanglingquan(GB34)	30 min, 6 times per wk/ 10 mg qn/70 mg tid	LC + SIL + SIM (oral)	10 mg qn/70 mg tid
Zhang 2017[37]	LC + MA + SIM (oral)	Taichong(LR3), Zusanli(ST36), Sanyinjiao(SP6), Fenglong(ST40), Ganshu(BL18)	30 min, 6 times per wk/ 10 mg qn	LC + SIM (oral)	10 mg qn
Zhang 2012[38]	LC + MA + PPC (oral)	Taichong(LR3), Guanyuan(CV4), Zusanli (ST36), Sanyinjiao(SP6), Hegu(LI4), Taixi(KI3), Fuliu(KI17), Neiguan(PC6), Shenshu(BL23)	30 min, 3 times per wk/ 456 mg tid	LC + PPC (oral)	456 mg tid

AT = acupuncture therapy, CM = conventional medicine, DGEC = diammonium glycyrrhizinate enteric capsule, EA = electroacupuncture, LC = lifestyle change, MA = manual acupuncture, PPC = polyene phosphatidylcholine capsule, qn = once every night, SIL = silybin capsules, SILME = silybin meglumine tablet, SIM = simvastatin tablet, TET = thread embedding therapy, tid = 3 times a day.

Table 3

Evaluation of methodological quality of the included studies.

Study ID (first author, year	Baseline	Randomization	Blind method	Withdrawal or dropout	Allocation concealment	Follow-up	Side effects	Jadad scores
Fei 2018[31]	Comparability	Mention not describe	NR	NR	NR	NR	NR	1
Hou 2016[32]	Comparability	Random number table	NR	EG:16 cases CG:13 cases	NR	NR	no	3
Huang 2016[33]	Comparability	Random number table	Single-blind	EG:2 cases CG:0 cases	NR	NR	no	3
Wang 2017[34]	Comparability	Mention not describe	NR	NR	NR	NR	EG:8 case	1
Yang 2019[35]	Comparability	Random number table	NR	EG:2 cases CG:1 cases	NR	NR	NR	3
Zhang 2016[36]	Comparability	Mention not describe	NR	NR	NR	NR	NR	1
Zhang 2017[37]	Comparability	Mention not describe	NR	NR	NR	NR	NR	1
Zhang 2012[38]	Comparability	Mention not describe	NR	NR	NR	NR	NR	1

CG = control group, EG = experiment group, NR = not reported.

sensitivity analysis was further analyzed, the heterogeneity was decreased ($I^2 = 37\%$) when Huang in 2016[33] was removed. Acupuncture seemed to be better in improving TC levels than CM with a significant difference (n = 491, MD = −0.71, 95% CI: −0.92 to −0.51, $P < .00001$) (Fig. 7A). Four studies[32,36–38] involving 270 patients reported TC between AT plus CM and CM. Still, there was significant difference between the AT plus CM group and the CM group (n = 270, MD = −1.37, 95% CI: −2.46 to −0.28, $P = .01$). Statistical heterogeneity was found ($I^2 = 96\%$), therefore, the subgroups were further analyzed. The results showed that EA plus CM could improve TC levels better than CM alone (n = 76, MD = −2.64, 95% CI: −3.11 to −2.17, $P < .00001$), whereas no significant effect was observed on TC levels between MA plus CM group and CM group (n = 194, MD = −0.95, 95% CI: −2.06–0.17, $P = .10$) (Fig. 7B).

3.3.2.2.2. Triglyceride. The 4 studies[31,33–35] investigated the efficacy of acupuncture on TG levels. Marked heterogeneity was found ($I^2 = 67\%$), therefore, A sensitivity analysis was conducted. The heterogeneity was decreased ($I^2 = 0\%$) when Wang in 2017[34] was removed. The results showed that patients in the AT group showed significantly lower TG levels (n = 409, MD = −0.87, 95% CI: −0.91 to −0.84, $P < .00001$) (Fig. 8A). Four studies reported TG[32,36–38] between AT plus CM and CM. Results from random-effects meta-analyses showed that AT plus CM was superior in improving TG levels compared with CM alone (n = 270, MD = −0.86, 95% CI: −1.39 to −0.34, $P = .001$). Statistical heterogeneity was found ($I^2 = 93\%$), therefore, the subgroups were further analyzed. The results showed that both EA plus CM and MA plus CM were superior to control groups in improving TG levels (EA plus CM: n = 76, MD = −1.75, 95% CI:

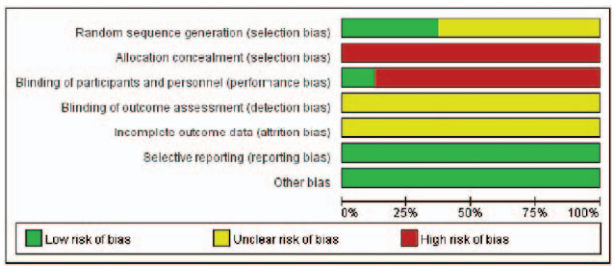

Figure 2. Risk of bias.

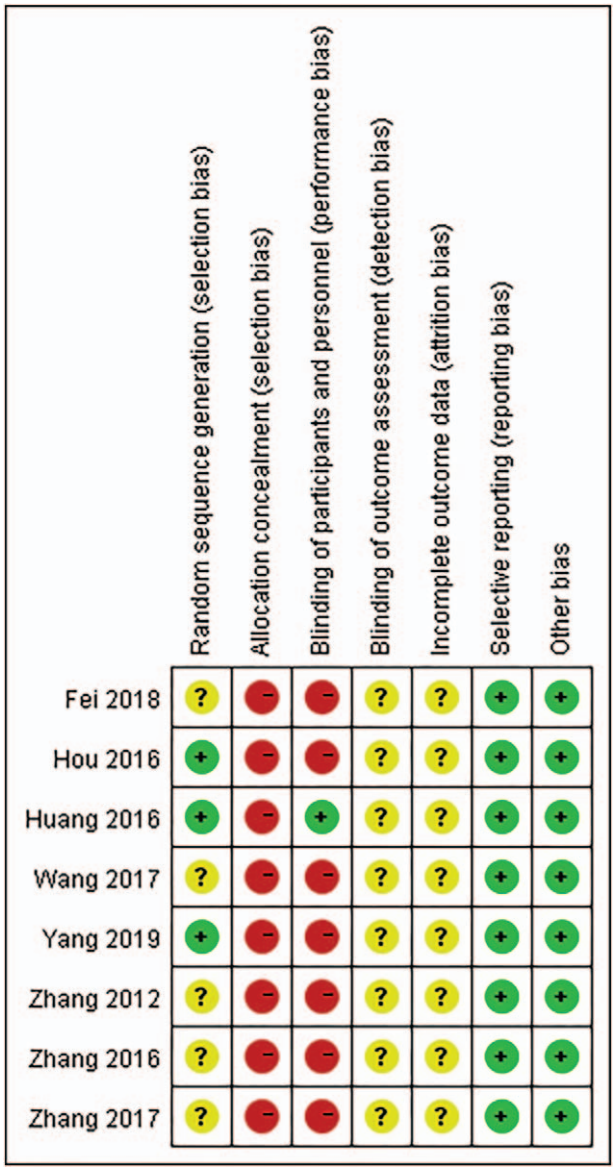

Figure 3. Summary of risk bias.

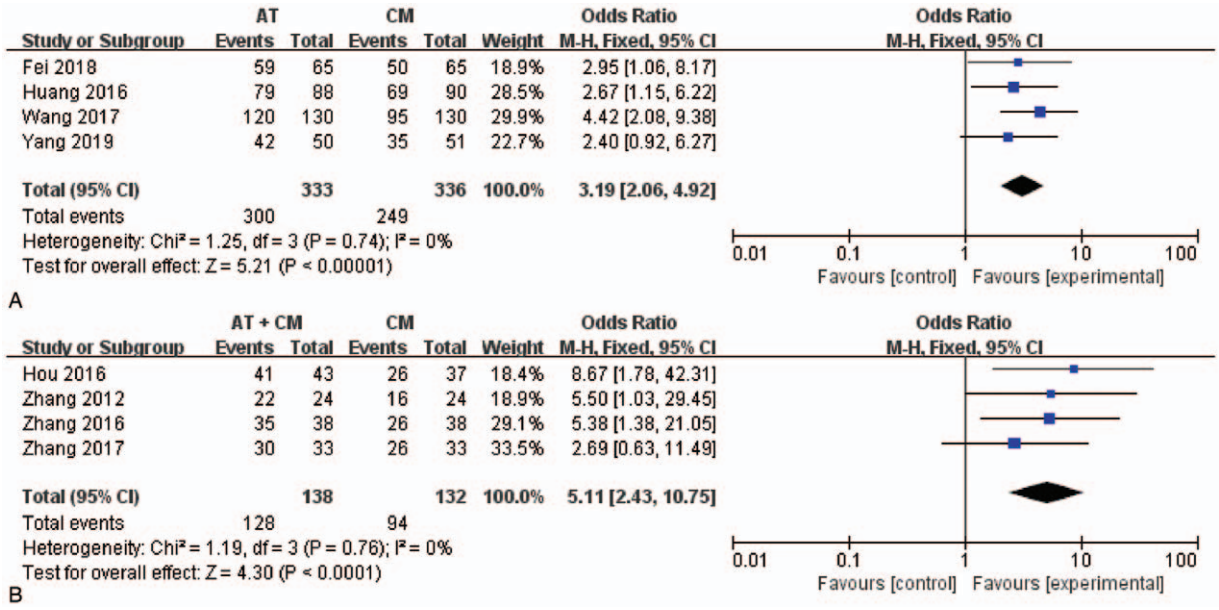

Figure 4. A) Efficacy of acupuncture on overall clinical efficacy. B) Efficacy of acupuncture plus conventional medicine on overall clinical efficacy. AT = acupuncture treatment, CI = confidence interval, CM = conventional medicine.

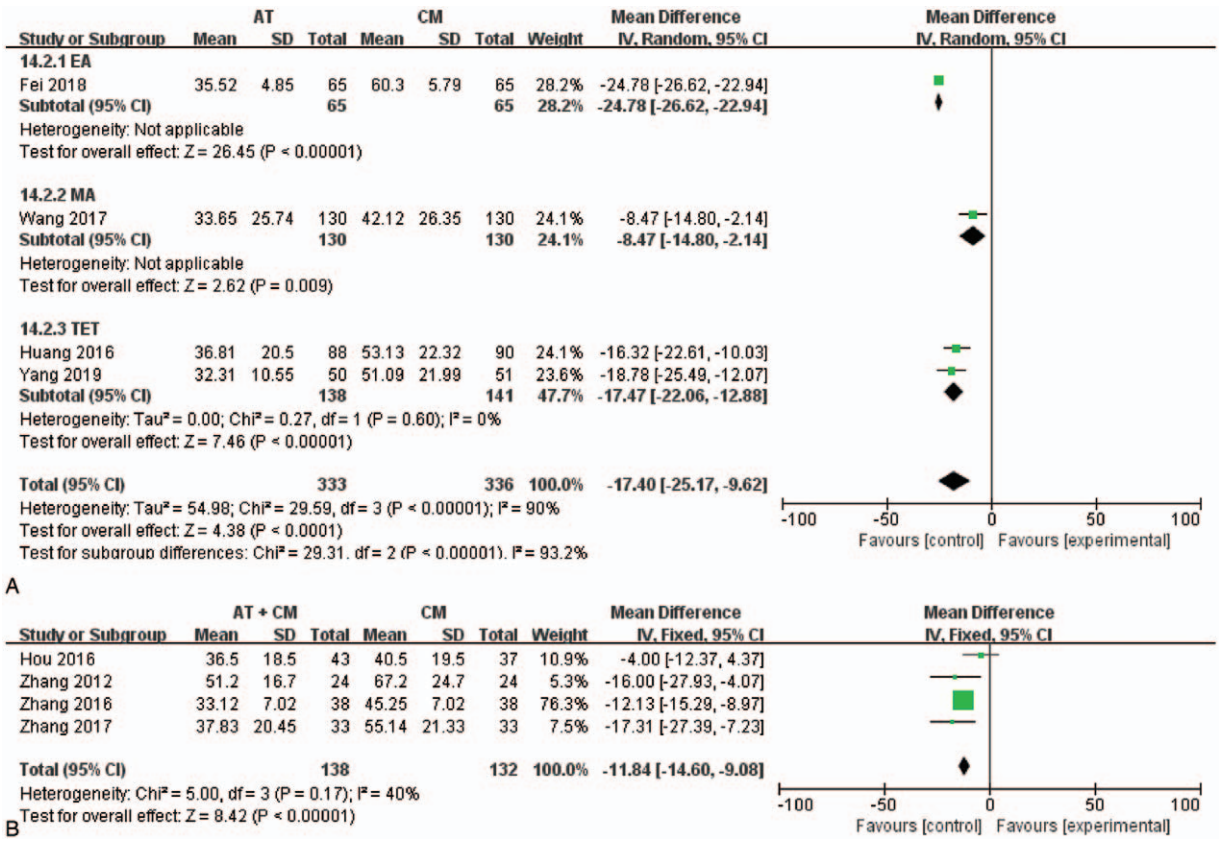

Figure 5. A) Efficacy of acupuncture on ALT. B) Efficacy of acupuncture plus conventional medicine on ALT. ALT = alanine aminotransferase, AT = acupuncture treatment, CI = confidence interval, CM = conventional medicine, EA = electroacupuncture, MA = manual acupuncture, SD = standard deviation, TET = thread embedding therapy.

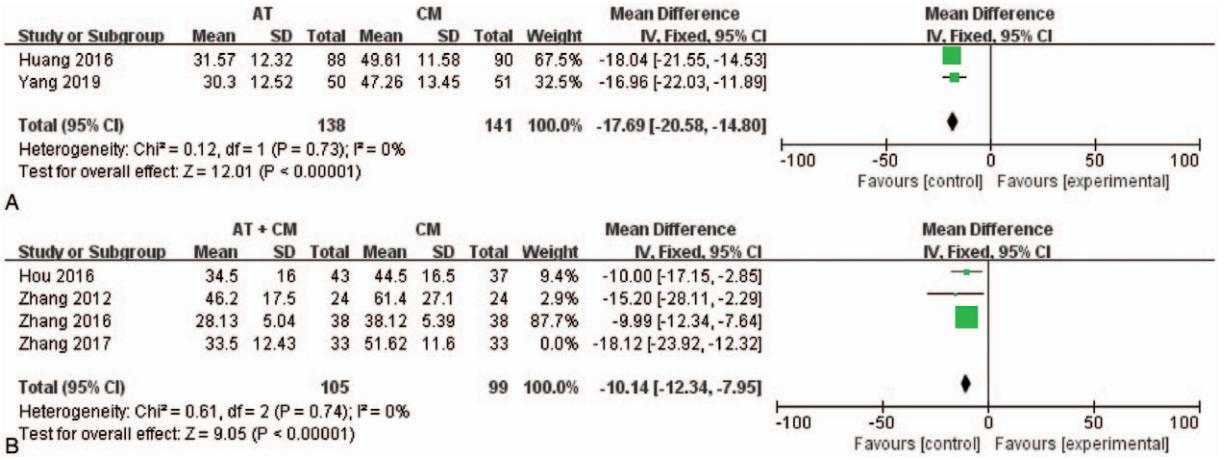

Figure 6. A) Efficacy of acupuncture on AST. B) Efficacy of acupuncture plus conventional medicine on AST. AST = aspartate aminotransferase, AT = acupuncture treatment, CI = confidence interval, CM = conventional medicine, SD = standard deviation.

−2.14 to −1.36, $P < .00001$; MA plus CM: n = 194, MD = −0.58, 95% CI: −1.11 to −0.06, $P = .03$) (Fig. 8B).

3.3.2.2.3. High-density lipoprotein cholesterol and low-density lipoprotein cholesterol. One study[31] including 130 patients reported HDL-C and LDL-C between AT and CM. The results favored AT compared with CM (HDL-C: MD = 0.87, 95% CI: 0.58–1.16, $P < .00001$, Fig. 9A; LDL-C: MD = −1.13, 95% CI: −1.46 to −0.80, $P < .00001$, Fig. 9B).

3.3.2.2.4. Body mass index. Two study [32,38] reported BMI between AT plus CM and CM, and the result showed no difference between the 2 groups in BMI levels (n = 128, MD = −1.67, 95% CI: −3.46–0.13, $P = .07$) (Fig. 10).

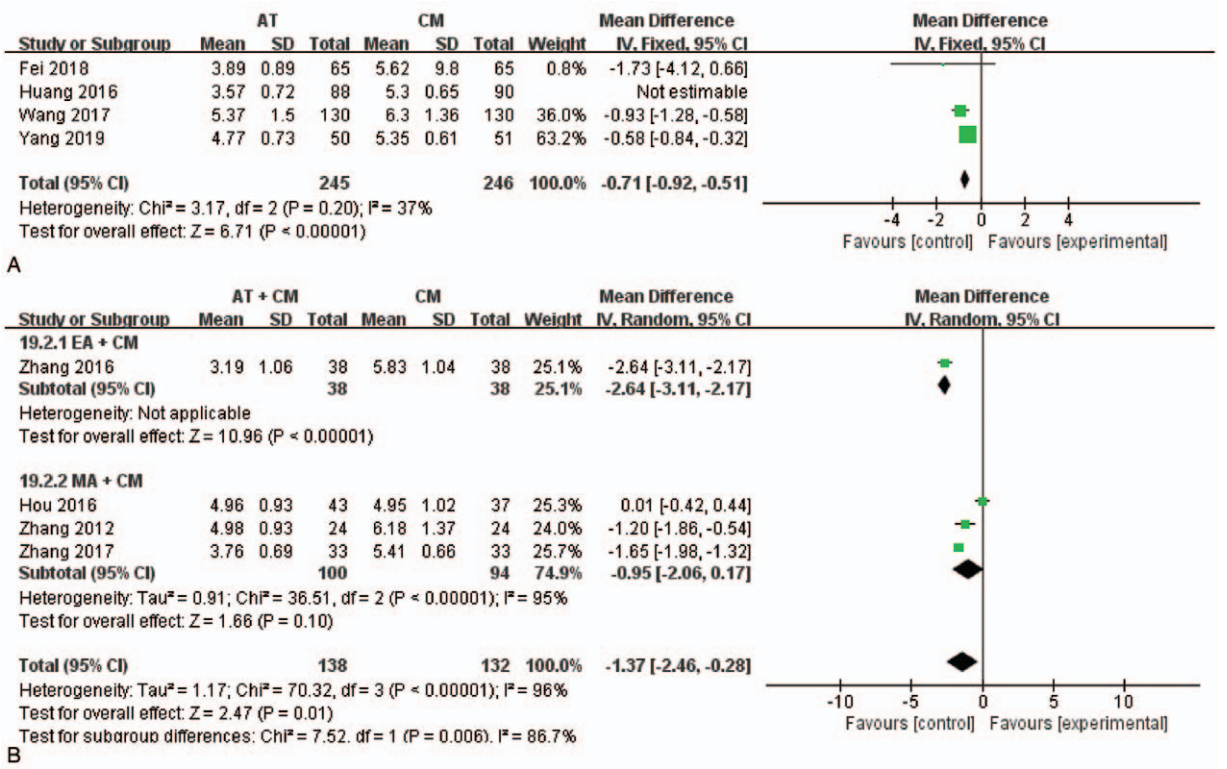

Figure 7. A) Efficacy of acupuncture on TC. B) Efficacy of acupuncture plus conventional medicine on TC. AT = acupuncture treatment, CI = confidence interval, CM = conventional medicine, EA = electroacupuncture, MA = manual acupuncture, SD = standard deviation, TC = total cholesterol.

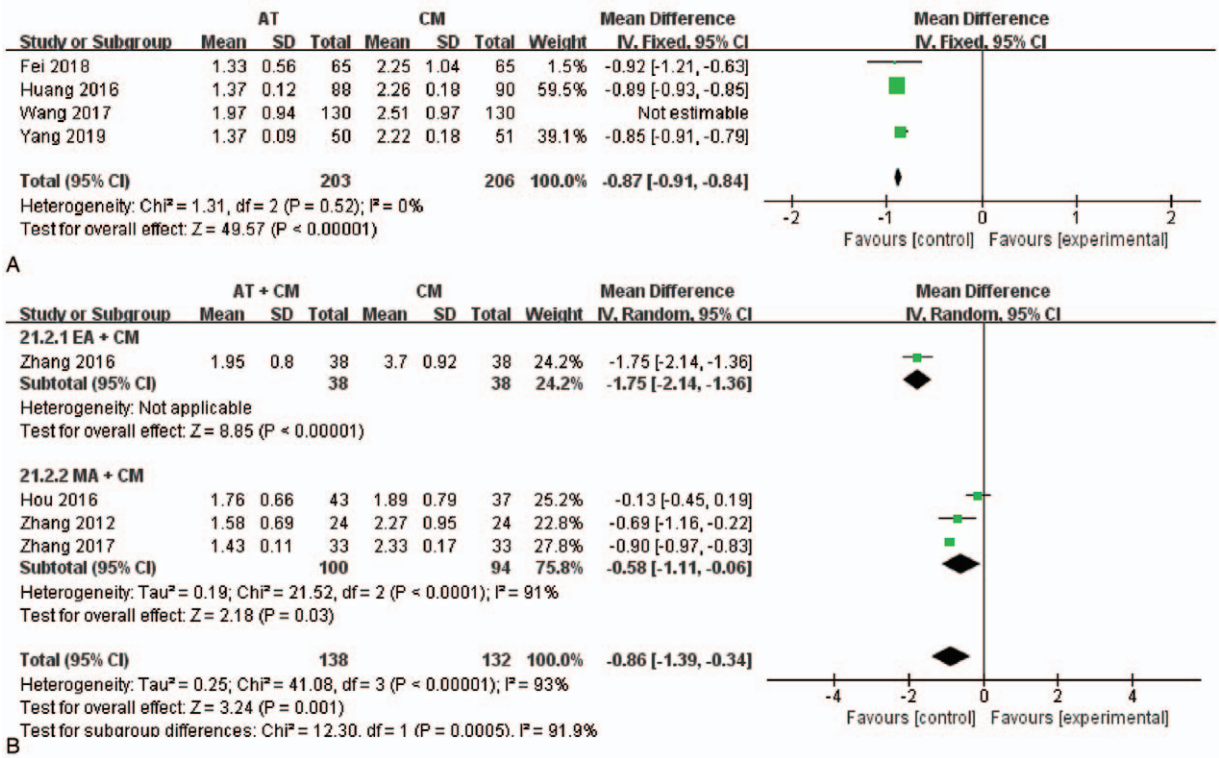

Figure 8. A) Efficacy of acupuncture on TG. B) Efficacy of acupuncture plus conventional medicine on TG. AT = acupuncture treatment, CI = confidence interval, CM = conventional medicine, EA = electroacupuncture, MA = manual acupuncture, SD = standard deviation, TG = triglyceride.

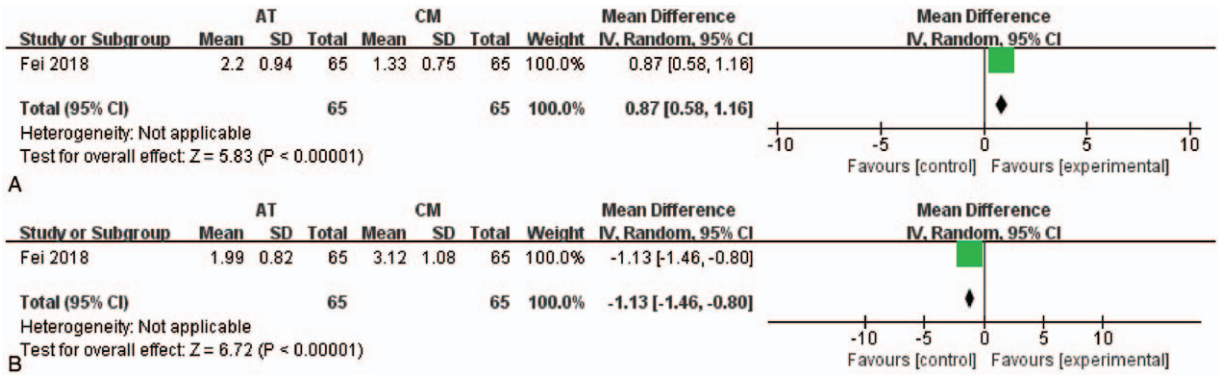

Figure 9. A) Efficacy of acupuncture on HDL-C. B) Efficacy of acupuncture on LDL-C. AT = acupuncture treatment, CI = confidence interval, CM = conventional medicine, HDL-C = high-density lipoprotein cholesterol, SD = standard deviation.

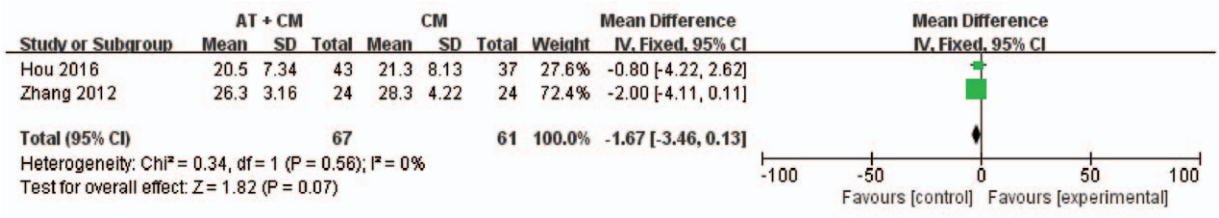

Figure 10. Efficacy of acupuncture plus conventional medicine on BMI. AT = acupuncture treatment, BMI = body mass index, CI = confidence interval, CM = conventional medicine, SD = standard deviation.

3.3.2.3. Adverse events. Three studies[32–34] reported side effects during treatment. One trial[34] recorded that 8 people felt pain on the site of needling in the experiment groups, which could be alleviated by adjusting the acupuncture direction. The other 2 trials[32,33] reported no side effects during treatment.

4. Discussion

Results from 8 RCTs with 939 patients were summarized in this meta-analysis. The results showed that acupuncture or acupuncture plus CM was superior in improving overall clinical efficacy and ALT, AST, TC, TG, HDL-C, LDL-C levels compared to CM used alone. On the other hand, available evidence did not show any differences on the following comparisons: the combined use of acupuncture and CM versus CM alone for improving BMI levels; and MA plus CM versus CM alone on TC levels according to the subgroup analysis. The above negative results may be related to a difference in the selection of stimulation methods, short observation period, and small sample size. In terms of adverse events, 8 patients presented with pain on the site of needling in acupuncture groups, which could be quickly relieved. Acupuncture could work as an adjuvant therapy to reinforce the effect of other conventional therapy for NAFLD.

The NAFLD is a metabolic disorder mainly caused by abnormal lipid metabolism and insulin resistance. Previous animals studies have demonstrated that electro-acupuncture on ST40, ST36, and SP6 could modify lipid metabolism, lower expressions of NF-κB and TLR4 in the liver, and reduce the impact of inflammation on NAFLD.[39] Acupuncture on ST40, LR3, ST36, and SP6 could regulate leptin and adiponectin.[40] Recent study showed that acupuncture on ST40, ST36, and LR3 could improve homeostasis model assessment of insulin resistance index.[41] Our review showed that LR3, ST36, ST40, and SP6 were major acupoints on NAFLD treatment, which is in accordance with previous animals findings. These acupoints may be considered as potential therapeutic regimen.

Previously, 1 systematic review have investigated the efficacy and safety of TET for NAFLD.[25] In their review, the experimental treatment contained Chinese herbal medicines in some studies, which were not used in control groups. In addition, 3 studies compared TET with EA and all the included studies did not reported the relevant information of lifestyle changes in the meta-analysis. BL18 (Ganshu) was the most frequently utilized acupoint in their review. We assessed the relative efficacy of acupuncture (MA, EA, TET) or acupuncture plus CM in the treatment and management of NAFLD. In addition, LR3, ST36, ST40, and SP6 could be considered as important therapeutic acupoints in our review, which were reported in many animals studies on NAFLD treatment.[39–41]

We have made efforts to perform a comprehensive analysis; however, some limitations must be recognized. First, significant heterogeneity was found for TC and TG between experimental groups and control groups. Therefore, after checking the included papers and extracted data, subgroup analysis by different acupuncture methods was used to explore the source of heterogeneity. However, subgroup analysis found that combinations of different acupuncture methods did not influence the heterogeneity. Thus, random-effects models were used for TC and TG between the 2 groups. Furthermore, a sensitivity analysis was performed by excluding the included studies 1 by 1, which showed that the parameters were stable. Second, only 1 study including 130 patients compared the effects of HDL-C and LDL-C, and only 2 studies including 128 patients compared the effects of BMI between the 2 groups; the sample size was too small.

The characteristics of acupuncture may be the source of heterogeneity. As shown in Tables 1 and 2, the selection of stimulation methods was different in the included studies. For patients with EA, the treatment courses were 1 month,[36] or 3 months,[31] the frequencies were 3 or 5 or 6 times per week and the duration of each treatment lasted 20 or 30 minutes. For patients with TET, the treatment courses were 3 months[35] or 6 months,[33] the frequencies were 1 time per week. For patients with MA, the treatment courses were 45 days,[38] 2 months,[32] or 3 months,[34,37] the frequencies were 3 times per week, 10 times 2 weeks, or 6 times per week, and the duration of each treatment was 30 minutes. In addition, the choice of acupoints and conventional drugs varied from study to study. In brief, all of the above-mentioned details may be the reasons for the heterogeneity of the included studies.

The limitations of this systematic review were as follows: First, the quality of the studies was poor because most studies had low methodological quality. Due to the particularity of AT methods, the blind method was difficult to implement clinically.[42] Only 1 study was a multi-center study and used a single-blind method.[33] Only 3 studies used random number tables to allocate participants.[32,33,35] All the included studies did not report follow-up visits and the treatment duration ranged from 1 month to 6 months, which were not sufficient to evaluate the long-term effect and safety of acupuncture in the treatment of NAFLD. In addition, none of the included studies reported recurrence rate and only 3 trials reported adverse effects,[32–34] which may lead to uncertain results and could not reflect overall trends truly. All participants were Chinese in the included studies, this limited geographical distribution and low-grade researches were difficult to conduct in future large-sized experiments. There were no studies comparing acupuncture versus no intervention or placebo/sham acupuncture, so the specific effect of acupuncture for NAFLD was not clear. In addition, we found that most of the studies were flawed according to the Cochrane Collaboration risk of bias tool.

Based on limitations of the included RCTs, several recommendations are made for further research. First, comparing acupuncture alone with standard care or sham acupuncture alone may provide results that can directly inform the specific effect of acupuncture. Second, future RCTs should use validated instruments for measuring outcomes. For example, imaging examination is currently the commonly used examination method for NAFLD, such as abdominal ultrasound and computerized tomography (CT), which should be adopted in future RCTs. Third, future RCTs should report adverse effect comprehensively so as to facilitate the safety assessment. Lastly, owing to the insufficient methodological quality and sample size, more multicenter, large-scale, long-term, rigorously designed standardized studies are needed.

5. Conclusion

This systematic review suggests that acupuncture may be effective and safe for the treatment of NAFLD. However, given the poor reporting and methodological flaws of existing studies, large-scale, long-term RCTs with rigorous methodological input are needed to clarify the role of acupuncture in this population.

Author contributions

Peiwen Chen and Zunming Zhou wrote the paper. All authors participated in the design of this study. Zunming Zhou, Peiwen Chen, Xin Zhong and Yunkai Dai drafted this manuscript and analyzed the data. Meiao Tan, Xuehong Ke and Gaochuan Zhang contributed materials/analysis tools. Zunming Zhou, Keer Huang, Peiwen Chen, Xin Zhong, Meiao Tan, Yunkai Dai read and approved the final manuscript. Zunming Zhou contributed to the study supervision.

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