Systematic Review and Meta-Analysis

Medicine

OPEN

The safety and efficacy of acupuncture in treating nonalcoholic fatty liver disease

A systematic review and meta-analysis based on randomized controlled trials

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Abstract

Background: Nonalcoholic fatty liver disease (NAFLD), the most common chronic liver ailment globally, remains a significant concern. Acupuncture has been increasingly utilized for the treatment of NAFLD in recent years. However, current evidence is insufficient to support its efficacy and safety. The aim of this study was to perform a recent and thorough meta-analysis concerning the impacts of acupuncture on NAFLD.

Methods: Randomized controlled trials (RCTs) investigating acupuncture for NAFLD were retrieved from 6 databases. The search encompassed the period from the inception of each database until February 28, 2024. We conducted literature screening based on predefined inclusion and exclusion criteria, resulting in the selection of 30 articles. Analysis of the data was carried out utilizing Review Manager 5.4 and Stata 15.1.

Results: The meta-analysis revealed a marked enhancement in the overall clinical effectiveness rate within the acupuncture group in comparison to the control group (OR = 3.36; 95% CI:2.62 to 4.31; $P < .00001$, $I^2 = 0\%$). Acupuncture exhibited positive impact on liver function recovery, blood lipid reduction, glucose regulation, improvement in insulin levels, antiliver fibrosis treatment, and imaging outcomes. Comprehensive analysis revealed that acupoint embedding (OR = 3.14; 95% CI: 2.113 to 4.62; $P < .00001$, $I^2 = 0\%$) demonstrated the most effective and stable therapeutic effect, followed by manual acupuncture (MA) (OR = 3.27; 95% CI: 2.19 to 4.90; $P < .00001$, $I^2 = 0\%$) and electroacupuncture (EA) (OR = 3.32; 95% CI: 1.69 to 6.52; $P < .0005$, $I^2 = 0\%$). In contrast, acupoint injection (AI) (OR = 5.74; 95% CI: 2.23 to 14.883; $P < .0003$, $I^2 = 0\%$) exhibited relatively modest effects, particularly in lipid reduction. No significant adverse reactions were observed with acupuncture treatments.

Conclusion: Acupuncture has demonstrated safety and efficacy in the treatment of NAFLD, significantly improving hepatic function, lowering glucose and lipid levels, and mitigating liver fibrosis. Nevertheless, these findings necessitate validation through large-scale, rigorously designed randomized controlled trials.

Abbreviations: AE = acupoint embedding, AI = acupoint injection, ALT = alanine aminotransferase, AST = aspartate aminotransferase, AT = acupuncure treatment, BMI = body mass index, CG = control group, CIV = collagen Type IV, CM = conventional medicine, DOI = duration of intervention, EA = electroacupuncture, e.g. = experiment group, FINS = fasting insulin, FPG = fasting plasma glucose, GGT = γ-glutamyl transpeptadase, HA = hyaluronic acid, HDL-C = high-density lipoprotein cholesterol, HOMA-IR = homestasis model assessment of insulin, LDL-C = low-density lipoprotein cholesterol, LN = laminin, MA = manual acupuncture, MAFLD = metabolic dysfunction associated fatty liver disease, NAFLD = nonalcoholic fatty liver disease, OR = odds ratio, PCIII = procollagen type III, PRISMA = preferred reporting items for systematic reviews and meta-analysis, RCTs = randomized controlled trials, SMD = standardized mean difference, TC = total cholesterol, TCM = traditional Chinese medicine, TG = triglyceride.

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

This research was funded by Inner Mongolia Autonomous Region Department of Education (NJZY22627), Inner Mongolia Medical University (YKD2023MS087).

The authors have no conflicts of interest to disclose.

The authors will make the raw data supporting this article's conclusions available without undue reservation. The data used to support the findings of this study are included within the article.

Consent for publication is not applicable.

In accordance with local legislation and institutional requirements, ethical review and approval were not required for the study of human participants. All authors read and approved the final manuscript.

Supplemental Digital Content is available for this article.

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How to cite this article: Liu C, Ao Y, Liu B, Huang J, Wang Q, Ao X, Wang X, Ban X. The safety and efficacy of acupuncture in treating nonalcoholic fatty liver disease: A systematic review and meta-analysis based on randomized controlled trials. Medicine 2025;104:18(e42272).

Received: 11 October 2024 / Received in final form: 10 February 2025 / Accepted: 11 April 2025

http://dx.doi.org/10.1097/MD.0000000000042272

1. Introduction

Nonalcoholic fatty liver disease (NAFLD), presents as widespread hepatocyte steatosis without alcohol or other recognized factors causing liver damage.[1,2] Since the concept of NAFLD was proposed in 1980, the name was changed to metabolic dysfunction-related fatty liver disease (MAFLD) in 2020, and then to metabolic dysfunction-related fatty liver disease (MASLD) was proposed to replace NAFLD in June 2023, and the name was changed to MASLD. However, to maintain the consistency of naming and the consistency of literature progress, many scholars still call NAFLD the name of the disease. Globally, it stands as the most widespread chronic liver ailment, boasting a global prevalence rate of 29.8% and an Asian prevalence of 27.4%, often coexisting with diabetes, hypertension, cardiovascular diseases, and cerebrovascular diseases.[3–5] NAFLD may progress to hepatitis, cirrhosis, or hepatocellular carcinoma. Furthermore, impaired hepatic function in NAFLD patients significantly compromises the liver's ability to metabolize inflammatory mediators and hormones, leading to systemic accumulation of metabolites that may induce or worsen metabolic disorders such as diabetes, hypertension, and hyperlipidemia. This establishes a detrimental cycle that profoundly impairs patients' quality of life and shortens their lifespan.[6–8] Individuals diagnosed with NAFLD experience a mortality rate documented to exceed 6 times that of the general populace, resulting in a lifespan reduction of 5 to 10 years.[3] Currently, treatment options for NAFLD are limited, with behavioral interventions such as diet and exercise constituting the primary approach.[9,10] However, adherence to behavioral interventions often presents challenges for NAFLD patients due to misconceptions and entrenched poor dietary and exercise habits, resulting in suboptimal therapeutic outcomes. Despite the availability of alternative treatment modalities and medications, their efficacy remains uncertain, hindering widespread adoption.[11] Hence, an imperative exists for the exploration of treatment modalities that are both convenient and efficacious, while also minimizing potential side effects. Acupuncture, with its extensive history in disease treatment, is increasingly recognized for its efficacy and safety, garnering global acceptance among patients. In China, acupuncture has been employed in NAFLD treatment for centuries.[12] The results of a meta-analysis, which included 12 randomized controlled trials (RCTs) involving a combined sample size of 1295 patients, revealed that acupuncture, either alone or combined with conventional medication, produced better clinical outcomes compared to conventional medication alone (RR = 1.25, 95% CI: 1.17 to 1.33; $P < .001$, $I^2 = 0\%$), resulting in significant enhancements in patients' biochemical parameters.[13] Another meta-analysis focusing on acupoint therapy, comprising 8 RCTs with 939 patients, suggested that acupoint therapy surpassed conventional medication in improving overall clinical outcomes (OR = 3.19, 95% CI: 2.06 to 4.92, $P < .00001$, $I^2 = 0\%$), with satisfactory safety profiles observed. Significantly, Taichong, Zusanli, Fenglong, and Sanyinjiao emerged as the principal acupoints for addressing NAFLD.[14] However, these analyses lacked the incorporation of recent studies, comprehensive comparison of acupuncture therapies, evaluation of imaging indicators, or inclusion of a sufficient quantity of high-quality literature. Thus, In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a thorough systematic review and meta-analysis were conducted on the most recent and extensive literature pertaining to RCTs. The objective of this endeavor was to assess the efficacy and safety of acupuncture in treating NAFLD, furnishing dependable evidence-based medical data to facilitate precise management of NAFLD through acupuncture.

2. Material and methods

2.1. Search strategy

This study followed the PRISMA guidelines and registered in the PROSPERO (CRD42024541067). An exhaustive search was carried out across 6 electronic databases, including China National Knowledge Network (CNKI), China Science and Technology Journal Database (VIP), Wanfang Database, Embase, PubMed, and Web of Science, spanning from their inception to February 29, 2024. Key search terms such as "nonalcoholic fatty liver disease," "nonalcoholic steatohepatitis," "acupoint embedding," "electroacupuncture (EA)," "acupuncture," "manual acupuncture," "acupoint injection," "MAFLD," "MASLD" and "NAFLD" were utilized. The search strategy employed a hybrid approach, incorporating both medical subject terms (MeSH) and relevant keywords. Detailed retrieval information for the remaining databases is provided in Table S1, Supplemental Digital Content, https://links.lww.com/MD/O765. The publications are not subject to any language restrictions.

2.2. Eligibility and exclusion criteria

We incorporated articles that fulfilled the following criteria: Population: According to the diagnostic criteria established by the World Health Organization, patients received a diagnosis of NAFLD; Intervention measures: Patients in the experimental group received acupuncture treatment, including manual acupuncture (MA), EA, acupoint embedding (AE), acupoint injection (AI), or acupuncture combined with drug therapy; Control group: Patients in the control group were administered drug therapy, sham acupuncture, other placebo treatments, or)no treatment; Outcome indicators: The primary outcome was the total effective rate of overall clinical efficacy of NAFLD, classified into cured, significantly effective, effective, and ineffective categories. Secondary outcomes included changes in alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transpeptadase (GGT), triglyceride (TG), total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), fasting plasma glucose (FPG), fasting insulin (FINS), homestasis model assessment of insulin (HOMA-IR), procollagen type III (PCIII), laminin (LN), hyaluronic acid (HA), collagen Type IV (CIV), body mass index (BMI), liver-spleen computed tomography (CT) ratio, Ultrasound, and adverse events; All studies provided sufficient data to calculate OR or Standardized Mean Difference (SMD) and were RCTs.

Exclusion criteria comprised: Systematic reviews, case reports, critical reviews, or animal studies; duplicate studies; studies employing inappropriate intervention or comparison methods, such as combining different acupuncture treatments in the control group; studies with incomplete outcome data.

2.3. Data extraction and quality assessment

Two authors (YgA and ChL) independently screened and evaluated the articles, adhering to the predefined inclusion and exclusion criteria. Extracted data included basic patient information, treatment regimens, outcome measures, and adverse reactions, Table 1 presents the characteristics of the studies included. Two additional authors (BxL and JH) independently assessed the risk of bias in the included trials using the Cochrane Bias Risk Tool. They evaluated random sequence generation, allocation concealment, blinding methods, incomplete outcome data, and selective reporting. The methodological quality of eligible articles was evaluated, with any discrepancies resolved through discussion.

2.4. Statistical analysis

For data processing, we employed RevMan 5.4 software. Heterogeneity among studies was assessed using the I^2 statistic. If the I^2 value was ≤ 50%, indicating low heterogeneity, we

Table 1

Characteristics of the included studies.

Study	Study period	Region	Study design	Intervention		Patients		DOI	Age		Gender (male/female)		Course of disease (yr)	
				e.g. (acupiont + frequency)	CG	EG	CG		EG	CG	EG	CG	EG	CG
Draz 2019[15]	2017/5 to 2018/12	Egypt	RCT	EA (LR3, LR14,GB 34,ST36, 3 times/wk)	Aerobic interval training	25	25	6 wk	45.72 ± 7.94	44.16 ± 6.61	0	50	NA	NA
Huang 2016[16]	2012/7 to 2014/12	China	RCT	AE (BL18, LR3, ST40, ST36, SP6, once/wk)	Polyene phosphatidylch oline capsules	88	90	6 wk	46 ± 12	43 ± 16	37/51	36/54	NA	NA
Jin 2006[17]	2003/1 to 2004/10	China	RCT	AI Tiopronin (ST36, 3 times/wk)	Tiopronin injection	47	46	12 wk	33.1 ± 7.8	31.4 ± 7.1	22/25	22/24	NA	NA
Liu 2010[18]	2009/1 to 2009/10	China	RCT	AE (BL17,BL18, CV12, CV6,ST36,G-B34,ST40, once/wk)	Tiopronin tablets plus xuezhikang capsule	30	30	8 wk	37.9 ± 1.5	38.1 ± 1.5	20/10	22/8	4.6 ± 0.5	4.5 ± 0.4
Taha 2021[19]	2019	Egypt	RCT	EA (LR14, LR3, ST36/ GB34, 3 times/wk）	Sham acupuncture	30	30	6 wk	45.30 ± 7.32	45.93 ± 6.86	NA	NA	NA	NA
Zhao 2023[20]	2021/6 to 2022/7	China	RCT	EA (CV12, CV4, ST25, SP15, LV13/ ST36 , SP6, LI4, LV3, 3 time/wk）	Sham acupuncture	27	30	12 wk	39.1 ± 10.8	41.6 ± 10.8	15/12	8/22	NA	NA
Cheng 2014[21]	2012/10 to 2013/6	China	RCT	EA (BL18, ST36, ST40, LR3, 6 time/wk）	UDCA	30	30	12 wk	49	30	23/7	22/8	1/6 to 12/5	1/6 to 11.8/5.1
Dong 2020[22]	2018/1 to 2018/12	China	RCT	EA (CV12, LI11, RN9, ST24, SP14, RN4, RN6, ST40, SP6, LR3, SP10, 3 times/wk)	Lifestyle control	41	44	12 wk	35 ± 8	37 ± 9	20/21	24/20	5.3 ± 4.3	5.1 ± 4.3
Hou 2016[23]	2012/1 to 2014/12	China	RCT	MA (ST36, ST40, SP6, CV12, LR3, 3 times/wk)	Diammonium glycyrrhizinate enteric-coated capsules	43	37	8 wk	45.12 ± 22.3	50.72 ± 19.3	25/18	21/16	15.82 ± 12.3	15.46 ± 10.13
He 2014[24]	2012/12 to 2013/12	China	RCT	MA (LI11,SJ6,LI4,CV12 ,ST36 ,SP9,ST40,SP6,SP10, LV3，3 times/wk)	Aerobic interval training + Silybin meglumine	72	72	4 wk	49.38 ± 7.39	49.32 ± 7.4	40/32	44/28	NA	NA
Hu 2006[25]	2001/12 to 2004/9	China	RCT	EA (ST40， 6 times/wk)	Atorvastatin + glucuronolactone	60	48	8 wk	41.8	41.9	43/17	29/19	1.4	1.4
Hu 2019[26]	2016/10 to 2018/2	China	RCT	MA (LI11, PC6, LI4, GB34, ST36, SP6, 3 times/wk)	Chinese herb medicine	37	33	12 wk	42.3 ± 9.3	43.3 ± 9.9	26/11	23/10	1.75 ± 1.39	1.83 ± 1.13
Zhu 2020[27]	2018/7 to 2018/12	China	RCT	MA (ST36, BL18, SP6, LR13, LR3, ST40, GB34, 5 times/wk）	Atorvastatin	48	48	12 wk	44 ± 4	45 ± 3	34/14	30/18	NA	NA
Li 2004[28]	2004	China	RCT	MA (① RN4, KI7, ST36 , SP6, LI4; ② BL23, KI3, LR3, PC6, 5 times/wk)	Xuezhikang + Fufang Danshen tablets	46	30	8 wk	25 to 54	30 to 51	34/12	23/7	1 to 7	0.67 to 5.7
Li 1999[29]	1999	China	RCT	MA (ST40, ST36, SP6, GB34, PC6,4 times/wk)	Fenofibrate + Vitamin	32	30	20 wk	20 to 63	28 to 45	28/4	27/3	2.8	2.5
Qian 2012[30]	2009	China	RCT	MA (RN4, ST36, CV12, LI4, ST40, LR3, PC6, 4 times/wk)	Shui Lin Jia tablet	30	25	12 wk	42.5	42.5	24/6	18/6	NA	NA
Wang 2011[31]	2010/1 to 2011/1	China	RCT	EA(LR13, BL18, ST36, GB34, SP6, ST40, LR3, 4 times/wk)	Simvastatin	30	29	4 wk	45.2	45.2	NA	NA	0.5 to 1.5	0.5 to 1.5
Zhang 2012[32]	2007 to 2010	China	RCT	MA (BL23,RN4,KI7,ST36 ,SP6,LI4,KI3,L-R3,PC6，4 times/wk)	Polyene phosphatidylcholine capsule	24	24	6 wk	56.7 ± 3.5	57.8 ± 4.2	9/15	10/14	NA	NA
Zhu 2016[33]	2014/6 - 2016/1	China	RCT	EA (ST40, 6 times/wk)	UDCA	40	32	10 wk	35.8 ± 6.7	35.8 ± 6.3	27/13	19/13	1.3 ± 0.7	1.4 ± 0.6
Yang 2019[34]	2017/1 to 2018/3	China	RCT	AE (BL20, BL21, BL18, ST36 , CV12, ST25, RN9, SP14, ST40, SP9, GB27, once/wk)	Polyene phosphatidylcholine capsule	52	52	12 wk	43.±12	41 ± 16	NA	NA	18.11 ± 3.24	16.96 ± 3.76
Tang 2023[35]	2020/6 to 2021/2	China	RCT	MA (ST36, PC6, GB34, SP6, GB24, LI11, ST40, CV12, LR14，6 times/wk)	Reducing glutathione injection + Silybin silybin capsule	40	40	12 wk	54.54 ± 4.67	55.56 ± 4.33	NA	NA	4.98 ± 1.32	4.54 ± 1.36
Xiong 2020[36]	2016/3 to 2017/2	China	RCT	AE (LR3,ST40,BL18,ST36, SP6, once/wk)	Aerobic exercise; polyene phosphatidyl choline + Bacillus subtilis diploxis	47	47	12 wk	42.8 ± 9.2	42.5 ± 9.1	NA	NA	3.86 ± 0.95	3.80 ± 0.91

(*Continued*)

Table 1
(Continued)

Study	Study period	Region	Study design	Intervention e.g. (acupiont + frequency)	CG	Patients EG	Patients CG	DOI	Age EG	Age CG	Gender (male/female) EG	Gender (male/female) CG	Course of disease (yr) EG	Course of disease (yr) CG
Li 2019[37]	2017	China	RCT	AE (BL18,BL20,ST36 (Zu San Li),CV12 (Zhongwan), ST25, once/wk)	Ligaron silymarin capsules	49	50	4 wk	46.00 ± 13.0	45.0 ± 12.0	NA	NA	16.00 ± 3.50	17.00 ± 3.70
He 2019[38]	2015/7 to 2017/10	China	RCT	AE (BL18, BL20, ST36, ST40, GB34, SP6, once/wk)	Polyene phosphatidylcholine capsule	45	45	12 wk	40.2 ± 17.4	41.5 ± 15.6	NA	NA	3.7 ± 0.6	3.5 ± 0.4
Liu 2022[39]	2019/1 to 2021/1	China	RCT	AE (BL18, LR3, ST40, ST36, SP6, once/wk)	Polyene phosphonoylcholine capsules	44	44	12 wk	16.37 ± 3.52	16.51 ± 3.48	NA	NA	5.84 ± 2.96	5.61 ± 2.72
Jin 2020[17]	2018/1 to 2019/8	China	RCT	AE (ST36, SP6, SP9, LR3, once/wk)	Aerobic exercise; +polyene phosphatidyl choline + Bacillus subtilis diploxis	50	50	12 wk	41.5 ± 7.22	42.09 ± 7.41	NA	NA	NA	NA
Zhang 2021[40]	2017/6 - 2019/6	China	RCT	AE (BL13, BL18, BL20, ST25, RN4, CV12, once/wk)	Zhibitai capsules	45	45	8 wk	46.02 ± 9.69	47.00 ± 9.95	NA	NA	NA	NA
Chen 2016[41]	2015	China	RCT	AI Vitamin B1 (ST36, 3 times/wk)	Casile tablets	35	25	4 wk	43	43	NA	NA	NA	NA
Chen 2014[21]	2013	China	RCT	AI tiopronin (ST36, KI7, ST40, ST36, SP6, 3 times/wk)	Polyene phosphatidyl choline injection	52	50	12 wk	41.87 ± 9.1	41.68 ± 8.8	NA	NA	4.56 ± 2.62	3.85 ± 2.86
Chen 2015[42]	2010 to 2014	China	RCT	AI astragalus injection (ST36, 3 times/wk)	Xuezhikang capsule	36	36	8 wk	43.41	40.24	NA	NA	8.5 ± 6.2	9.0 ± 5.8

Abbreviations: CG = control group, EG = experiment group, RCT = randomized controlled trial, UDCA = ursodeoxycholic acid.

combined the data using a fixed-effects model. Conversely, if I^2 >50%, indicating high heterogeneity, a random-effects model was utilized for meta-analysis. The inclusion of subgroup analysis or sensitivity analysis was deemed necessary in order to ascertain the underlying cause of heterogeneity. Overall clinical efficacy, ultrasound effectiveness rate, and liver-spleen CT ratio were analyzed as classified and counted data using OR and 95% confidence intervals (CI). ALT, AST, TC, TG, etc, were treated as continuous data, with SMDs as the effect size. The formula for calculating the effective rate of counting data is:

Total effective rate % = (number of cured cases + number of obviously effective cases + number of effective cases)/ number of total patients × 100%. the standard deviation (SD) of the change from baseline to post-therapy was calculated through this formula (R1 = 0.5)[43]:

$$\mathrm{SD\,(Change)} = \sqrt{\mathrm{SD(B)}^2 + \mathrm{SD(F)}^2 - (2 \times \mathrm{R1} \times \mathrm{SD\,(B)} \times \mathrm{SD\,(F)})}$$

The symbols SD (B) and SD (F) denote the SDs prior to and following the intervention, respectively. The linear regression method (Egger regression tests) provided by Stata 15.1 software (Stata Corp, College Station) and the funnel plot generated by Review Manager 5.4.1 (Cochrane Collaboration, Oxford, UK) were employed to identify potential publication bias.[44] Statistical significance was established at a significance level of $P < .05$. Additionally, according to GRADE, each outcome's evidence was evaluated and graded as "high," "moderate," "low," or "very low" quality to draw conclusions.[45]

3. Results

3.1. Study selection

Figure 1 illustrates the flowchart detailing the database search and selection process. Initially, a total of 898 relevant studies were identified through systematic literature searches conducted across various databases: PubMed (n = 72), Embase (n = 124), Web of Science (n = 51), CNKI (n = 250), WANFANG (n = 250), and VIP (n = 151). After removing 494 duplicate papers, the remaining 404 paper titles and abstracts were reviewed, resulting in unrelated to the topic (n = 192), cell or animal experiments (n = 19), reviews and meta-analyses (n = 92), and case reports (n = 14). Following the examination of 87 full papers, incorrect RCTs (n = 17) and studies with insufficient data (n = 21), noncore journals (Not included by Peking University Peking University and core journals of Science and Technology in China) (n = 19) were excluded. In the end, 30 studies encompassing a collective of 2846 patients were included.

3.2. Research characteristics

Among the 30 included articles, 6 were in English, while the rest were in Chinese. Two articles originated from Egypt, while the others were from China. The intervention modalities employed in the treatment group included MA, electroacupuncture (EA), AE, and AI. In contrast, sham acupuncture and conventional treatments such as exercise, Western medicine, and traditional Chinese medicine (TCM) were utilized in the control group.

Of the 30 studies, 8 focused on EA,[15,19–22,25,31,33] 8 on MA,[23,24,26–30,32] 10 on AE,[16,18,34–40,46] and 4 on AI.[17,41,42,47] Acupoints involved in treatment included ST36 (Zusanli, n = 27), ST40 (Fenglong, n = 18), SP6 (Sanyinjiao, n = 17), LR3 (Taichong, n = 14), BL18 (Ganshu, n = 11), CV12 (Zhongwan, n = 10), GB34 (Yanglingquan, n = 8), PC6 (Neiguan, n = 6), ST25 (Tianshu, n = 4), and BL20 (Pishu, n = 4), SP9 (Yinlingquan, n = 3). Various acupuncture treatments were administered at different weekly frequencies, with AE performed approximately once a week, AI 3 to 4 times a week, and MA and EA 5 to 6 times a week. Table 1 displays the essential characteristics of the included studies.

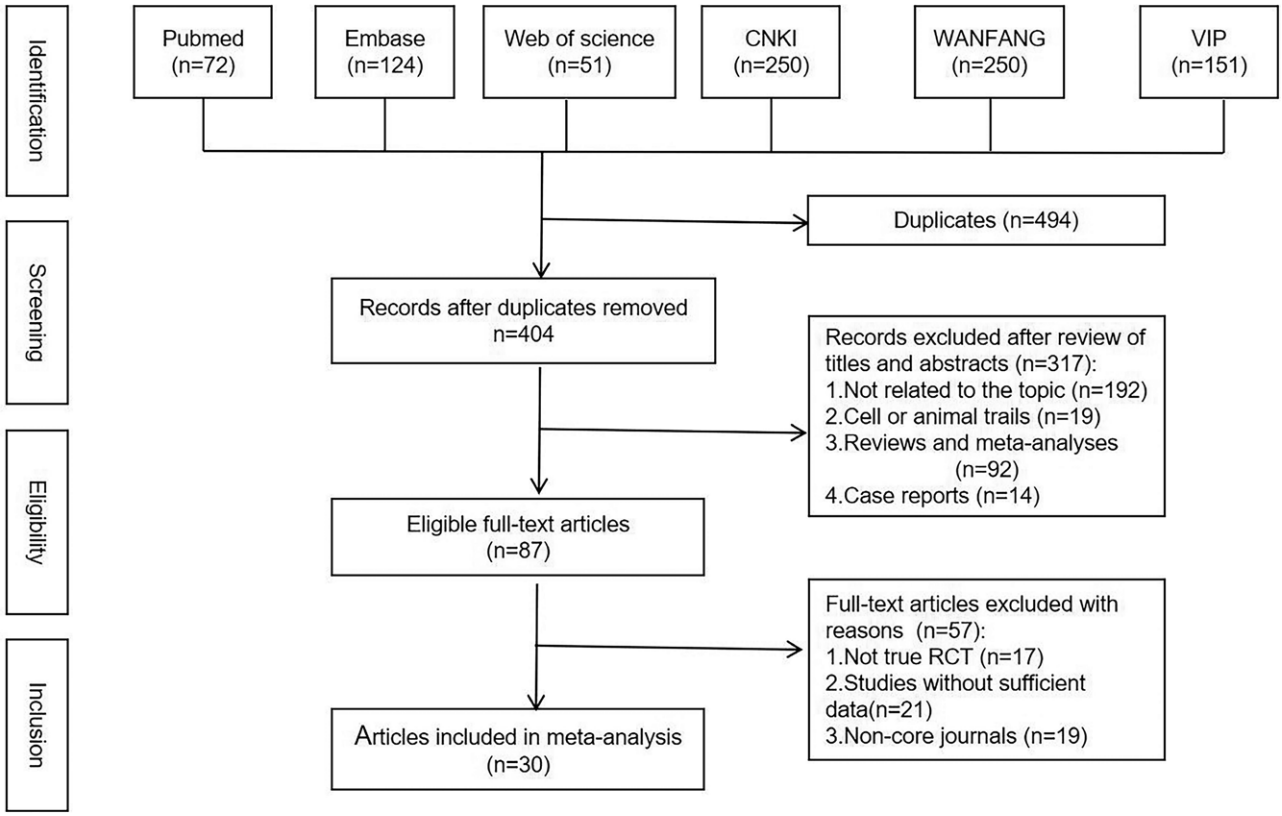

Figure 1. Flowchart of the systematic search and selection process.

3.3. Bias risk assessment

Eighteen studies provided details of random sequence generation using random tables or group randomization and were classified as low risk, while 4 studies mentioned incorrect randomization methods and were classified as high risk. Six studies mentioned specific assignment schemes, while the remaining ones did not. Additionally, 4 studies had incomplete outcome measures. Due to the challenges of implementing blind methods in acupuncture treatment, only 2 groups with a sham acupuncture control group were considered low risk, while the rest were deemed high risk. Figure 2 summarizes the assessment of bias risk.

3.4. Effects of acupuncture

3.4.1. Primary outcome- overall clinical efficacy. A synthesis of overall clinical effectiveness data concerning NAFLD was derived from 24 studies, encompassing 2636 patients. These studies showed minimal heterogeneity. Employing a fixed-effect model, acupuncture showcased a notable influence on the overall clinical effectiveness of NAFLD (OR = 3.36, 95% CI: 2.62 to 4.31; $P < .00001$, $I^2 = 0\%$) (Fig. 3A). Subgroup analysis was conducted based on different treatment types, intervention durations, patient ages, and disease courses (Table 2), with combined data indicating stable overall clinical efficacy rates for MA, EA, AE, and AI in NAFLD patients. Significant effects were observed across all age groups regardless of disease duration or treatment duration.

The funnel plot exhibited some indication of publication bias (Fig. 4A); nevertheless, Egger test did not yield statistically significant results ($P = .01$) and indicated an absence of publication bias.

3.4.2. Secondary outcomes.

3.4.2.1. Liver tests/enzymes outcomes.

3.4.2.1.1. Change in AST. Twenty-one articles involving 1693 participants reported changes in AST levels. Acupuncture demonstrated a substantial decrease in AST levels in comparison to the control group (SMD = −0.51, 95% CI: −0.70 to −0.32; $P < .00001$, $I^2 = 73\%$) (Fig. 3B). Given the substantial heterogeneity observed, subgroup analyses were performed based on different treatment methods, intervention duration, patient age, and disease course (Table 2). The comprehensive analysis demonstrated that acupuncture exerted a beneficial effect on the reduction of AST levels in comparison to the control group. (SMD = −0.70, 95% CI: −0.855 to −0.55; $P < .00001$, $I^2 = 12\%$). MA, EA, and AI showed no significant impact on AST improvement. Furthermore, The pooled data revealed no significant reduction in AST levels among patients under the age of 40 who received acupuncture (SMD = −0.11, 95% CI: −0.42 to 0.20; $P = .48$; $I^2 = 56\%$). The funnel plot's visual assessment indicated a slight presence of publication bias (Fig. 4B); nevertheless, Egger test did not produce statistically significant findings ($P = .086$), suggesting no publication bias.

3.4.2.1.2. Change in ALT. Twenty-eight studies involving 2293 participants reported changes in ALT. These studies did not show significant heterogeneity among them. Using a fixed-effect model for analysis revealed that acupuncture significantly decreased ALT levels with an SMD value of −0.51 (95% CI: −0.59 to −0.43; $P < .00001$, $I^2 = 41\%$) as illustrated in Figure 3C. We conducted subgroup analyses based on different treatment types, intervention durations, patient ages, and courses of diseases as presented in Table 2. The combined data demonstrated that MA, EA, AE, and AI all had notable effects in reducing patients' ALT levels regardless of regardless of the length of the course of the disease and the length of the treatment time. The visual inspection of the funnel plot revealed no indication of publication bias (Fig. 4C), a finding reinforced by the nonsignificant outcomes of Egger test ($P = .733$).

3.4.2.1.3. Change in GGT. Eleven articles involving 890 participants reported changes in GGT. No notable heterogeneity

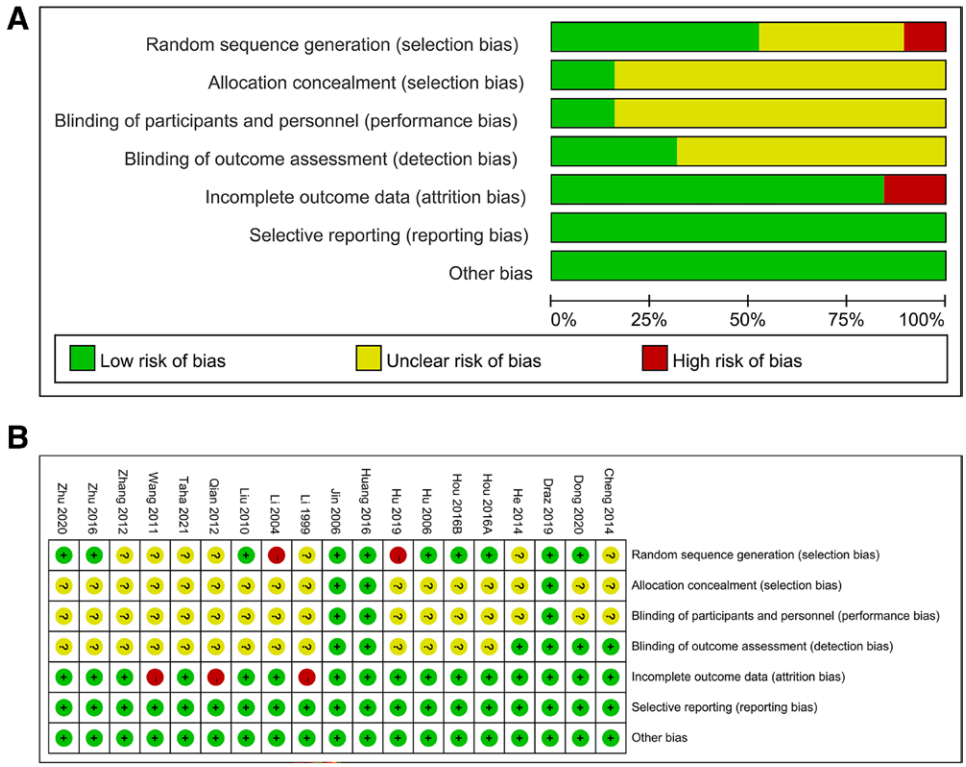

Figure 2. Risk of bias assessment. (A) Risk of bias graph. (B) Risk of bias summary.

was observed among the studies. Consequently, a fixed-effect model was employed, acupuncture treatment was found to reduce GGT (SMD = −0.38, 95% CI: −0.51 to −0.25; $P < .00001$, $I^2 = 44\%$) (Fig. 3D). We performed subgroup analyses for different types of treatment, duration of intervention, patient age, and disease course (Table 3). The combined data showed that MA and AE had no significant effect on reducing GGT in patients. However, significant effects were observed for patients of all ages, regardless of the length of the disease course and the duration of treatment time. The funnel plot analysis visually indicated the absence of publication bias (Fig. 4D), a finding further supported by the nonsignificant results obtained from Egger test ($P = .456$).

3.4.2.2. Serum lipid.

3.4.2.2.1. Change in TC. Twenty-eight studies with 2383 participants reported changes in TC. To address the substantial heterogeneity observed among these studies, we employed a random-effects model, which revealed that acupuncture demonstrated a significant reduction in TC (SMD = −0.51, 95% CI: −0.66 to −0.36; $P < .00001$, $I^2 = 68\%$) (Fig. 3E). We performed subgroup analyses for different types of treatment, duration of intervention, patient age, and course of disease (Table 2). The combined data showed that AI had no significant effect on reducing TC in patients. However, significant effects were observed for patients of all ages, regardless of the length of the disease course or treatment time. Visual evaluation showed slight publication bias in the funnel plot (Fig. 4E), but The findings of Egger test did not attain statistical significance ($P = .175$), indicating the lack of publication bias.

3.4.2.2.2. Change in TG. A total of 29 studies involving 2269 participants reported changes in TG levels. Since the studies demonstrated insignificant heterogeneity, a fixed-effect model was utilized to depict the reduction of TG levels through acupuncture. (SMD = −0.54, 95% CI: −0.73 to −0.34; $P < .00001$, $I^2 = 82\%$) (Fig. 3F). Subgroup analyses were performed to examine various treatment types, intervention durations, patient ages, and disease courses. (Table 3). The combined data indicated that AI had no significant effect on reducing TG in patients. Significant effects were observed for patients of all ages regardless of the length of the disease course or treatment duration. Upon visual inspection of the funnel plot, a slight suggestion of publication bias was noted (Fig. 4F); however, Egger test did not yield statistically significant findings ($P = .926$), indicating the absence of publication bias.

3.4.2.2.3. Change in HDL-C. Six studies involving 499 participants reported changes in HDL levels. The studies exhibited no substantial heterogeneity. Employing a fixed-effect model, the results indicated that acupuncture treatment did not lead to a reduction in HDL levels (SMD = −0.18, 95% CI: 0.00–0.36; $P < .05$, $I^2 = 0\%$) (Fig. 5A). Considering the generally recognized benefits of maintaining high levels of HDL for cardiovascular and cerebrovascular diseases, acupuncture treatment proved advantageous in helping patients maintain optimal HDL levels. Visual examination of the funnel plot indicated no presence of publication bias (Fig. 4G). Egger test yielded nonsignificant results ($P = .655$), indicating an absence of publication bias.

3.4.2.2.4. Change in LDL-C. Changes in low-density lipoprotein cholesterol (LDL-C) were reported in 7 studies involving 556 participants. The studies exhibited no significant heterogeneity, and a fixed-effect model demonstrated the beneficial effects of acupuncture treatment on reducing LDL (SMD = −0.44, 95% CI: −0.61 to −0.27; $P < .00001$, $I^2 = 20\%$) (Fig. 5B). A visual assessment of the funnel plot revealed the absence of publication bias (Fig. 4H), while Egger test indicated no statistical significance ($P = .39$), and absence of publication bias.

3.4.2.3. Change in glucose metabolism index.

3.4.2.3.1. Change in FPG. Five studies with 454 participants reported changes in FPG. The studies did not exhibit any

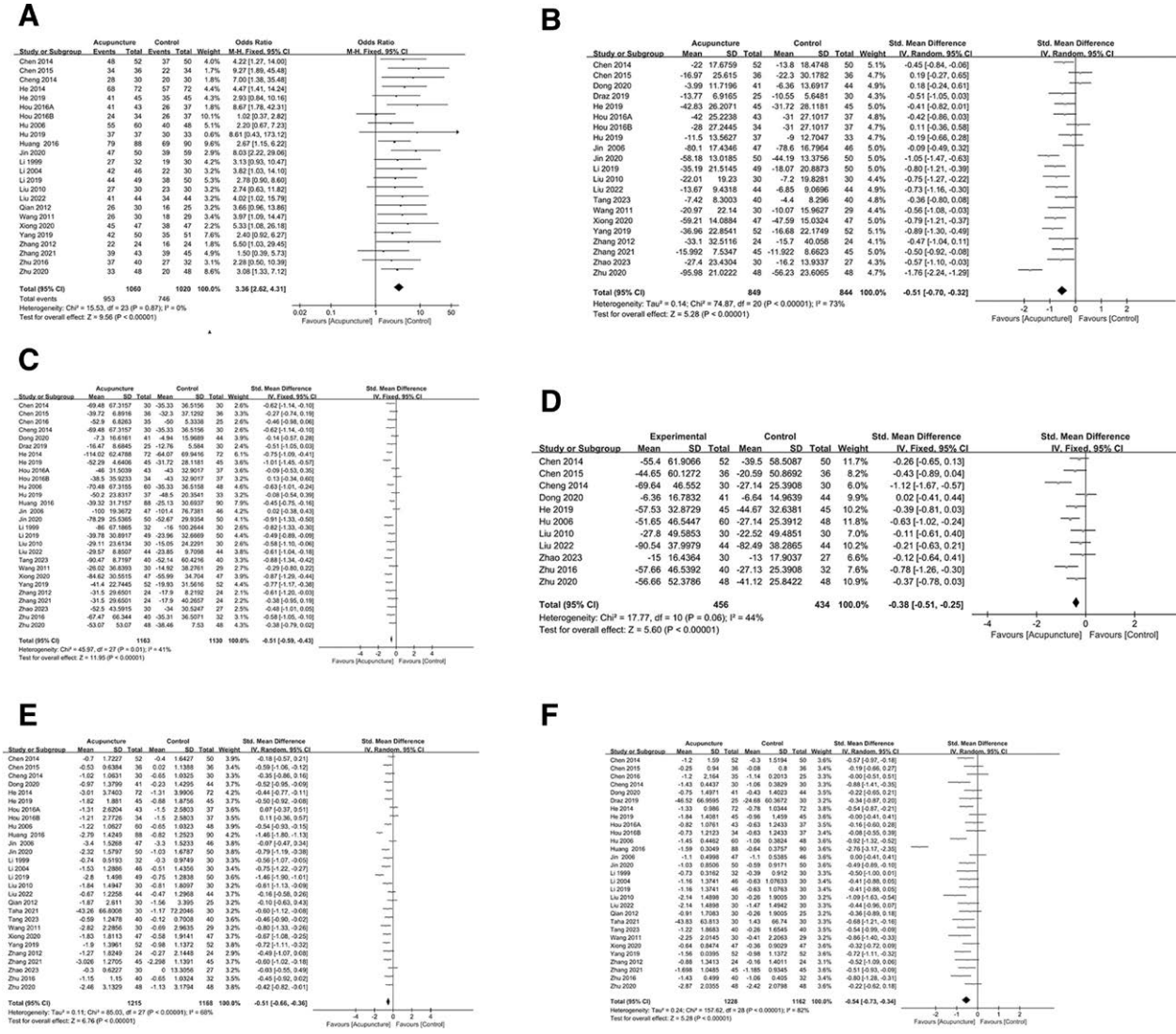

Figure 3. Forest plots of outcomes. (A) Overall clinical efficacy, (B) AST, (C) ALT, (D) GGT, (E) TC, (F) TG. ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGT = γ-glutamyl transpeptadase, TC = total cholesterol, TG = triglyceride.

substantial heterogeneity., and using a fixed-effect model, the results showed that acupuncture treatment was beneficial in reducing FPG (SMD = −0.27, 95% CI: −0.46 to 0.09; $P < .004$, $I^2 = 39\%$) (Fig. 5C). The visual evaluation of the funnel plot showed no publication bias (Fig. 4I), While the Egger test returned a statistically significant outcome ($P = .037$), indicating the existence of publication bias.

3.4.2.3.2. Change in FINS. Three research investigations involving 301 individuals documented alterations in FINS. Substantial heterogeneity was noted among these studies and the random-effects model showed that acupuncture treatment was beneficial in reducing FINS (SMD = −0.52, 95% CI: −0.87 to 0.16; $P < .005$; $I^2 = 56\%$) (Fig. 5D). Visual evaluation of funnel plots showed no publication bias (Fig. 6A), and the statistical significance of Egger test was not observed ($P = .547$), suggesting the absence of publication bias.

3.4.2.3.3. Change in HOMA-IR. Four investigations encompassing a cumulative of 358 subjects documented alterations in HOMA-IR. Substantial variability was evident across these studies, and utilizing a random-effects model, the findings indicated that acupuncture treatment did not effectively reduce HOMA-IR (SMD = −0.49, 95% CI: −0.99 to 0.01; $P = .06$, $I^2 = 81\%$) (Fig. 5E). Visual evaluation of funnel plots showed no publication bias (Fig. 6B), and Egger test did not yield statistically significant results ($P = .51$), indicating the lack of publication bias.

3.4.2.4. Indicators of hepatic fibrosis. Liver fibrosis refers to the diffuse excessive deposition and abnormal distribution of liver extracellular matrix (i.e. collagen, glycoprotein, and proteoglycan, etc), which is the pathological repair response of the liver to chronic injury, a key step in the development of various chronic liver diseases to cirrhosis and an important link affecting the prognosis of chronic liver diseases. The indexes of liver fibrosis include PCIII, CIV (type IV collagen), LN, HA, etc. The continuous increase of PCIII indicates the deterioration of liver fibrosis and the formation and development of cirrhosis, and the increase of IV-C content can more sensitively reflect the liver fiber process. LN reflects the progression and severity of liver fibrosis, and. HA is also a sensitive indicator of liver fibrosis and cirrhosis.

3.4.2.4.1. Change in PCIII. Three studies with 240 participants reported changes in PCIII. No significant heterogeneity was detected among these studies. Employing a fixed-effect model,

Table 2

Subgroup analysis.

Subgroup	Overall clinical efficacy				Change in AST				Change in ALT				Change in TC			
	Study	OR [95% CI]	*P*-value	I^2	Study	SMD [95% CI]	*P*-value	I^2	Study	SMD [95% CI]	*P*-value	I^2	Study	SMD [95% CI]	*P*-value	I^2
Total	24	3.36 [2.62, 4.31]	< .00001	0	21	−0.51 [−0.71, −0.31]	< .00001	75%	28	−0.51 [−0.59, −0.43]	< .00001	41%	28	−0.53 [−0.68, −0.38]	< .00001	68%
Types of acupuncture																
Manual acupuncture	9	3.27 [2.19, 4.90]	< .00001	0	5	−0.55 [−1.19, 0.1]	.1	89%	7	−0.39 [−0.56, −0.22]	< .00001	62%	8	−0.32 [−0.53, −0.11]	.003	42%
Electroacupuncture	4	3.32 [1.69, 6.52]	.0005	0	4	−0.34 [−0.73, 0.06]	.09	59%	7	−0.46 [−0.64, −0.28]	< .00001	0	7	−0.48 [−0.65, −0.30]	< .00001	0
Acupoint embedding	9	3.14 [2.13, 4.62]	< .00001	0	9	−0.70 [−0.85, −0.55]	< .00001	12%	10	−0.68 [−0.82, −0.55]	< .00001	5%	10	−0.75 [−1.02, −0.47]	< .00001	77%
Acupoint injection	2	5.74 [2.23, 14.83]	.0003	0	3	−0.13 [−0.49, 0.23]	.47	54%	4	−0.28 [−0.52, −0.05]	.02	30%	3	−0.25 [−0.55, 0.04]	.09	31%
Course of treatment																
≥12 wk	13	3.57 [2.58, 4.94]	< .00001	0	12	−0.59 [−0.87, −0.31]	< .0001	80%	14	−0.56 [−0.68, −0.45]	< .00001	57%	12	−0.47 [−0.72, −0.22]	.0003	76%
< 12 wk	11	3.08 [2.09, 4.54]	< .00001	7%	8	−0.39 [−0.65, −0.13]	.003	58%	14	−0.45 [−0.57, −0.32]	< .00001	8%	15	−0.57 [−0.76, −0.39]	< .00001	60%
The mean/median age																
≥40 yr	17	3.35 [2.53, 4.43]	< .00001	0	15	−0.64 [−0.85, −0.44]	< .00001	68%	20	−0.53 [−0.63, −0.43]	< .00001	44%	17	−0.32 [−0.48, −0.16]	< .0001	42%
<40 yr	5	3.21 [1.73, 5.97]	.0002	0	5	−0.11 [−0.42, 0.2]	.48	56%	7	−0.41 [−0.58, −0.24]	< .00001	34%	6	−0.53 [−0.75, −0.31]	< .00001	0
Course of the disease																
≥3 yr	6	4.81 [2.72, 8.48]	< .00001	0	8	-0.39 [−0.65, −0.12]	.004	66%	8	−0.63 [−0.79, −0.46]	< .00001	44%	9	−0.43 [−0.58, −0.29]	< .00001	0
<3 yr	9	2.64 [1.76,3.96]	< .00001	0	5	-0.38 [−0.69, −0.06]	.02	57%	9	−0.42 [−0.57, −0.27]	< .00001	52%	7	−0.52 [−0.92, −0.11]	.01	81%

Abbreviations: AST = aspartate aminotransferase, ALT = alanine aminotransferase, CI = confidence intervals, OR = odds ratio, SMD = standardized mean difference, TC = total cholesterol.

acupuncture treatment demonstrated efficacy in reducing PCIII levels (SMD = −0.26, 95% CI: −0.51 to 0.00; $P = .05$, $I^2 = 0\%$) (Fig. 5F). Visual evaluation of funnel plots showed no publication bias (Fig. 6C), and the nonsignificant result of Egger test ($P = .641$) indicates the absence of publication bias.

3.4.2.4.2. Change in LN. Three studies involving 240 participants reported alterations in LN. No significant heterogeneity was detected among these studies. Using a fixed-effect model, acupuncture treatment was determined to be efficacious in decreasing LN levels (SMD = −0.79, 95% CI: −1.05 to 0.53; $P < .00001$, $I^2 = 0\%$) (Fig. 5G). Visual inspection of the funnel plot did not reveal any signs of publication bias (Fig. 6D), while Egger test indicated statistical significance ($P = .023$), suggesting the presence of publication bias.

3.4.2.4.3. Change in HA. Three studies with 240 participants reported changes in HA. These studies exhibited no substantial heterogeneity, and using a fixed-effect model, Acupuncture therapy proved effective in decreasing HA levels (SMD = −1.19, 95% CI: −1.46 to 0.91; $P < .00001$, $I^2 = 0\%$) (Fig. 5H). Visual evaluation of funnel plots showed no publication bias (Fig. 6E), and the results from Egger test were not statistically significant ($P = .296$), indicating the lack of publication bias.

3.4.2.4.4. Change in CIV. Three studies, involving a total of 240 participants, documented alterations in CIV. These studies exhibited no significant heterogeneity, and a fixed-effect model was utilized. Acupuncture therapy demonstrated effectiveness in reducing CIV levels (SMD = −0.39, 95% CI: −0.65 to 0.14; $P = .003$, $I^2 = 0\%$) (Fig. 7A). Visual evaluation of funnel plots showed no publication bias (Fig. 6F), and Egger test did not demonstrate statistical significance ($P = .158$), indicating the absence of publication bias.

3.4.2.5. Imaging index.

3.4.2.5.1. Ultrasound efficiency. Nine studies involving 908 participants reported changes in Ultrasound detection. There was no significant heterogeneity observed among the studies. The fixed-effect model was applied, Acupuncture treatment demonstrated a beneficial impact on the improvement rate of Ultrasound detection (OR = 2.83, 95% CI: 2.05–3.91; $P < .00001$, $I^2 = 0$) (Fig. 7B). Analyses within subgroups were performed according to different types of treatment, duration of intervention, patient age, and course of disease (Table 3). The pooled data indicated that MA Had no significant impact on the rate of ultrasound improvement in patients. However, Significant effects were observed for patients of all ages regardless of the disease duration or treatment length. Visual evaluation of funnel plots revealed no evidence for publication bias (Fig. 6G), and Egger test yielded nonsignificant results ($P = .251$), indicating an absence of publication bias.

3.4.2.5.2. Liver and spleen CT ratio. Three studies with 90 participants reported changes in the liver-spleen CT ratio. These studies showed no significant heterogeneity, and the fixed-effect model indicated that acupuncture had no significant effect on reducing the CT ratio between the liver and spleen (OR = 1.28, 95% CI: 0.74 to 2.22; $P = .37$; $I^2 = 0\%$) (Fig. 7C). Visual evaluation of funnel plots showed no publication bias (Fig. 6H), and Egger test did not show statistical significance ($P = .812$), suggesting no presence of publication bias.

3.4.2.6. Change in BMI. Seven studies with 503 participants reported changes in BMI. There was no significant heterogeneity noted among the studies. and when employing a fixed-effect model, acupuncture treatment did not show a notable decrease in BMI (SMD = −0.68, 95% CI: −1.29 to −0.08; $P < .00001$, $I^2 = 92\%$) (Fig. 7D). Subgroup analysis showed that significant variability existed in the improvement effect of acupuncture on

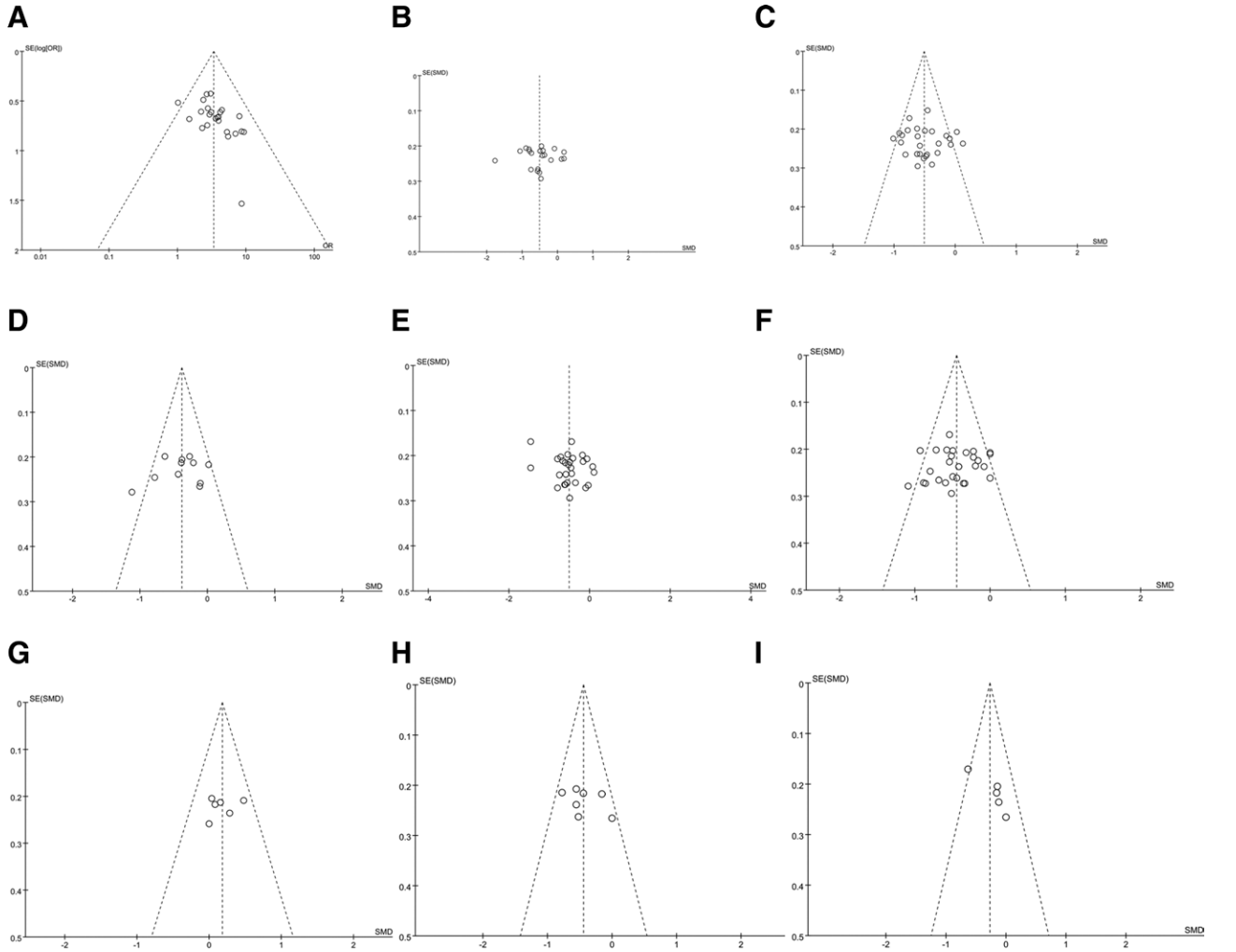

Figure 4. Forest plots of outcomes. (A) HDL, (B) LDL, (C) FPG, (D) FINS, (E) HOMA-IR, (F) PCIII, (G) LN, (H) HA. FINS = fasting insulin, FPG = fasting plasma glucose, HA = hyaluronic acid, HDL = high-density lipoprotein, HOMA-IR = homestasis model assessment of insulin, LDL = low-density lipoprotein, LN = laminin, PCIII = procollagen Type III.

patients' BMI of all ages, regardless of the duration of disease and treatment time (Table 3). Therefore, acupuncture could not be considered effective in improving BMI in NAFLD patients. Visual inspection of the funnel plot indicated no evidence of publication bias (Fig. 6I), and Egger test yielded nonsignificant results ($P = .251$), suggesting no presence of publication bias.

3.4.2.7. Adverse events. Side effects were reported in only one study.[18] The study noted that a patient in the wire embedding group experienced severe pain, delayed local absorption, and induration. The patient received treatment with hot compresses, leading to complete absorption of the wire body over the entire treatment course. Other patients in this group did not report any significant discomfort. In the Western medicine group, 2 patients experienced symptoms such as rash and jaundice after taking Cathailey. It is noteworthy that no side effects were reported in the remaining trials.

3.4.2.8. Sensitivity analysis. A comparative analysis of overall clinical effective rate, AST, ALT, GGT, TC, TG, BMI, and Ultrasound was conducted to evaluate their impact on the pooled effect. Sensitivity analysis, which involved systematically excluding each study one by one, was undertaken to assess the impact of individual studies on the findings. The findings revealed that the exclusion of any specific study did not alter the significance of the new effect values for overall clinical effective rate (Fig. 8A), AST (Fig. 8B), ALT (Fig. 8C), GGT (Fig. 8D), TC (Fig. 8E), TG (Fig. 8F), ultrasound (Fig. 8G), and BMI (Fig. 8H). However, when data from Huang 2016 and Tang 2023 were excluded, heterogeneity in changes in TC and BMI disappeared completely ($I^2 = 33\%$, $P < .00001$, and $I^2 = 10\%$, $P = .002$, respectively). This indicates that Huang 2016 and Tang 2023 are major contributors to the heterogeneity observed in changes in TC and BMI.

3.4.2.9. GRADE grading. We evaluated the quality of all evidence according to the GRADE criteria and found that the Overall Clinical Efficacy, Change in AST ALT, GGT, ultrasound efficiency, HDL, LDL, and HA were of high quality. Changes in TC, TG, BMI, PCIII, CIV, and the liver and spleen CT ratio were of moderate quality. Changes in FPG, FINS, HOMA-IR, and LN were of low quality, as detailed in Table 4.

4. Discussion

NAFLD, a metabolic disorder, impacts multiple systems, frequently linked with obesity, metabolic syndrome, and type 2 diabetes mellitus. Pharmacological interventions for NAFLD are presently limited, with lifestyle modifications serving as the cornerstone of treatment.[48] Nevertheless, the majority of patients find it challenging to adhere to these interventions. Furthermore, certain medications are employed for antidiabetic, antilipid therapy, and natural bile therapy in managing this condition.

Table 3

Subgroup analysis.

Subgroup	Change in TG				Change in BMI				Change in GGT				Efficiency in ultrasound			
	Study	SMD [95% CI]	*P*-value	I^2	Study	SMD [95% CI]	*P*-value	I^2	Study	SMD [95% CI]	*P*-value	I^2	Study	OR [95% CI]	*P*-value	I^2
Total	30	−0.54 [−0.73, −0.34]	< .00001	82%	8	−0.68 [−1.29, −0.08]	.03	92%	11	−0.38 [−0.51, −0.25]	< 0.00001	44%	9	2.83 [2.05, 3.91]	< .00001	0
Types of acupuncture																
Manual acupuncture	8	−0.35 [−0.51, −0.19]	< .0001	0	3	−0.17 [−0.44, 0.11]	.25	0	1	−0.37 [−0.78,0.03]	0.07	NA	1	3.13 [0.56, 17.34]	.19	NA
Electroacupuncture	8	−0.66 [−0.85, −0.47]	< .00001	20%	2	−0.26 [−0.60, 0.07]	.12	0	5	−0.49 [−0.70, −0.29]	< 0.00001	72%				
Acupoint embedding	10	−0.73 [−1.22, −0.23]	.004	92%	2	−1.93 [−5.4, 1.54]	.27	98%	3	−0.25 [−0.51, 0.01]	0.05	0	6	2.68 [1.89, 3.82]	< .00001	0
Acupoint injection	4	−0.21 [−0.49, 0.07]	.15	39%	1	−0.71 [−1.11, −0.31]	.0005		2	−0.33 [−0.63, −0.03]	0.03	0	2	3.92 [1.53, 10.09]	.005	0
Course of treatment																
≥12 wk	14	−0.57 [−0.95, −0.28]	.003	90%	4	−0.97 [−1.96, 0.03]	.06	95%	6	−0.30 [−0.48, −0.12]	0.001	57%	7	2.67 [1.86, 3.84]	< .00001	0
< 12 wk	15	−0.50 [−0.66, −0.34]	< .00001	41%	2	−0.17 [−0.49, 0.16]	.32	0	5	−0.48 [−0.68, −0.28]	< 0.00001	11%	2	3.56 [1.71, 7.43]	.0007	0
The mean/median age																
≥40 yr	20	−0.52 [−0.87, −0.25]	.0002	86%	5	−0.97 [−1.96, −0.03]	.06	95%	5	−0.42 [−0.61, −0.23]]	0.0001	0	9	2.83 [2.05, 3.91]	< .00001	0
< 40 yr	6	−0.57 [−0.92, −0.22]	.002	72%	2	−0.17 [−0.49, 0.16]	.32	0	6	−0.34 [−0.53, −0.16]	0.0003	66%				
Course of the disease																
≥ 3 yr	9	−0.45 [−0.66, −0.24]	< .0001	48%	4	−1.16 [−2.39, 0.07]	.07	96%	6	−0.23 [−0.41, −0.05]	0.01	0	4	2.93 [1.72, 4.98]	< .0001	0
< 3 yr	8	−0.56 [−0.78, −0.33]	< .00001	48%	3	−0.17 [−0.44, 0.11]	.25	0	2	−0.69 [−0.99, −0.39]	< 0.00001	0	3	2.42 [1.35, 4.35]	.003	0

Abbreviations: BMI = body mass index, CI = confidence intervals, GGT = γ-glutamyl transpeptadase, OR = odds ratio, SMD = standardized mean difference, TG = triglyceride.

However, the utilization of these drugs is significantly restricted due to the requirement for long-term use and the potential for adverse reactions leading to drug-induced liver injury.[49] Acupuncture, as a TCM modality, provides benefits including minimal adverse reactions and enhanced control over confounding factors in clinical studies. Several investigations have demonstrated the efficacy of acupuncture in treating NAFLD. with minimal adverse reactions reported.[15–42,46,47] Acupuncture exerts its effects through various targets, levels, and pathways, encompassing Suppression of inflammatory responses, control of lipid metabolism, insulin resistance management, reduction of oxidative stress injury, and modulation of endoplasmic reticulum stress.[49]

This systematic review and comprehensive analysis encompassed a total of 30 studies. The findings revealed several key discoveries. Firstly, acupuncture exhibits a significant therapeutic effect on NAFLD, resulting in varied improvements in liver function, blood lipids, glucose and insulin levels, liver fibrosis, and imaging outcomes. Subgroup analysis (Tables 2 and 3) indicates that AE demonstrates the most favorable and consistent therapeutic effect among treatment modalities, followed by EA; and MA and AI show limited efficacy. Secondly, concerning patients' age, acupuncture demonstrates promising treatment effects in older individuals but less satisfactory outcomes in younger patients. Regarding the reduction of AST and BMI levels, subgroup analysis highlights significant instability in the effectiveness of acupuncture therapy, warranting further research to determine its impact. Lastly, the top 10 acupoints utilized during acupuncture treatment for NAFLD were identified, offering valuable insights for clinical practice. Overall, acupuncture appears as a promising treatment option for NAFLD.

Acupuncture, as a TCM technique, has an extensive history in the treatment of NAFLD. Its therapeutic mechanisms encompass several key aspects: According to TCM theory, acupuncture can harmonize the zang-fu organs, balance Yin and Yang, unblock meridians, regulate Qi and blood, support the body's defenses, and expel pathogens. By stimulating specific acupoints, these techniques adjust the functions of the zang-fu organs and restore the balance of Yin and Yang, achieving what is described as "Yin Ping Yang Mi" (Yin and Yang in harmony). Additionally, acupuncture facilitates the smooth flow of Qi and blood through the meridians, stimulates the body's positive energy, enhances disease resistance, strengthens organ function, and promotes the recovery of liver diseases by maintaining a state of "positive Qi stored within, evil cannot invade." From a modern medical perspective, acupuncture have been shown to significantly modulate the neuroendocrine immune system, improve insulin sensitivity, regulate hormones related to fat metabolism, and adjust gut microbiota. Insulin resistance plays a critical role in the pathogenesis of nonalcoholic liver disease. Acupuncture can enhance endocrine function, increase insulin sensitivity, alleviate leptin resistance, regulate adiponectin levels, and promote lipolysis and lipid consumption. Furthermore, acupuncture boosts immune defense, activates immune cells, regulates immune balance, and reduces liver inflammation. By improving gut-liver axis function and enhancing intestinal microecology, acupuncture helps mitigate liver inflammation and damage.[50]

Different therapeutic modalities operate through distinct mechanisms. The AE induces soft and sustained stimulation via the liquefaction, decomposition, and absorption of the thread body at the acupuncture point. This continuous stimulation enhances the circulation of qi and blood in the meridians, modulates visceral functions, maintains vagal nerve activation, prolongs anti-inflammatory and metabolic regulatory effects, promotes macrophage polarization to the M2 phenotype, inhibits hepatic stellate cell activation, delays liver fibrosis, and regulates hormones associated with fat metabolism.[51,52] Our study concludes that The AE for NAFLD offers numerous advantages, including significant therapeutic efficacy, multi-targeted

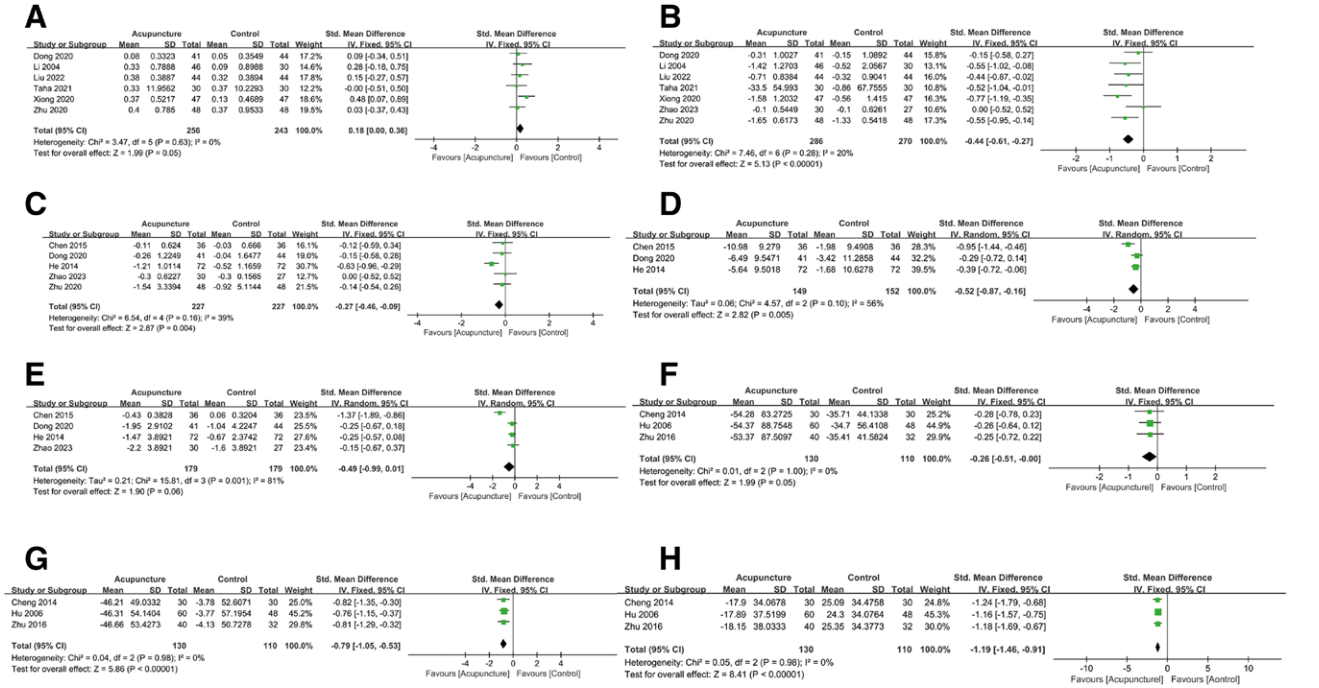

Figure 5. Forest plots of outcomes. (A) CIV, (B) ultrasound efficiency, (C) liver and spleen CT ratio, (D) BMI. BMI = body mass index, CIV = collagen Type IV.

comprehensive regulation, convenient administration, high patient compliance, high safety, and economic benefits, making it a treatment method worthy of clinical promotion. EA integrates electrical stimulation with traditional needle acupuncture, where pulse currents are delivered via an EA device to stimulate acupoints and produce therapeutic effects. MA, on the other hand, relies on the practitioner's skillful manipulation of needles using their fingers, allowing for flexible adjustments in technique and intensity based on the patient's physical condition and constitution. The findings of this study indicate that both EA and MA are effective in treating NAFLD, although their efficacy is not as pronounced as that of AE. However, these 2 methods are simpler to perform and thus merit clinical promotion. AI involves administering drugs directly into specific acupoints, combining both pharmacological and acupoint stimulation effects. Our analysis revealed that its therapeutic outcomes were less favorable compared to the aforementioned 3 methods, possibly due to rapid drug absorption, short duration of action, and relatively weaker efficacy. In summary, all 4 therapies modulate the neuroendocrine immune system through acupoint stimulation, but each has distinct advantages. Clinical treatment should be tailored to the patient's specific conditions, selecting the most appropriate individualized regimen.

The differential efficacy of acupuncture in treating NAFLD among older vs younger patients may be attributed to the interaction of multiple factors. Firstly, age-related differences in pathophysiological characteristics play a significant role.[53] Older patients often exhibit metabolic slowdown, decreased insulin sensitivity, and chronic low-grade inflammation, all of which are closely linked to the progression of NAFLD. Acupuncture can modulate vagus nerve activity, inhibit the release of pro-inflammatory cytokines such as TNF-α and IL-6, and improve insulin resistance. The pathological state of elderly patients may be more responsive to acupuncture's regulatory effects. Conversely, NAFLD in younger patients is frequently associated with obesity, high-fat diets, sedentary lifestyles, and more active hepatic steatosis and inflammation. These metabolic disturbances are often driven by strong external stimuli, such as excessive caloric intake, making it challenging for local acupuncture regulation to fully counteract persistent adverse metabolic stress. Secondly, Compliance and Lifestyle Intervention: Elderly patients exhibit higher levels of compliance with treatment protocols.[54] They typically place greater emphasis on health management, enabling them to consistently adhere to acupuncture treatments and dietary controls. Additionally, they face relatively fewer external pressures, which facilitates the manifestation of acupuncture's therapeutic effects. In contrast, younger individuals often struggle to maintain lifestyle adjustments (such as abstaining from alcohol and engaging in regular exercise) due to work-related stress and social commitments. This group is also more likely to be continuously exposed to high-risk factors (such as late-night activities and alcohol consumption), thereby diminishing the effectiveness of acupuncture therapy. last, Psychological Factors Elderly patients exhibit a higher degree of trust in traditional therapies compared to younger individuals who tend to have lower confidence in these methods.[55] Positive psychological factors can significantly enhance the efficacy of acupuncture treatment. Psychological influences impact the neuroendocrine immune system via the neuroendocrine-immune network. A positive mental state promotes balanced and coordinated nervous system regulation, thereby enhancing the effectiveness of acupuncture on nerve reflex arcs. For instance, in a relaxed psychological state, acupuncture stimulation more effectively modulates the tension between sympathetic and parasympathetic nerves through neural pathways, improving organ function. Mental states influence endocrine hormone secretion; anxiety and depression may cause endocrine disorders such as increased cortisol levels. Combining acupuncture with a positive mental state optimizes endocrine regulation, promoting the secretion of neurotransmitters and hormones like endorphins, which alleviate pain, improve mood, and boost immunity. A positive mental state also enhances immune function by increasing immune cell activity and immune factor secretion, synergizing with acupuncture's regulatory effects to promote disease recovery.

Regarding the selection of acupoints, based on TCM theory, nonalcoholic fatty liver disease (NAFLD) is characterized by liver qi stagnation and spleen deficiency with phlegm-dampness accumulation, primarily affecting the liver, spleen, and stomach. NAFLD primarily affects the liver, involving the spleen and stomach, and is characterized by spleen deficiency, liver

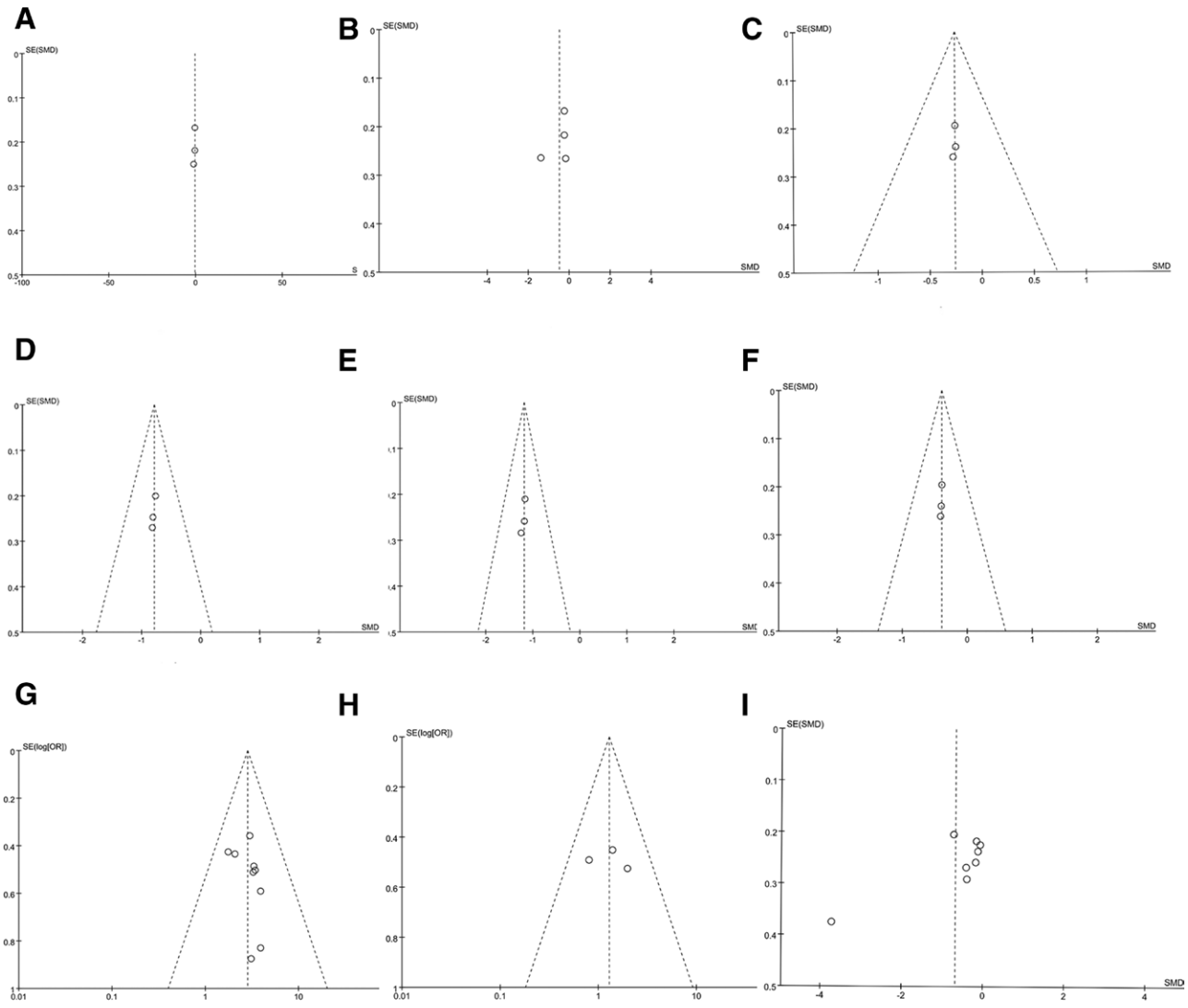

Figure 6. Funnel plots of (A) overall clinical efficacy, (B) AST, (C) ALT, (D) GGT, (E) TC, (F) TG, (G) HDL, (H) LDL, (I) FPG. ALT = alanine aminotransferase, AST = aspartate aminotransferase, FPG = fasting plasma glucose, GGT = γ-glutamyl transpeptadase, HDL = high-density lipoprotein, LDL = low-density lipoprotein, TC = total cholesterol, TG = triglyceride.

depression, and qi stagnation, with phlegm and dampness as key pathological factors. Spleen deficiency results in the formation of dampness and phlegm, which then transforms into adipose tissue. The accumulation of fat in the bloodstream disrupts normal fat metabolism, enhances insulin resistance, and disrupts sugar metabolism. Acupuncture stimulates specific acupoints, regulating qi flow in the corresponding liver and spleen meridians, effectively soothing liver function and promoting spleen regulation. Additionally, it aids in eliminating phlegm and dampness.[56] For example, acupoints such as ST36 (Zusanli), SP6 (Sanyinjiao), CV12 (Zhongwan), ST25 (Tianshu), and BL20 (Pishu) can regulate gastrointestinal activity by enhancing motility, increasing the efficacy of digestive enzymes, and suppressing appetite. Furthermore, they accelerate fat transportation, metabolism, and degradation within the body, facilitating spleen regulation and dampness removal. Specifically targeting the reduction of phlegm and dampness is achieved through ST40 (Fenglong). LR3 (Taichong) and BL18 (Ganshu) harmonize liver–spleen functions and regulate endocrine activity, providing dual benefits of hepatoprotection and lipid-lowering effects.[57]

This study presents the latest and most comprehensive collection of RCT literature, comparing various types of acupuncture and incorporating imaging indicators to thoroughly Assess the safety and effectiveness of acupuncture for treating NAFLD. Nevertheless, our study has several potential limitations. Firstly, due to the absence of a blind method, only 2 studies in the control group were able to employ sham acupuncture, while the remaining control groups utilized drugs or lifestyle changes that could not be implemented using a blind method. Secondly, The majority of the studies included had limited sample sizes, resulting in certain outcome indicators being based on only 3 to 5 papers. This limitation greatly undermines the reliability of the conclusions. Therefore, future investigations require larger-scale and high-quality studies for further analysis. Finally, heterogeneity arises from variations in interventions, treatment durations, patients' disease statuses, and the use of different acupoint combinations, all of which might impact the pooled effectiveness of key outcomes in our research.

5. Conclusion

In conclusion, acupuncture shows promising potential as a safe and efficient treatment option for NAFLD, leading to improvements in hepatic functionality, reductions in glucose

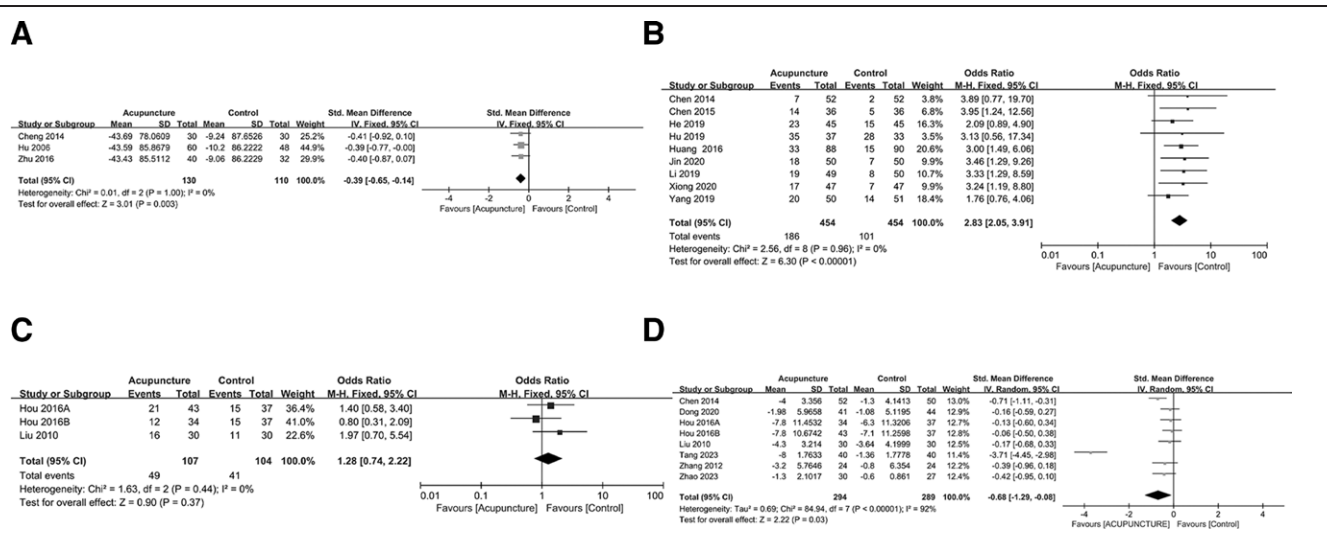

Figure 7. Funnel plots of (A) FINS, (B) HOMA-IR, (C) PCIII, (D) LN, (E) HA, (F) CIV, (G) ultrasound efficiency, (H) liver and spleen CT ratio, (I) BMI. BMI = body mass index, CIV = collagen Type IV, FINS = fasting insulin, HA = hyaluronic acid, HOMA-IR = homestasis model assessment of insulin, LN = laminin, PCIII = procollagen Type III.

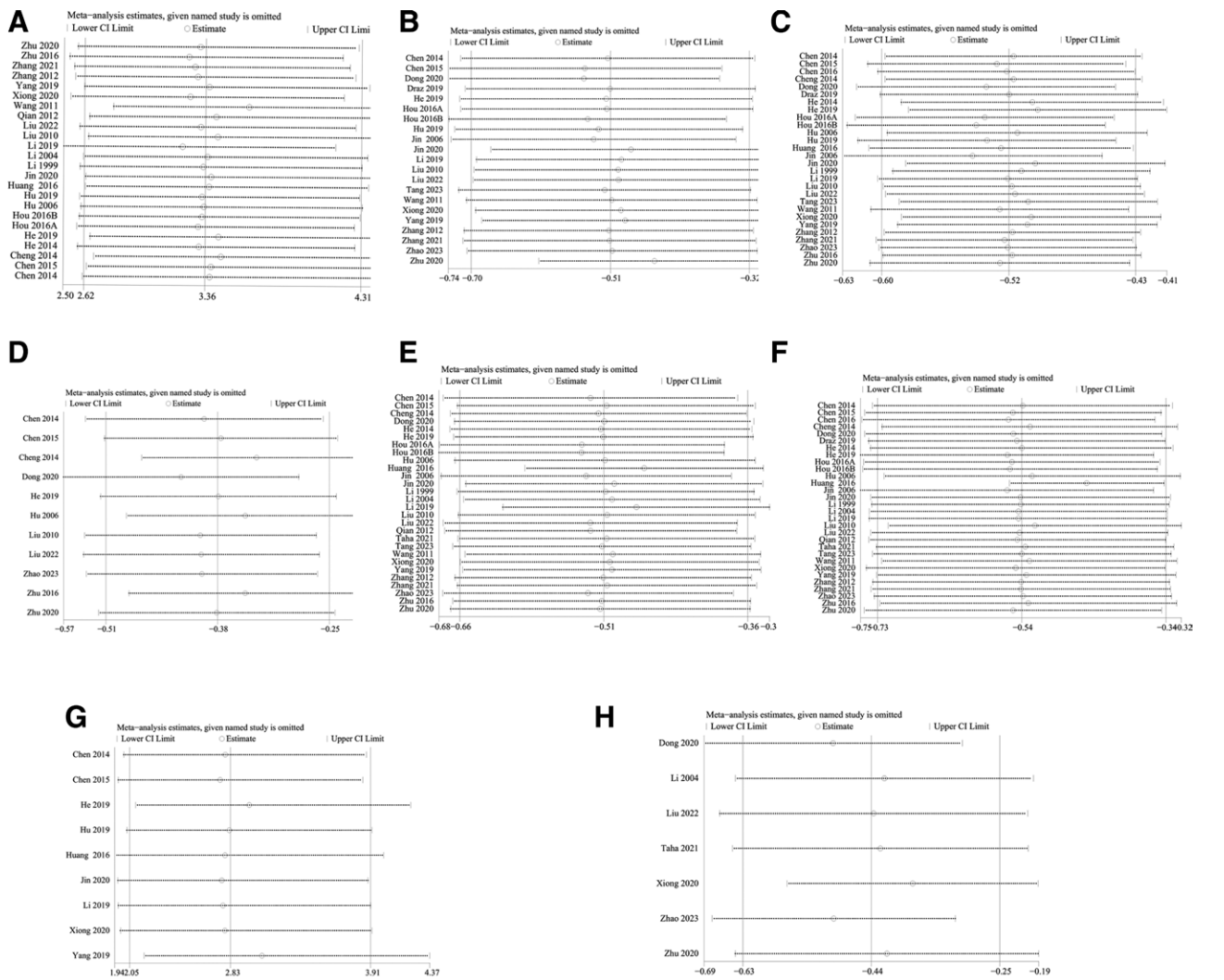

Figure 8. Sensitivity analysis. (A) Overall clinical efficacy, (B) AST, (C) ALT, (D) GGT, (E) TC, (F) TG, (G) ultrasound efficiency, (H) BMI. ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, GGT = γ-glutamyl transpeptadase, TC = total cholesterol, TG = triglyceride.

Table 4

GRADE rating of outcomes.

Outcomes	No. of studies	Metrics	Estimates	95% CI	I^2; *P*-value	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Plausible confounding	Magnitude of effect	Dose–response gradient	GRADE
Overall clinical efficacy	24	OR	3.36	2.62, 4.31	0%; $P = .97$	No serious risk	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Would not reduce effect	No	No	High
Change in AST	21	SMD	−0.51	−0.71, −0.31	75%; $P < .00001$	No serious risk	Serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Would not reduce effect	No	No	High
Change in ALT	28	SMD	−0.51	−0.59, −0.43	41%; $P = .01$	No serious risk	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Would not reduce effect	No	No	High
Change in TC	28	SMD	−0.53	−0.68, −0.38	68%; $P < .00001$	No serious risk	Serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Would not reduce effect	No	No	Moderate
Change in TG	30	SMD	−0.54	−0.73, −0.34	82%; $P = .05$	No serious risk	Serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Would not reduce effect	No	No	Moderate
Change in BMI	8	SMD	−0.68	−1.29, −0.08	92%; $P = .36$	No serious risk	Serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Would not reduce effect	No	No	Moderate
Change in GGT	11	SMD	−0.38	−0.51, −0.25	44%; $P = .06$	No serious risk	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Would not reduce effect	No	No	High
Efficiency in ultrasound	9	OR	2.83	2.05, 3.91	0%; $P = .96$	No serious risk	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Would not reduce effect	No	No	High
Chang in HDL	6	SMD	0.18	0.00, 0.36	0%; $P = .63$	No serious risk	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Would not reduce effect	No	No	High
Change in LDL	7	SMD	−0.44	−0.61, −0.27	20%;$P = .28$	No serious risk	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Would not reduce effect	No	No	High
Change in FPG	5	SMD	−0.27	−0.46, −0.09	39%;$P = .16$	No serious risk	No serious inconsistency	No serious indirectness	Serious imprecision	Strongly suspected	Would not reduce effect	No	No	Low
Change in FINS	3	SMD	−0.52	−0.87, −0.16	56%;$P = .10$	No serious risk	Serious inconsistency	No serious indirectness	Serious imprecision	Undetected	Would not reduce effect	No	No	Low
Change in HOMA-IR	4	SMD	−0.49	−0.99, 0.01	81%,$P = .001$	No serious risk	Serious inconsistency	No serious indirectness	Serious imprecision	Undetected	Would not reduce effect	No	No	Low
Change in PCIII	3	SMD	−0.26	−0.51, −0.00	0%; $P = 1.00$	No serious risk	No serious inconsistency	No serious indirectness	Serious imprecision	Undetected	Would not reduce effect	No	No	Moderate
Change in LN	3	SMD	−0.79	−1.05, −0.53	0%; $P = .98$	No serious risk	No serious inconsistency	No serious indirectness	Serious imprecision	Strongly suspected	Would not reduce effect	No	No	Low
Change in HA	3	SMD	−1.19	−1.46, −0.91	0%; $P = .98$	No serious risk	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Would not reduce effect	No	No	High
Chang in CIV	3	SMD	−0.39	−0.65, −0.14	0%; $P = 1.00$	No serious risk	No serious inconsistency	No serious indirectness	Serious imprecision	Undetected	Would not reduce effect	No	No	Moderate
Liver and spleen CT ratio	3	OR	1.28	0.74, 2.224	0%; $P = .44$	No serious risk	No serious inconsistency	No serious indirectness	Serious imprecision	Undetected	Would not reduce effect	No	No	Moderate

Abbreviations: AST = aspartate aminotransferase, ALT = alanine aminotransferase, BMI = = body mass index, CI = confidence intervals, CIV = collagen Type IV, FINS = Fasting Insulin, FPG = Fasting Plasma Glucose, GGT = γ-glutamyl transpeptadase, HA = hyaluronic acid, HDL = high-density lipoprotein , HOMA-IR = homestasis model assessment of insulin, LDL = low-density lipoprotein, LN = laminin, OR = odds ratio, PCIII = procollagen Type III, SMD = standardized mean difference, TC = total cholesterol, TG = triglyceride.

and lipid levels, and mitigation of liver fibrosis. Recommended Acupuncture Treatment Scheme: The proposed treatment method is acupoint embedding. The acupoints selected are as follows: ST36 (Zusanli), ST40 (Fenglong), SP6 (Sanyinjiao), LR3 (Taichong), BL18 (Ganshu), CV12 (Zhongwan), GB34 (Yanglingquan), PC6 (Neiguan), ST25 (Tianshu), BL20 (Pishu), and SP9 (Yinlingquan). Patients aged 45 years or older exhibit significantly better treatment outcomes compared to those under 45 years of age. For younger patients, combining exercise and diet management is recommended. This study proposes an enhanced treatment regimen and a more personalized therapeutic strategy for managing NAFLD. However, further validation of these findings requires large-scale RCTs.

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Visualization: Xiufeng Ban.
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