Chaihu Shugan San for Non-Alcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis

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Abstract: *Objective:* This study aimed to explore the therapeutic efficacy and risk profile of Chaihu Shugan San (CS) as an intervention for non-alcoholic fatty liver disease (NAFLD) through a comprehensive, up-to-date meta-analysis of published randomized controlled trials (RCTs)

Methods: We searched the following databases: PubMed, Web of Science, China Biomedical Literature Database (CBM), VIP, China National Knowledge Infrastructure (CNKI), and Wanfang Data for RCTs on CS for NAFLD from database inception to May 31, 2025. Having been screened according to the pre-defined criteria, the selected studies underwent data extraction and risk of bias assessment. The meta-analysis was conducted utilizing RevMan 5.4 software. Primary outcome measures consisted of overall clinical efficacy rate, liver function, and lipid profiles.

Results: A total of 27 RCTs concerning 2,592 patients were selected. Meta-analysis results demonstrated that in contrast to the control group, CS significantly enhanced the overall clinical efficacy rate (odds ratio(OR) = 4.17, 95% confidence intervals(CI): 3.19–5.47, P < 0.00001, I^2 = 0%). Regarding liver function, CS significantly reduced aspartate aminotransferase(AST) (mean differences(MD) = -11.44, 95% CI: -14.75 to -8.13, P = 0.0003; I^2 = 61%), alanine aminotransferase(ALT) (MD = -13.57, 95% CI: -15.64 to -11.49, P < 0.00001; I^2 = 31%), and γ-glutamyl transpeptadase(GGT) (MD = -10.41, 95% CI: -15.75 to -5.07, P < 0.00001; I^2 = 0%); Regarding lipid profiles, CS significantly improved total cholesterol(TC) (MD = -1.24, 95% CI: -1.73 to -0.75, P < 0.00001; I^2 = 92%), triglyceride(TG) (MD = -0.76, 95% CI: -0.98 to -0.53, P < 0.00001; I^2 = 82%), high-density lipoprotein cholesterol(HDL-C) (MD = 0.26, 95% CI: 0.09–0.42, P < 0.00001; I^2 = 84%), and reduced low-density lipoprotein cholesterol(LDL-C) (MD = -0.56, 95% CI: -0.96 to -0.15, P < 0.00001; I^2 = 92%). Subgroup analysis indicated that the use of CS alone demonstrated greater efficacy in reducing liver function indicators (AST and ALT) than CS combined with traditional Chinese medicine, Western medicine, or even a composite of both traditional Chinese and Western medicines. Furthermore, the analysis showed that better outcomes were particularly evident in older patients and those with a shorter duration of disease. No significant adverse reactions were reported in either group.

Conclusion: CS effectively improves multiple liver function and lipid metabolism indicators in NAFLD patients, with superior efficacy in older patients. However, existing evidence primarily stems from studies with small sample sizes or methodological limitations. Future high-quality, large-scale, rigorously designed RCTs are necessary to substantiate its long-term efficacy and safety further.

Keywords: Chaihu Shugan San, Non-alcoholic fatty liver disease, Systematic review, Meta-analysis.

1. INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), also referred to as metabolic dysfunction-associated fatty liver disease (MAFLD), is a long-standing liver disease primarily marked by excessive fat accumulation within hepatocytes, occurring in individuals without a history of ethanol abuse (alcohol intake < 40 grams per week). The global prevalence of NAFLD is approximately 29.8%, reaching 27.4% in Asia, with about half of patients also having diabetes, hypertension, or cardiovascular/cerebrovascular diseases [1]. Its clinical manifestations primarily include dull pain in the hepatic region, fatigue, and obesity. In traditional Chinese medicine (TCM) theory, NAFLD may be categorized under syndromes such as “flank pain,” “mass accumulation,” or “phlegm-turbidity.” Its pathogenesis is primarily associated with impaired liver qi stagnation, spleen deficiency with dampness obstruction, and mutual entanglement of phlegm and blood stasis, closely linked to modern medical concepts of lipid metabolism abnormalities and insulin resistance [2]. Currently, no particularly effective treatment exists for NAFLD. Lifestyle interventions (including dietary adjustments and regular exercise) are recommended as first-line treatment [3]. However, due to insufficient patient awareness of the disease and the difficulty in altering long-term unhealthy habits, treatment adherence is generally low, often resulting in suboptimal outcomes from behavioral interventions [4]. On the other hand, although various drugs are in the research phase, inconsistent efficacy, potential side effects, or long-term safety concerns have prevented their widespread clinical application. Therefore, developing new therapeutic agents that combine efficacy, safety, and ease of administration has become an urgent need in NAFLD research.

CS originates from Jingyue Quanshu (Comprehensive Treatise of Jingyue), composed of Bupleurum, Paeonia alba, Citrus aurantium, Ligusticum, Cyperus, and *Citrus peel*. It possesses the effects of

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soothing the liver, regulating qi, promoting blood circulation, and alleviating pain [5]. This formula is frequently employed to treat fatty liver disease, chronic hepatitis, gastritis, and other conditions caused by liver qi stagnation. Its core mechanism lies in harmonizing liver qi and improving qi and blood circulation, thereby alleviating hepatic discomfort and metabolic disorders [6]. Traditional Chinese medicine theory posits that liver qi stagnation is the core pathogenesis of NAFLD, and CS directly addresses this cause by regulating liver qi and resolving phlegm and stasis. Clinical studies demonstrate that this formula significantly reduces serum lipid levels (TC, TG, LDL-C) and liver enzymes (ALT, AST, GGT) in patients, while increasing HDL-C and Nesfatin-1 levels and improving insulin sensitivity [7]. Pharmacological studies indicate that its active components (*e.g.*, *quercetin, kaempferol*) inhibit hepatic lipogenesis and promote lipolysis by modulating nuclear receptors such as FXR and PPARα [8]. Thus, CS not only alleviates clinical symptoms but may also reverse the pathological progression of fatty liver disease at the molecular level.

Although CS shows promising clinical potential for treating NAFLD, current systematic reviews and meta-analyses remain scarce and suffer from limitations such as insufficient literature inclusion, poor methodological quality, incomplete search strategies, inadequate heterogeneity handling, and insufficient publication bias assessment. This study therefore systematically retrieved relevant RCTs from multiple databases and employed more rigorous statistical methods, including sensitivity analysis, subgroup analysis, and offered higher-quality evidence-based medical clinical recommendations .

2. MATERIALS AND METHODS

2.1. Search Strategy

A systematic search was employed in PubMed, Web of Science, the Chinese Biomedical Literature Database (CBM), VIP, China National Knowledge Infrastructure (CNKI), and Wanfang Data's self-built database for relevant literature published up to May 31, 2025. Chinese search terms comprised “non-alcoholic fatty liver disease,” “non-alcoholic steatohepatitis,” “MAFLD,” “NAFLD,” and “Chaihushugansan.” English queries combined subject headings with free-text terms. The search process was not restricted by language (Table **A1**).

2.2. Inclusion Criteria

(1) Study Type: Randomized controlled trial (RCT) evaluating the efficacy and safety of CS therapy for NAFLD;

(2) Study Population: Patients meeting the diagnostic criteria of the “Diagnosis and Treatment Guidelines for Non-Alcoholic Fatty Liver Disease (2010 Revised Edition)” [9], regardless of gender, age, ethnicity, or nationality;

(3) Intervention Measures: The experimental group received CS monotherapy or combined with other Chinese herbal medicines; the control group received Western medicine treatment or no intervention;

(4) Outcomes: Primary endpoint was the clinical total effective rate for NAFLD, categorized into four levels (cure, marked improvement, improvement, no improvement) per relevant guidelines which was calculated as the percentage of total effective cases relative to total cases [15]. Secondary endpoints include ALT, AST, GGT, TG, TC, LDL-C, HDL-C, and adverse events;

(5) Data completeness: The study must provide Adequate data to compute odds ratios (OR) or weighted mean differences (MD/SMD).

2.3. Exclusion criteria

(1) Non-RCT studies such as those with neither random assignment nor a control group, reviews, animal experiments, conference reports, case reports, abstracts, and theses;

(2) Studies with unclear or non-standardized diagnostic criteria;

(3) Duplicate publications;

(4) Literature from which required data cannot be extracted.

2.4. Literature Screening and Quality Assessment

Independent screening of the literature and extraction of data were undertaken by two researchers, utilizing a predefined data collection form for information entry. Discussion or adjudication by a third researcher served as the mechanism for resolving disagreements. EndNote software was used to manage the literature and eliminate duplicate records. The Jadad Quality Scale was implemented to analyze the methodological quality of selected studies, evaluating three aspects: random sequence generation, blinding, and documentation of withdrawals and losses to follow-up. Studies scoring ≥4 points were considered high quality, 3 points indicated moderate quality, and ≤2 points denoted low quality.

2.5. Data Extraction

Extracted data involve the first author, publication year, region, sample size, patient age, intervention

measures, treatment duration, disease course, and outcome measures. Clinical efficacy is categorized according to the following criteria:

(1) Cure: Complete resolution of clinical symptoms and signs, normalization of TC and TG levels, and disappearance of fatty liver features on imaging studies;

(2) Improvement: Symptoms and signs substantially alleviated, with TC and TG levels reduced by ≥10% from baseline or approaching normal, and imaging showing marked improvement;

(3) No effect: Failure to meet the above criteria.

2.6. Statistical Analysis

Meta-analysis was employed utilizing RevMan 5.4 software. Binary variables were described as odds ratios (OR) with 95% confidence intervals (CI), while continuous variables were described as standardized mean differences (MD) with 95% CI. Heterogeneity was evaluated employing the I^2 statistic: the fixed-effect model was employed when $I^2 < 50\%$, and the random-effects model when $I^2 \geq 50\%$. Subgroup analyses or sensitivity analyses were adopted to examine sources of heterogeneity. Publication bias was evaluated utilizing Egger's test in Stata 12.1 software. Statistical significance was evaluated based on a p-value of less than 0.05. The formula for calculating the effective rate of count data is:

Overall effective rate % = (Number of cured cases + Number of significantly effective cases + Number of effective cases) / Total number of patients × 100%.

For continuous variables measured before and after intervention, the standard deviation of the change value was calculated using the following formula:

SD (B) and SD (F) represent the standard deviation before and after the intervention, respectively, the correlation coefficient R was set to 0.5.The linear regression method (Egger's regression tests) provided by Stata 15.1 software (Stata Corp, College Station, TX, USA) and the funnel plot generated by Review Manager 5.4.1(Cochrane Collaboration, Oxford, UK) were employed to identify potential publication bias [16]. Statistical significance was assessed employing a threshold of $p < 0.05$.Additionally, according to GRADE, each outcome's evidence was evaluated and graded as "high", "moderate", "low", or "very low" quality to draw conclusions [17].

3. RESULTS

3.1. Study Selection and Characteristics

The database search and selection process flowchart is displayed in Figure **1**. The initial search yielded 412 relevant publications. After stepwise screening, 27 randomized controlled trials (RCTs) meeting the criteria [7, 10-35] were ultimately included, involving a total of 2,592 patients. The literature screening process is detailed in Figure **1**. The scope of our review was restricted to studies conducted within

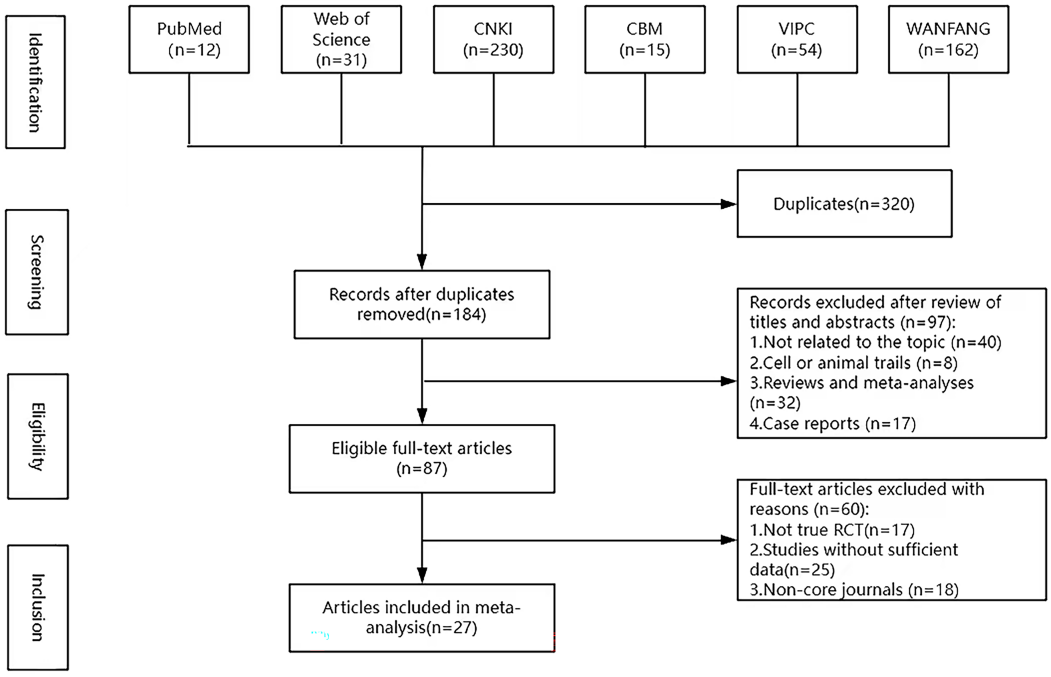


Figure 1: Flowchart of the systematic literature search and study selection process.

Table 1: This Table Summarizes the Baseline Characteristics of the Randomized Controlled Trials Included in the Meta-Analysis

Study	Study Period	Region	Study Design	Age	Interventionp		Patients		Follow-up (week)	Course of Disease (year)	
					Chaihushugansan	Control	Chaihushugansan	Control		Chaihushugansan	Control
Fu 2011	NA	China	RCT	NA	Chaihu Shugan Powder	Compound Danshen Dropping Pills and Gynostemma Pentaphyllum Total Extract Tablets	50	20	12	NA	NA
He 2022	2020.6-2021.6	China	RCT	18-60	Chaihu Shugan Powder	Polyene Phosphatidylcholine Capsules	57	58	17	NA	NA
Wu 2023	2021.2-2023.2	China	RCT	29-65/30-63	Chaihu Shugan Powder	Polyene Phosphatidylcholine Capsules	41	41	12	1-5	1-5
Zhou 2021	2020.3-2021.3	China	RCT	23-68/20-70	Bupleurum Liver-Soothing Powder combined with Coptis Gallbladder-Warming Decoction	Polyene Phosphatidylcholine Capsules	40	42	12	1.5-7.5	2-6
Yue 2013	2010.2-2012.9	China	RCT	26-59/28-56	Chaihu Shugan Powder	Silybin Capsules	130	126	12	NA	NA
Shi 2010	2008.6-2009.6	China	RCT	23-69/23-68	Chaihu Shugan Powder	lovastatin	55	55	12	NA	NA
Zhang 2013	2012	China	RCT	37-65/36-64	Chaihu Shugan Powder	Dongbao Gan Tai Tablets	30	30	12	0.5-10	0.5-12
Zhang 2010	NA	China	RCT	29-65/30-66	Chaihu Shugan Powder	Nicotinic acid inositol tablets, vitamin E and vitamin C	65	65	8	NA	NA
Zhao 2008	NA	China	RCT	18-65/20-67	Chaihu Shugan Powder, dietary control and Lipibot Tablets	dietary control and Lipibot Tablets	38	36	NA	0.17-10	0.1-8
Fang 2016	2013.5-2014.5	China	RCT	36-73/33-75	Chaihu Shugan Powder	Yishanfu, taurine, metronidazole and intravenous polymyxin B	63	63	4	1-2	1-2
Cao 2015	2011.1-2012.12	China	RCT	48.7±9.7/51.2±9.4/50.1±10.0	Chaihu Shugan Powder	Silybin Capsules	36	36	24	4.1±2.3	3.8±2.5
Zhu 2018	2015.6-2016.12	China	RCT	34-65/30-69	Chaihu Shugan Powder	Polyene Phosphatidylcholine Capsules	40	30	16	6.54±2.78	7.18±3.15
Yang 2008	NA	China	RCT	29-71	Chaihu Shugan Powder	Glucosamine dihydrochloride, reduced glutathione, liver hydrolyzed peptide intravenous injection	33	37	NA	NA	NA
Teng 2011	2004-2010	China	RCT	24-58	Chaihu Shugan Powder	Polyene Phosphatidylcholine Capsules	30	30	12	NA	NA
Tan 2018	2015.1-2016.12	China	RCT	31-67	Chaihu Shugan Powder	Insulin exenatide injection by subcutaneous administration	66	67	12	5.49±1.34	5.27±1.24
Pan 2009	2006.3-2007.12	China	RCT	21-68/23-67	Chaihu Shugan Powder	Dongbao Gan Tai Tablets	41	41	12	NA	NA
Wang 2010	2007.3-2009.3	China	RCT	26-62/29-65	Chaihu Shugan Powder	Nifobet sustained-release capsules	54	54	12	3.2±0.4	3.1±0.8
Wang 2007	2001.3-2006.12	China	RCT	17-68/19-66	Chaihu Shugan Powder	Lipibot Tablets	46	45	4	NA	NA
Hu 2015	2013.1-2014.8	China	RCT	23-67	Chaihu Shugan Powder	Silybin Capsules	62	62	12	NA	NA
Su 2021	2018.2-2020.5	China	RCT	38-65	Chaihu Shugan Powder	Polyene phosphatidylcholine capsules, metronidazole tablets, taurine capsules and intravenous polymyxin B	36	35	8	16.72±5.18	15.73±5.08

Xie 2021	2019.1-2020.1	China	RCT	NA	Chaihu Shugan Powder	Placebo: Flour, additives and spices	40	40	12	NA	NA
Zhao 2021	2019.3-2020.2	China	RCT	38-71/35-75	Chaihu Shugan Powder	Taurine Capsules, Metronidazole, Yishanfu Capsules and Intravenous Polymyxin B	23	24	8	NA	NA
Huang 2020	NA	China	RCT	20-60/21-59	Chaihu Shugan Powder, Atorvastatin and Vitamin E	Atorvastatin and Vitamin E	20	20	24	8.4±9.7	9.3±8.9
Luo 2020	2014.7-2016.6	China	RCT	35-75/38-76	Chaihu Shugan Powder	Silybin Capsules	78	77	12	10.15±2.04	10.41±1.93
Huang 2017	2015.1-2017.3	China	RCT	25-70/24-69	Chaihu Shugan Powder and Simvastatin Tablets	Simvastatin tablets, reduced glutathione and glucose intravenous infusion	72	72	8	NA	NA
Chen 2022	2018.1-2021.3	China	RCT	36-72	Chaihu Shugan Powder and Ezetimibe	Ezetimibe	30	30	24	NA	NA
Lei 2019	2018.10-2019.10	China	RCT	30-67/28-70	Chaihu Shugan Powder	Polyene Phosphatidylcholine Capsules	40	40	12	2.56±0.55	2.71±0.61

China and published within the timeframe of 2007 to 2025. Patient ages ranged from 20 to 75 years. The intervention in the treatment group consisted of either the single-herb formula CS or its modified versions, while the control group primarily received Western medicine or a placebo. Treatment cycles lasted 3 to 6 months, with patient disease duration ranging from 2 months to 12 years. The basic characteristics of the selected studies are displayed in Table **1**.

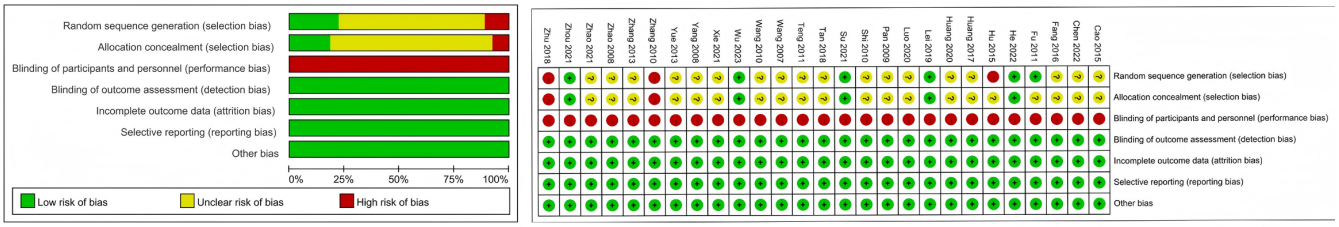
3.2. Risk of Bias Assessment

The Cochrane risk of bias tool was performed to evaluate the methodological quality of the included studies. Among them, 19 studies detailed random sequence generation methods (*e.g.*, random number tables) and were categorized as “low risk”; 2 studies had inadequate randomization methods and were graded as “high risk”; 6 studies did not explicitly describe the randomization scheme and were judged to be “uncertain risk.” Due to the unique nature of CS preparations, none of the studies implemented blinding; thus, all blinding-related items were rated as “high risk.” The summary of risk of bias is presented in Figure **2**.

3.3. Meta-Analysis Results

3.3.1. Primary Outcome: Overall Response Rate

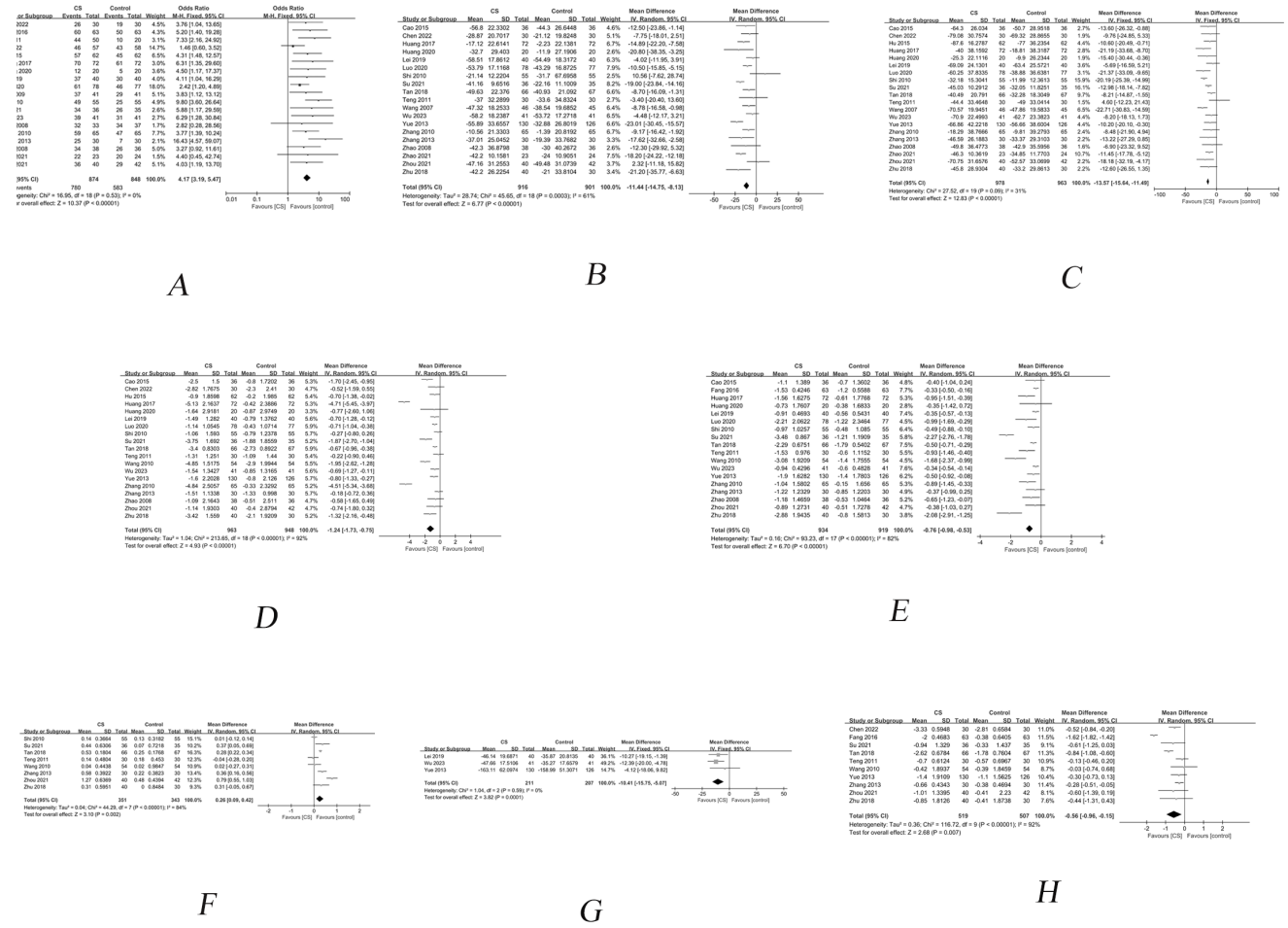
A total of 19 studies stated the clinical overall response rate, involving 1,722 patients (874 in the treatment group and 848 in the control group). No heterogeneity existed among studies (I^2 = 0%, P = 0.53), allowing analysis employing a fixed-effect model. Results demonstrated the treatment group had a substantially higher clinical response rate than the control group (OR = 4.17, 95% CI: 3.19–5.47, P < 0.00001) (Figure **3A**). Subgroup analyses were employed in accordance with patient age and disease duration (Figure **5A**, Figure **6A**). Pooled data indicated that CS demonstrated greater efficacy in patients aged ≥45 years and with disease duration <6 years. The intervention measures were further categorized into three groups: CS alone, CS combined with traditional Chinese medicine, and CS combined with Western medicine, as well as a comprehensive group involving CS combined with both traditional Chinese medicine and Western medicine. We employed a subgroup analysis of the intervention. (Figure **7A**), The pooled data indicated that the combination of CS, traditional Chinese medicine, and Western medicine manifested



A B

A: Risk of bias graph **B**: Risk of bias summary

Figure 2: Assessment of the risk of bias in the included studies.



A: Overall clinical efficacy **B**: AST **C**: ALT **D**: GGT **E**: TC **F**: TG **G**. HDL-C **H**. LDL-C

Figure 3: Forest plots show the meta-analysis results for the primary and secondary outcomes.

the highest efficacy in improving the overall clinical effectiveness rate (OR = 6.02, 95% CI: 3.09 – 11.69, P < 0.00001). Visual funnel plots displayed mild publication bias (Figure **4A**), and Egger's test yielded an appreciable result (P = 0.008), suggesting potential publication bias.

3.3.2. Secondary Outcomes

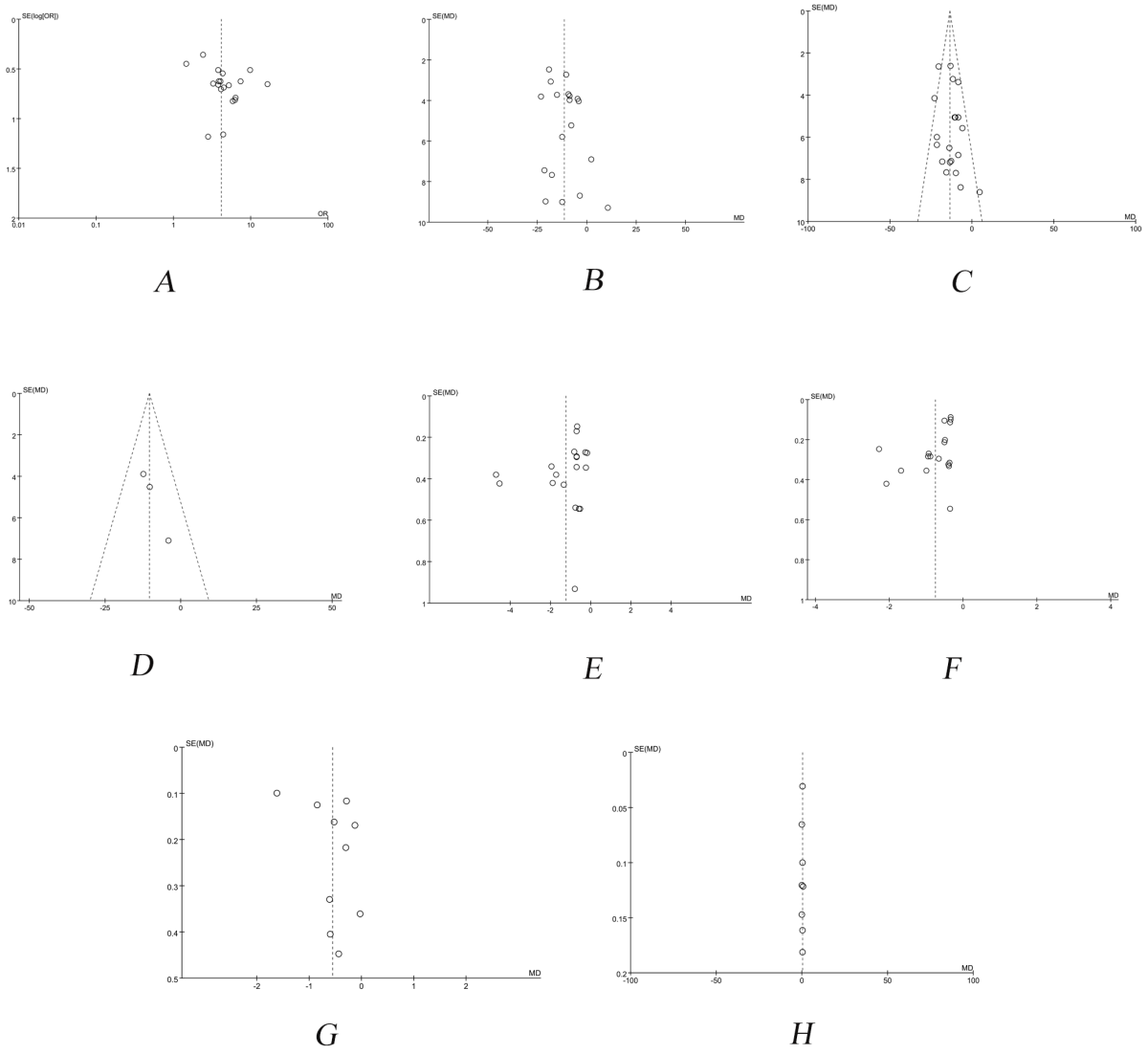
3.3.2.1. Liver function outcomes

3.3.2.1.1. Aspartate aminotransferase

A total of 19 studies (n=1817) reported AST levels. Significant heterogeneity existed among studies (I^2 = 61%, P < 0.00001); thus, a random-effects model was employed. The reduction in AST was dramatically greater in the treatment group than in the control group (MD = -11.44, 95% CI: -14.75 to -8.13, P < 0.00001) (Figure **3B**), indicating that CS has a marked effect in lowering AST. Subgroup analyses by patient age and disease duration were conducted (Figure **5B**, Figure **6B**). Pooled data showed CS produced more pronounced effects in patients aged ≥45 years and with disease duration <6 years. The intervention measures were further categorized into three groups: CS alone, CS combined with traditional Chinese medicine, and CS combined with Western medicine, as well as a comprehensive group involving CS combined with both traditional Chinese medicine and Western medicine. Subgroup analysis was performed (Figure **7B**). The pooled data indicated that the CS demonstrated the highest efficacy in lowering AST (MD = -15.24, 95% CI: -21.65 – -8.83, P < 0.00001). No evidence of publication bias was indicated by the visual examination of the funnel plots. (Figure **4B**), Egger's test (P = 0.575) did not indicate considerable publication bias.

3.3.2.1.2. Alanine Aminotransferase

A total of 20 studies (n=1941) reported ALT levels. No heterogeneity existed among studies (I^2 = 31%, P < 0.00001), and a fixed-effect model was utilized. The treatment group manifested a sharply greater reduction in ALT (MD = -13.57, 95% CI: -15.64 to -11.49, P = 0.09) (Figure **3C**), indicating that CS markedly lowers ALT levels. Subgroup analyses by patient age and disease duration were conducted (Figure **5C**, Figure **6C**). Pooled data showed CS produced greater effects in patients aged ≥45 years and with disease duration <6 years. The intervention measures were further categorized into three groups: CS alone, CS combined with traditional Chinese medicine, and CS combined



A: Overall clinical efficacy **B**: AST **C**: ALT **D**: GGT **E**: TC **F**: TG **G**. HDL-C **H**. LDL-C

Figure 4: Funnel plots were used to assess the potential for publication bias across the studied outcomes.

with Western medicine, as well as a comprehensive group involving CS combined with both traditional Chinese medicine and Western medicine. Subgroup analysis was performed (Figure **7C**). The pooled data indicated that the CS demonstrated the highest efficacy in lowering ALT (MD = -13.54, 95% CI: -18.72 – -8.73, P < 0.00001). The funnel plot showed no apparent publication bias upon visual inspection. (Figure **4C**), Egger's test (P = 0.23) indicated no significant publication bias.

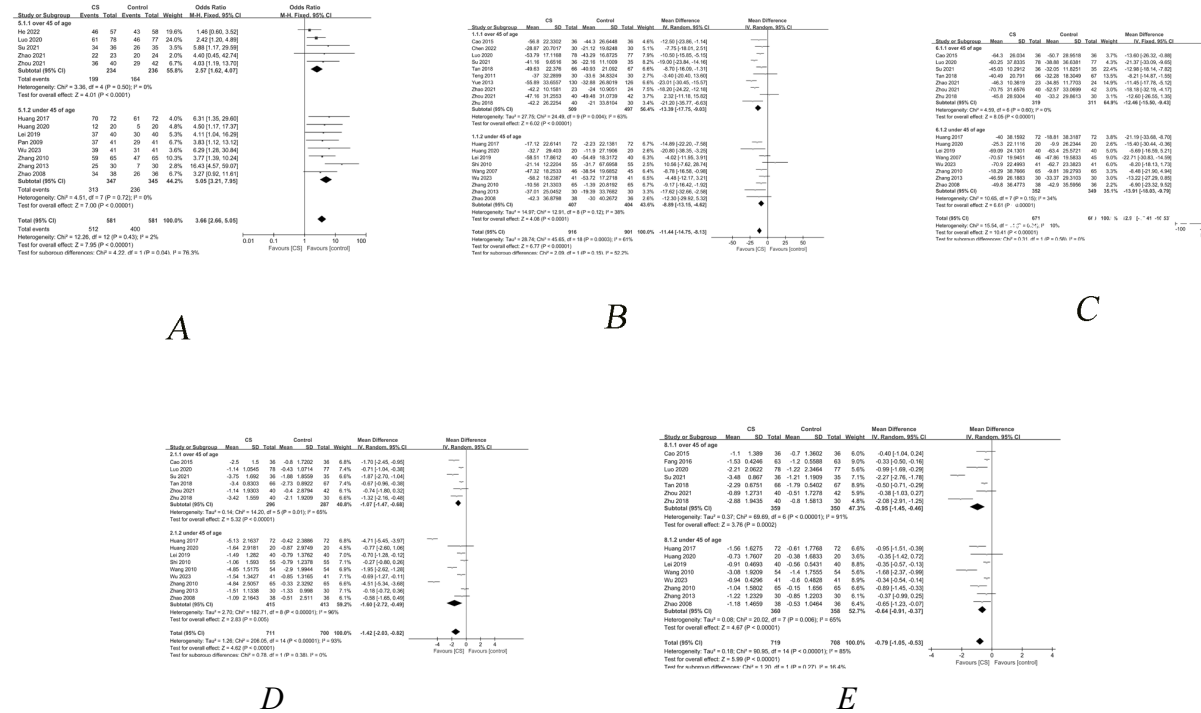
3.3.2.1.3. GGT

A total of 10 studies (n=418) were selected in the analysis. No heterogeneity existed between studies (I^2 = 0%, P = 0.59). The fixed-effect model demonstrated a more pronounced decline in GGT levels in the treatment group (MD = -10.41, 95% CI: -15.75 to -5.07, P =0.0001) (Figure **3G**). Based on a visual inspection of the funnel plot, publication bias appeared unlikely. (Figure **4D**), Egger's test (P = 0.145) displayed no signs of publication bias.

3.3.2.2. Serum lipids

3.3.2.2.1. Total cholesterol

A total of 19 studies (n=1911) reported TC levels. High heterogeneity (I^2 = 92%) necessitated a random-effects model. Treatment groups demonstrated greater TC reduction (MD = -1.24, 95% CI: -1.73 to -0.75, P < 0.00001) (Figure **3D**). Subgroup analyses by age and disease duration both showed high heterogeneity (I^2 > 65% in both). We conducted subgroup analyses by patient age and disease duration (Figure **5D**, Figure **6D**). Pooled data indicated CS had a more pronounced effect in patients aged ≥45 years and with disease duration <6 years. The intervention measures were further categorized into three groups: CS alone, CS combined with traditional Chinese medicine, and CS combined with Western medicine, as well as a comprehensive group involving CS combined with both traditional Chinese medicine and Western medicine. Subgroup analysis was performed (Figure **7D**). The pooled data indicated that the CS, together with traditional Chinese medicine, demonstrated the



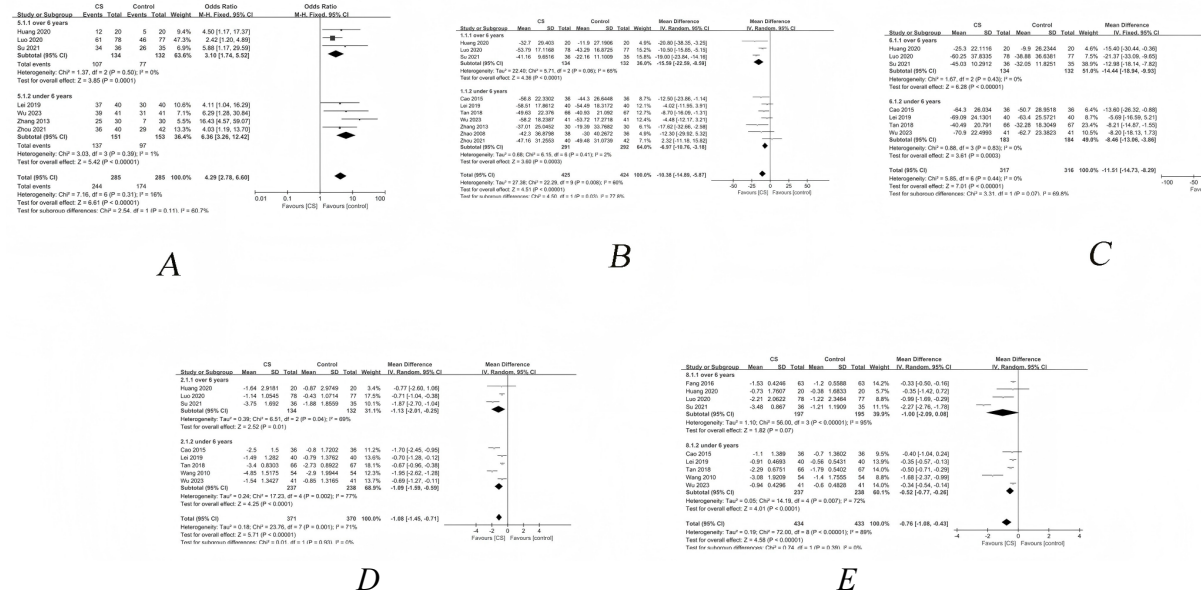
A: Overall clinical efficacy **B**: AST **C**: ALT **D**: TC **E**: TG

Figure 5: Subgroup analyses were performed to evaluate the influence of patient age on the treatment outcomes.

highest efficacy in lowering TC (MD = -1.54, 95% CI: -2.79 – -0.30, P < 0.00001). However, the differences among the groups were minimal. Visual assessment of the funnel plot indicated mild publication bias (Figure **4E**), while Egger's test showed no statistical significance (P = 0.816), suggesting no publication bias.

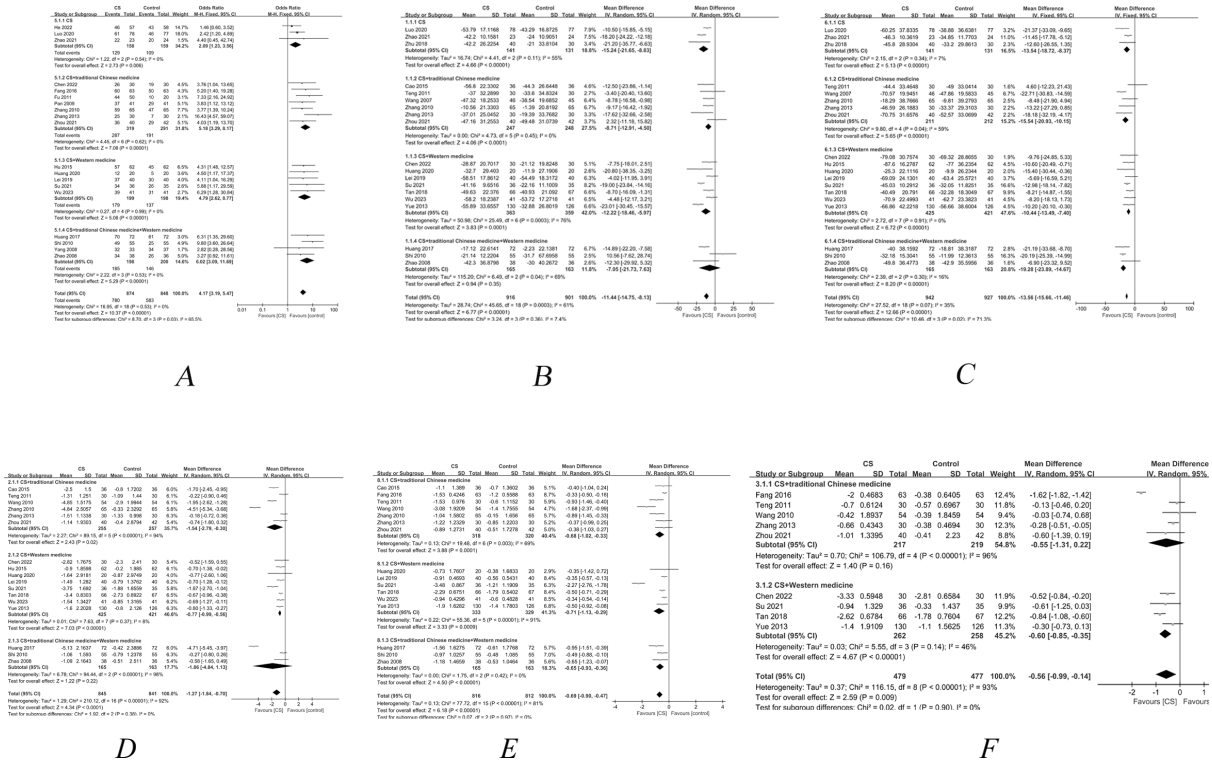
3.3.2.2.2. Triglycerides

A total of 18 studies (n=1853) were included in the analysis. High heterogeneity was present (I^2 = 82%). The random-effects model showed a greater fall in TG in the treatment group (MD = -0.76, 95% CI: -0.98 to -0.53, P < 0.00001) (Figure **3E**). Subgroup analyses by patient age and disease duration were conducted (Figure **5E**, Figure **6E**). Pooled data indicated CS demonstrated greater efficacy in patients aged ≥45 years with disease duration <6 years. The intervention measures were further categorized into three groups: CS alone, CS combined with traditional Chinese medicine, and CS combined with Western medicine, as well as a comprehensive group involving CS combined



A: Overall clinical efficacy **B**: AST **C**: ALT **D**: TC **E**: TG

Figure 6: Subgroup analyses were conducted to explore the impact of treatment course on the results.



A: Overall clinical efficacy **B**: AST **C**: ALT **D**: TC **E**: TG **F**: LDL-C

Figure 7: Subgroup analyses were carried out to examine the effects of different medicine.

with both traditional Chinese medicine and Western medicine. Subgroup analysis was performed (Figure **7E**). The pooled data indicated that the differences among the groups were minimal. Visual assessment of the funnel plot indicated mild publication bias (Figure **4F**), while Egger's test showed no statistical significance (P = 0.072), indicating no publication bias.

3.3.2.2.3. High-density lipoprotein cholesterol

Eight studies (n=694) showed heterogeneity (I^2 = 84%). The random-effects model indicated a greater increase in HDL-C levels in the treatment group (MD = 0.26, 95% CI: 0.09–0.42, P < 0.00001) (Figure **3F**). Subgroup analysis by patient age and disease duration (Table **2**) showed that CS had a more pronounced effect in patients aged ≥45 years with disease duration <6 years. Visual inspection of the funnel plot revealed mild publication bias (Figure **4G**), but Egger's test was non-significant (P = 0.685), indicating no publication bias.

3.3.2.2.4. Low-density lipoprotein cholesterol

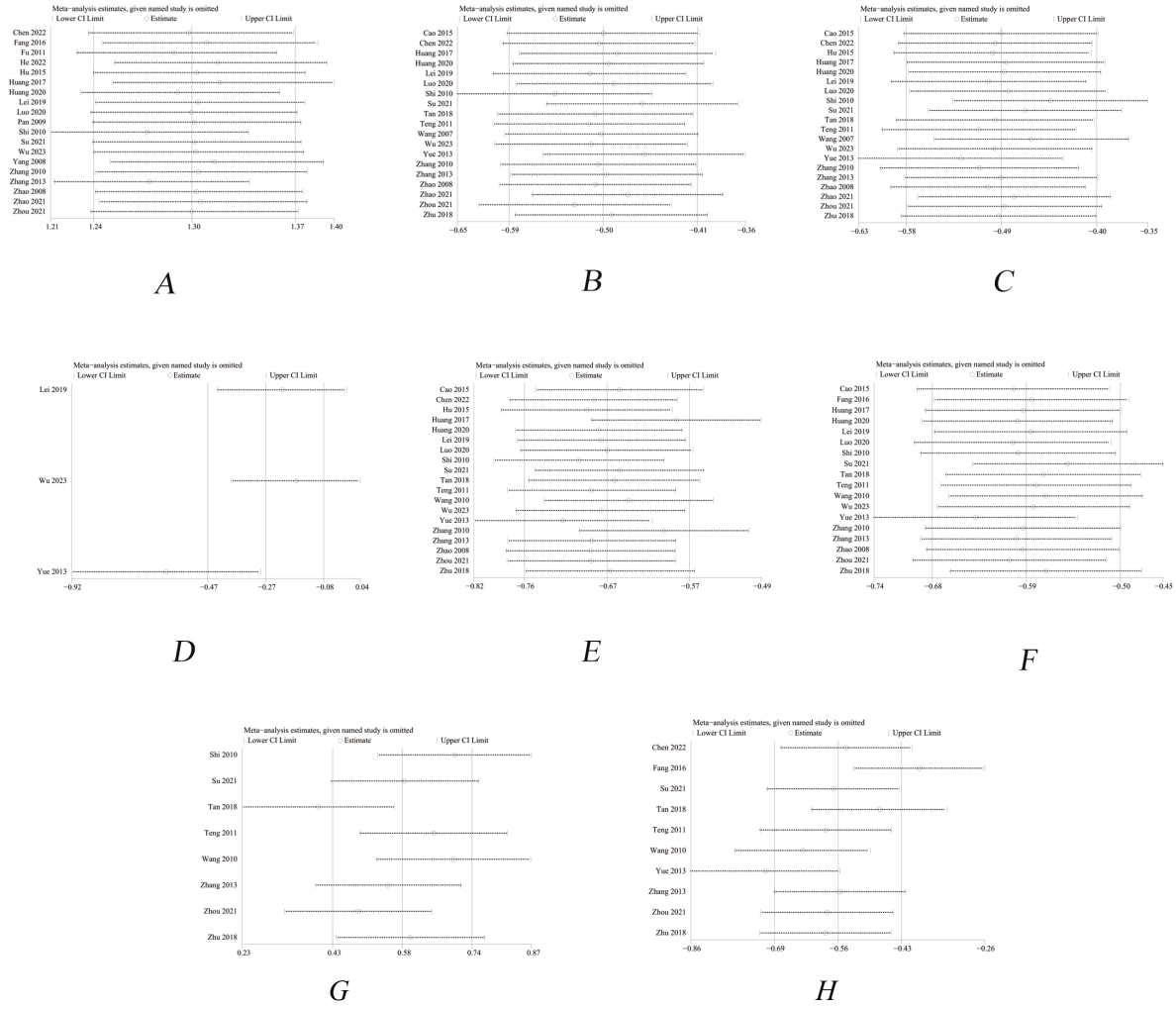
Ten studies (n=1026) illustrated high heterogeneity (I^2 = 92%). The random-effects model indicated a more pronounced reduction in LDL-C in the treatment group (MD = -0.56, 95% CI: -0.96 to -0.15, P < 0.00001). (Figure **3H**). Subgroup analyses by patient age and disease duration (Table **2**) revealed that CS demonstrated greater efficacy in patients aged ≥45 years and with disease duration <6 years. The intervention measures were further categorized into three groups: CS alone, CS combined with traditional Chinese medicine, and CS combined with Western medicine, as well as a comprehensive group involving CS combined with both traditional Chinese medicine and Western medicine. Subgroup analysis was performed (Figure **7F**). The pooled data indicated that the differences among the groups were minimal. No evidence of publication bias was identified by visual inspection of the funnel plot (Figure **4H**), while Egger's test documented no statistical significance (P = 0.284), suggesting no publication bias.

3.3.2.4. Adverse Reactions

Two studies reported adverse reactions. In one study, two cases of upper abdominal discomfort occurred in the treatment group, while three cases of dizziness and one case of nausea were reported in the control group. In the other study, one case of dizziness and two cases of skin itching occurred in the treatment group, and two cases of skin itching and two cases of nausea were reported in the control group. No serious adverse events were described.

3.3.2.5. Sensitivity Analysis

The stability of the primary outcome measures for the fixed-effect model was assessed by sequentially excluding individual studies. Results showed that after sequentially excluding any single study, the combined effect sizes for the clinical total response rate (Figure



A: Overall clinical efficacy **B**: AST **C**: ALT **D**: GGT **E**: TC **F**: TG **G**: HDL-C **H**: LDL-C

Figure 8: Sensitivity analysis was performed by sequentially omitting individual studies to test the robustness of the meta-analysis results.

8A), AST (Figure **8B**), ALT (Figure **8C**), GGT (Figure **8D**), TC (Figure **8E**), TG (Figure **8F**), HLD-C (Figure **8G**), LDL-C (Figure **8H**) remained stable, indicating robust results.

3.3.2.6. GRADE Grading

The GRADE methodology was utilized to assess the certainty of the evidence. Ultimately, the clinical overall response rate, ALT, GGT, HDL, and LDL were graded as high quality, while AST, TC, and TG were scored as moderate quality (Table **2**).

4. DISCUSSION

This study employed a systematic review and meta-analysis of current randomized controlled trials evaluating CS therapy for non-alcoholic fatty liver disease (NAFLD). Findings demonstrated that adding CS to standard care, with or without conventional medicine, significantly improves the overall clinical response rate in NAFLD patients. It also enhanced liver function (ALT, AST, GGT), lipid metabolism (TC, TG, LDL-C, HDL-C), and liver imaging findings, while demonstrating good safety.

NAFLD is a metabolic liver disease closely associated with obesity, metabolic syndrome, and type 2 diabetes, for which no specific therapeutic agents currently exist [36]. Although lifestyle intervention is recognized as the first-line strategy, poor long-term adherence limits clinical benefits [37]. While certain hypoglycemic, lipid-regulating, or cholagogue drugs have been explored for NAFLD treatment, their potential hepatotoxicity risks or requirement for long-term administration hinder widespread adoption. Against this backdrop, CS, as a traditional Chinese herbal formula, demonstrates potential as a complementary or alternative therapy due to its multi-component, multi-target holistic regulatory properties and relatively favorable safety profile [38].

The present study demonstrated that CS treatment for NAFLD yielded multifaceted improvements. Its reduction in liver enzymes (ALT, AST, GGT) suggested potential alleviation of hepatocyte injury, while its lipid-regulating effects (Decreasing TC, TG, LDL-C, and raising HDL-C) contributed to improving lipid metabolism disorders. Subgroup analysis further

Table 2: The Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) Ratings for the Quality of Evidence of each Outcome are Presented in this Table

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	19	OR	4.11	3.13, 5.42	0%; P= 0.53	No serious risk	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Would not reduce effect	No	No	High
Change in AST	19	MD	-11.44	-14.75,-8.13	61%;P= 0.0003	No serious risk	Serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Would not reduce effect	No	No	Moderate
Change in ALT	20	MD	-13.57	-15.64, -11.49	31%;P= 0.09	No serious risk	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Would not reduce effect	No	No	High
Change in TC	19	MD	-1.24	-1.73,-0.75	92%; P<0.00001	No serious risk	Serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Would not reduce effect	No	No	Moderate
Change in TG	18	MD	-0.47	-0.97, -0.52	82%; P<0.00001	No serious risk	Serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Would not reduce effect	No	No	Moderate
Change in GGT	10	MD	-10.41	-15.75, -5.07	0%; P = 0.59	No serious risk	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Would not reduce effect	No	No	High
Chang in HDL	8	MD	0.26	0.09,0.42	84%; P= 0.002	No serious risk	Serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Would not reduce effect	No	No	High
Change in LDL	10	MD	-0.56	-0.96,-0.15	92%;P = 0.007	No serious risk	Serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Would not reduce effect	No	No	High

suggested that CS combined with other Chinese herbal medicines yielded superior efficacy compared to monotherapy, particularly in elderly patients and those with shorter disease duration. This may be attributed to synergistic effects of compound formulations, higher reversibility in early-stage disease, and more regular lifestyles and better dietary discipline among elderly patients.

From a traditional Chinese medicine perspective, the pathogenesis of NAFLD centers on impaired liver qi regulation, spleen deficiency with dampness obstruction, and mutual entanglement of phlegm and blood stasis [39]. Within the CS formula, *Bupleurum* and *Paeonia lactiflora* regulate and soften the liver, *Citrus aurantium* and *Citrus reticulata* regulate qi and strengthen the spleen, while *Ligusticum chuanxiong* and *Cyperus rotundus* promote blood circulation and qi flow. Collectively, the formula achieves the effects of regulating liver qi, resolving depression, regulating qi, strengthening the spleen, transforming phlegm, and removing stasis [40], precisely targeting the core pathogenesis of NAFLD. From a modern pharmacological perspective, the therapeutic effects of CS may primarily be mediated through the following pathways: (1) regulating the expression of nuclear receptors (*e.g.*, FXR, PPARα) and transcription factors (*e.g.*, SREBP-1c) to inhibit hepatic lipid synthesis and promote fatty acid β-oxidation [41-42]; (2) improving insulin signaling pathway sensitivity to reduce hepatic insulin resistance [43]; (3) Suppressing inflammatory cytokine release and oxidative stress responses to protect hepatocytes from secondary injury [44]. Multiple studies [45-46] indicate that active components in CS (*e.g.*, *baicalin, quercetin, kaempferol*) synergistically modulate these pathways, thereby intervening in NAFLD progression at the molecular level. Additionally, the findings of this study regarding the multi-target regulatory mechanism of CS align closely with current cutting-edge insights into other active components of traditional Chinese medicine for treating NAFLD. For instance, berberine—an isoquinoline alkaloid extracted from herbs such as Coptis chinensis and Phellodendron amurense—has been extensively supported by high-level evidence for its efficacy and mechanisms in treating NAFLD. A recent randomized clinical trial further confirmed that berberine supplementation significantly reduces hepatic fat content and improves liver enzyme profiles in NAFLD patients [47]. Recent studies indicate that berberine can dual-regulate hepatic lipid synthesis and catabolism by activating the AMPK-SIRT1-PGC-1α signaling axis [48]. On one hand, it inhibits SREBP-1c-mediated de novo lipogenesis (DNL); on the other, it enhances PPARα-mediated fatty acid β-oxidation (FAO), thereby fundamentally reshaping hepatic lipid metabolic homeostasis [49]. Importantly, emerging evidence suggests that berberine's modulation of gut microbiota and its metabolites, such as bile acids, also plays a crucial role in its lipid-lowering effects by activating systemic signaling pathways like FXR [50]. Furthermore, a 2023 study

provided structural insights into berberine's direct interaction with AMPK, solidifying its role as a key metabolic regulator [51]. This mode of action—coordinating multiple downstream pathways by regulating core metabolic hubs such as AMPK—complements the synergistic mechanism of CS, which exerts effects through multiple targets including FXR and PPARα. Together, these findings underscore the unique therapeutic advantages and scientific rationale of traditional Chinese medicine and its active components in treating complex metabolic disorders through a “multi-component, multi-target” approach.

Several limitations of this study should be acknowledged. First, the selected studies generally had small sample sizes, and most did not employ blinding or allocation concealment, potentially affecting the reliability of results. Second, variations in CS formulations, dosages, and treatment durations may have contributed to clinical heterogeneity. Although subgroup and sensitivity analyses explored sources of heterogeneity, high heterogeneity persisted for some outcome measures. Furthermore, funnel plots and Egger's test manifested potential publication bias in the overall response rate, necessitating cautious interpretation of positive findings.

5. CONCLUSION

This study demonstrated that CS effectively improved multiple key clinical indicators in patients with NAFLD. The treatment substantially declined liver enzyme levels (ALT, AST, GGT), regulated dyslipidemia (descending TC, TG, LDL-C, and increasing HDL-C), and partially improved hepatic imaging findings. Furthermore, it exhibits good safety with no reports of serious adverse reactions. This study supports evidence and a foundation for the clinical promotion of CS treatment for NAFLD. However, current evidence primarily stems from studies with limited methodological quality and small sample sizes, with some results exhibiting heterogeneity and potential publication bias. Thus, subsequent research should employ more rigorous, multicenter, double-blind randomized controlled designs with larger samples to verify these results, with particular focus on its long-term efficacy, mechanisms of action, and clinical application value.

Appendix

Table A1: The Complete Search Strategy used for the PubMed, Web of Science, CBM, VIP, CNKI, and Wanfang Data is Detailed in this Table

Table A1: search strategy
PubMed
((((((((((((((Non-alcoholic Fatty Liver Disease) OR (Non alcoholic Fatty Liver Disease)) OR (NAFLD)) OR (MAFLD)) OR (MASLD)) OR (Nonalcoholic Fatty Liver Disease)) OR (Fatty Liver, Nonalcoholic)) OR (Fatty Livers, Nonalcoholic)) OR (Liver, Nonalcoholic Fatty)) OR (Livers, Nonalcoholic Fatty)) OR (Nonalcoholic Fatty Liver)) OR (Nonalcoholic Fatty Livers)) OR (Nonalcoholic Steatohepatitis)) OR (Nonalcoholic Steatohepatitides)) OR (Steatohepatitides, Nonalcoholic)) OR (Steatohepatitis, Nonalcoholic)) AND (Chaihushugansan)
CBM
("柴胡疏肝散"［不加权：扩展］OR 柴胡疏肝散）AND ("非酒精性脂肪性肝病"［不加权：扩展］OR 非酒精性脂肪性肝病 OR 非酒精性肝炎 OR ("脂肪肝"[不加权:扩展]OR 脂肪肝）OR NAFLD））
Web of Science
(((((Inflammatory Bowel Diseases) OR ((Inflammatory Bowel Disease) OR (Bowel Diseases, Inflammatory))) OR ((Crohn Disease) OR ((((((((((Crohn's Enteritis) OR (Regional Enteritis)) OR (Crohn's Disease)) OR (Crohns Disease)) OR (Inflammatory Bowel Disease 1)) OR (Granulomatous Enteritis)) OR (Ileocolitis)) OR (Granulomatous Colitis)) OR (Terminal Ileitis)) OR (Regional Ileitides)) OR (Regional Ileitis)))) OR ((Colitis, Ulcerative) OR (((Idiopathic Proctocolitis) OR (Ulcerative Colitis)) OR (Colitis Gravis)))) AND (risk OR incidence)) AND (systematic review OR meta-analysis) (Topic)
CNKI
柴胡疏肝散 and 非酒精性脂肪肝病+脂肪肝+非酒精性肝炎+NAFLD
WANFANG
柴胡疏肝散 与 非酒精性脂肪肝病 OR 脂肪肝 OR 非酒精性肝炎 OR NAFLD
VIP
柴胡疏肝散 与 非酒精性脂肪肝病 OR 脂肪肝 OR 非酒精性肝炎 OR NAFLD

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