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Chinese herbal medicine therapy for hyperlipidemic acute pancreatitis: a systematic review and meta-analysis of randomized controlled trials

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Abstract. – OBJECTIVE: Chinese herbal medicine (CHM) has been widely used in the treatment of hyperlipidemic acute pancreatitis (HLAP), but the credibility of the evidence for this practice is unclear. We systematically reviewed the efficacy and safety of CHM therapy for HLAP.

MATERIALS AND METHODS: In this systematic review and meta-analysis, we searched the Cochrane Central Register of Controlled Trials, Ovid MEDLINE, PubMed, EMBASE, CBM, CNKI, VIP, and Wanfang databases from inception to October 16, 2022, for randomized controlled trials comparing the combination of CHM and Western medicine therapy vs. Western medicine therapy alone in HLAP adults. This study is registered with PROSPERO (No. CRD 42022371052).

RESULTS: A total of 50 eligible studies involving 3,635 patients were assessed in this meta-analysis. Compared with Western medicine therapy, the combination of CHM increased the total effective rate by 19% in HLAP patients [relative risk (RR): 1.19, 95% CI: (1.16, 1.23)]. There were significant differences between the two groups in improving clinical symptoms, promoting serum amylase and triglyceride recovery, reducing mortality [RR: 0.28, 95% CI: (0.14, 0.56)] and complication rates [RR:0.40, 95% CI: (0.31, 0.52)], and shortening the length of hospital stay [MD: -3.96, 95% CI: (-4.76, -3.16)]. Adverse reactions were similar between groups. Findings were robust in the sensitivity analysis.

CONCLUSIONS: The combined CHM treatment was more effective than Western medicine alone in HLAP patients. However, due to the methodological shortcoming of the eligible studies, caution is needed when interpreting these findings.

Key Words:
Hyperlipidemic acute pancreatitis, Chinese herbal medicine, Meta-analysis.

Introduction

Acute pancreatitis (AP) is a prevalent abdominal disease in clinical emergencies, with an incidence rate of 34 cases per 100,000 person-years annually[1]. It has been reported that hyperlipidemia is the third most common risk factor for AP, following gallstones and alcohol misuse[2]. In China, however, hyperlipidemia has surpassed alcohol misuse to become the second leading cause of pancreatitis since 2010, accounting for 18.2% of cases[3,4].

Hyperlipidemic acute pancreatitis (HLAP) is characterized by more severe clinical manifestations than other AP causes. Its occurrence is closely associated with elevated serum levels of triacylglycerol (TG). Currently, the initial treatment for HLAP is the same as for other causes of AP, which mainly involves close monitoring of vital signs, pain relief, maintenance of fluid balance, nutrition management, and treatments based on etiology and aimed at early complications. In addition, the treatment of HLAP is suggested to cover dietary modifications, lipid-lowering medication, and other auxiliary lipid-lowering means to control blood lipids[5]. Despite significant advances in treating HLAP, few improvements in mortality and complication rates have been achieved. Therefore, there is an urgent need for alternative and complementary therapies to address this issue.

In recent years, Chinese herbal medicine (CHM) treatment has received significant attention and has been widely used for improved efficacy in the treatment of HLAP. Multiple randomized clinical trials[6-11] have demonstrated that the combination of CHM and Western medicine treatment can effectively alleviate patients' clinical symptoms, promote the recovery of amylase

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and triglycerides, and thus reduce mortality and complications. However, the data have not yet been synthesized for analysis. Hence, the purpose of this study was to evaluate the efficacy of the combined CHM therapy in patients with HLAP through a systematic review and meta-analysis.

Materials and Methods

A systematic review was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[12,13]. The protocol of this study has been registered on PROSPERO (Registration No.: CRD42022371052)[14].

Literature Search

A systematic search was performed in the following eight databases from inception to October 16, 2022: PubMed, the Cochrane Central Register of Controlled Trials, Ovid MEDLINE, EMBASE, CNKI, CBM, Wanfang, and VIP database. The retrieval was conducted using a combination of Mesh terms and free words. The primary search terms were listed as follows: "hyperlipidemic acute pancreatitis", "hyperlipidemias", "hypertriglyceridemia", "pancreatitis", "traditional Chinese medicine", "Chinese herbal medicine", "integrative medicine", and "alternative medicine". References to relevant reviews and original studies were screened to find more potential eligible studies. In addition, attempts were made to contact the corresponding authors to obtain the missing or unpublished data. There were no restrictions on the publication date, status, or language.

Selection Criteria

Participants

Adults with HLAP above 18 years old (diagnosed in line with any standardized diagnostic criterion[15-19]) were included as the participants.

The specific diagnostic criteria were listed as follows:

(a) The patients shall be positively diagnosed with AP and meet two of the following three criteria: (1) sudden, acute, persistent, and severe upper abdominal pain; (2) levels of serum amylase and/or lipase at least three times higher than the normal standard; and (3) imaging characteristics reflecting AP diagnostic indices (abdominal ultrasound, contrast-enhanced CT, or MRI).

(b) A serum triglyceride (TG) level higher than 11.3 mmol/L, or chylomicronemia with a TG level ranging between 5.6 and 11.3 mmol/L.

Intervention

The intervention applied in the experimental group was CHM in combination with conventional Western medicine (the combined CHM group). The control group was administered conventional Western medicine.

Outcomes

The total effective rate was considered the primary outcome[20]. The duration of symptom resolution (abdominal distension relief time, abdominal pain relief time, and recovery time for anal defecation/ exhaust), recovery time for plasma amylase and triglyceride, mortality, the complication rate, length of hospital stay, and adverse reactions were treated as the secondary outcomes.

Study Style

Prospective randomized controlled trials (RCT).

Exclusion Criteria

The following were the exclusion criteria: (1) reviews, animal studies, case studies, empirical presentations, cohort studies, and retrospective studies; (2) studies lack of primary and secondary outcomes or insufficient data; and (3) incomplete articles and duplicate publications.

Data Extraction and Quality Assessment

Two reviewers (W, -X Guo and Y Song) extracted the data and assessed the quality of the literature using a pre-defined form. Data on authors, publication date, study types, patient characteristics (age, gender, and sample size), intervention methods for experimental and control groups, outcomes, treatment durations, and presence of shedding or follow-up were all extracted. Disputes were resolved by a third-party reviewer (X, -G Lu).

The Cochrane Risk of Bias Tool was used to evaluate the quality of RCTs incorporated into this meta-analysis[21]. Seven aspects were judged for measurement of potential bias in RCTs, with each aspect rated as a low (L), unclear (U), or high (H) risk of bias.

Statistical Analysis

The meta-analysis was executed using the Review Manager (version 5.2, Review Manager Web, The Cochrane Collaboration, Copenhagen, Denmark) software and Stata (version 15.1, StataCorp LLC, College Station, TX, USA). The results were presented as relative risk (RR) with a 95% confidence interval (CI) for dichotomous data. The pooled results were considered statistically significant when $p<0.05$ and the 95% CI did not contain

the value 1 (RR). In terms of continuous data, the results were presented as mean difference (MD) with a 95% CI. The results were interpreted as statistically significant when $p<0.05$ and the 95% CI did not include 0 (MD). To estimate the heterogeneity between studies, we applied the χ^2 (threshold $p=0.10$) and quantified it through the I^2 statistic. The fixed-effects model was considered appropriate when the studies were identified with low statistical heterogeneity ($p>0.1$ and $I^2<50\%$). In contrast, the random-effects model was employed when the studies exhibited substantial statistical heterogeneity ($p<0.1$ and $I^2>50\%$). The robustness of the data was verified through sensitivity analysis. Publication bias was visualized as a funnel plot and quantified *via* the Egger test[22].

Results

Literature Search Results

Figure 1 presented the PRISMA flow diagram. The literature search yielded 1,047 literature citations, but only a total of 668 records were retained after the exclusion of duplicates. Another 533 articles were excluded after brief reading of their titles and abstracts. The full texts of the remaining 135 articles were downloaded and assessed for eligibility. At last, 50 eligible RCTs were acquired for this meta-analysis[6-11,23-66].

Characteristics and Methodological Quality of Eligible Studies

Table I demonstrated the primary characteristics of the 50 studies for analysis. The studies, involving 3,635 participants, were published from 2011 to 2022. Except for only one article authored in English[33], the remaining 49 were all published i n Chinese. The sample sizes ranged from 35 to 177, and the course of treatment lasted for three to 28 days. The interventions explored in all the studies were CHM in combination with conventional Western medicine *vs.* conventional Western medicine. The CHMs explored in these studies mainly included Da Chaihu Decoction, Da Chengqi Decoction, Danshen extracts, Qingyi Decoction, Chaishao Chengqi Decoction, etc.

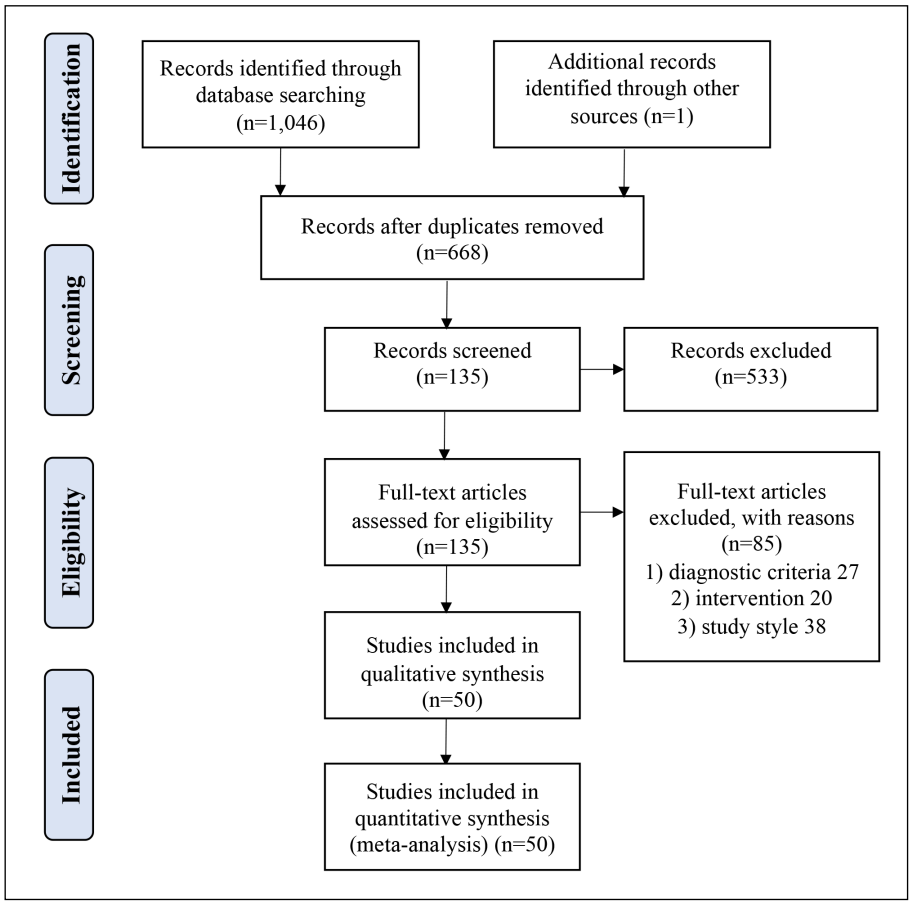

Figure 1. Study flow diagram.

Table I. The characteristics of the 50 eligible studies.

Study	Age (years)	Sex (M/F)	Sample (T/C)	Intervention		Outcomes	Duration (Days)
				T	C		
Chen 2016[6]	T 34.68±3.92 C 35.07± 4.12	T 29/19 C 16/9	73 (48/25)	Compound Danshen injection, 20 ml bid, iv drip+WM	WM	①⑤⑥	10d
Chen 2020[23]	T 43.73±10.99 C 43.43±11.35	T 17/13 C 16/14	60 (30/30)	Chaiqing Jiangzhi Decoction, 300 ml, *via* nasogastric tube +WM	WM	①②⑦	7d
Feng 2022[24]	T 34.4±5.2 C 38.7±3.9	T 19/21 C 20/20	80 (40/40)	Da Chaihu Decoction and Shengjiang powder+WM	WM	①⑦⑧	7d
Gao 2017[25]	52.6±4.8	47/33	80 (40/40)	Salviae Miltiorrhizae and Ligustrazine Hydrochloride injection, 10 ml, iv drip+SST 50 μg.h/1, continuous infusion+WM	WM+SST 250 μg.h/1, continuous infusion	②	14d
Guo 2018[26]	T 48.3±4.8 C 48.6 ±5.3	T 53/36 C 52/36	177 (89/88)	Chaishao Chengqi Decoction, 200 ml, *via* nasogastric tube +WM	WM+Low-Molecular-Weight Heparins Calcium injection	①②③⑧	7d
Guo 2022[27]	T 48.72±8.61 C 46.12±9.96	T 18/12 C 20/10	60 (30/30)	Qingyi Jiangzhi Decoction, 150 mL, bid, *via* nasogastric tube+WM	WM	①②	7d
He 2016[7]	T 36.6±13.2 C 35.3±14.2	T 31/9 C 34/6	80 (40/40)	Da Chaihu Decoction, 250 mL, bid, *via* nasogastric tube+ Dachenqi Decoction, enema+WM	WM	①②③⑥	7d
Huang 2016[8]	47±3	50/34	84 (42/42)	Qingyi Decoction, 200 ml, bid, *via* nasogastric tube; 100 ml, every 4 hours, enema+WM	WM	①⑤⑥	7d
Jiang 2016[9]	T 35.77±4.63 C 36.19±1.52	T 19/12 C 17/13	61 (31/30)	Shenxiong glucose injection, 200 ml, QD, iv drip+hemofiltration+WM	WM+hemofiltration	①②⑤⑥⑦	7-14d
Lei 2018[28]	T 56±5 C 58±5	T 9/11 C 12/8	40 (20/20)	Da Chaihu Decoction, 100 mL, bid, oral+WM	WM	①	5d
Li 2012[66]	T 48±16.25 C 46±11.5	T 16/12 C 17/11	56 (28/28)	Qingyi Decoction, 200 ml, bid, *via* nasogastric tube+ Dachenqi Decoction, 300 ml, enema+Mirabilite, external application+WM	WM	③⑦	14-28d

Table continued

Table I *(Continued)*. The characteristics of the 50 eligible studies.

Study	Age (years)	Sex (M/F)	Sample (T/C)	Intervention		Outcomes	Duration (Days)
				T	C		
Li 2015[10]	47.8±9.5	42/28	70 (36/34)	Salviae Miltiorrhizae and Ligustrazine Hydrochloride injection, 10 ml, iv drip+Qingyi Decoction, 50 ml, qid+WM	WM	①⑤⑥	5d
Li 2019[29]	T 53.44 ± 1.20 C 54.40 ± 1.25	T 33/17 C 35/15	100 (50/50)	Da Chaihu Decoction, 100 mL, bid, *via* nasogastric tube+WM	WM	①②③	7d
Liu 2014[31]	T 58.9±11 C 60.2±13	NR	68 (38/30)	Da Chaihu Decoction, 100 mL, bid, *via* nasogastric tube+WM	WM	①②③	7d
Liu 2015[30]	T 58.9±9.5 C 54.6±10.75	T 26/14 C 29/11	80 (40/40)	Da Chaihu Decoction + Radix et Rhizoma Rhei, 30 g, external application+WM	WM	①②③	7d
Liu 2020[33]	T 39.3±3.6 C 40.8±4.4	T 12/8 C 13/7	40 (20/20)	Dachenqi Decoction, one dose a day, bid+WM	WM	①	NR
Liu 2021[32]	T 47.41±4.91 C 47.25±4.86	T 30/25 C 29/26	110 (55/55)	Dachenqi Decoction, 200 ml, bid, oral+WM	WM	①②⑧	7d
Liu and Zhao 2014[34]	T 41.2±8.6 C 42.6±9.7	T 24/22 C 26/20	92 (46/46)	Traditional Chinese Single herbal Decoction, 100 ml, bid, *via* nasogastric tube/oral+WM	WM	⑤⑥⑦	NR
Lu 2019[35]	T 55.78±8.27 C 55.56±8.21	T 9/8 C 10/8	35 (17/18)	Da Chaihu Decoction, 250 ml, bid, *via* nasogastric tube+Dachenqi Decoction, enema, QD+WM	WM	①②③⑥	7d
Qiu 2018[36]	T 41.72±9.20 C 39.61±10.30	T 20/11 C 17/14	62 (31/31)	Salviae Miltiorrhizae and Ligustrazine Hydrochloride injection+WM	WM+SST 250 μg.h/1, continuous infusion	①②③⑦⑧	7d
Qu 2021[37]	T 47.29±13.15 C 47.53±13.32	T 25/18 C 28/15	86 (43/43)	Chaihuang Qingyi Huoxue Decoction, 100 ml, tid, *via* nasogastric tube+WM	WM	②	7d
Ren 2017[38]	T 49.8±5.43 C 50.14±5.72	T 22/21 C 24/19	86 (43/43)	Danshen injection, 20 ml, QD/ bid, iv drip+insulin+WM	WM+insulin	①②	10d
Shi 2017[39]	T 44.23±9.14 C 46.79±8.21	T 21/15 C 26/10	72 (36/36)	Modified Shanzha da Chaihu Decoction, 50 ml, *via* nasogastric tube, qid+SST 250 μg.h/1, continuous infusion+WM	WM+SST 250 μg.h/1, continuous infusion	①②⑦	28d

Table continued

Table I *(Continued)*. The characteristics of the 50 eligible studies.

Study	Age (years)	Sex (M/F)	Sample (T/C)	Intervention		Outcomes	Duration (Days)
				T	C		
Sun 2019[40]	T 45.12±8.5 C 46.5±8.5	T 17/9 C 15/11	52 (26/26)	Da Chaihu Decoction, 75 ml, bid, *via* nasogastric tube+Mirabilite, bid, external application+Danshen injection, 20 ml, QD, iv drip+WM	WM	①②③④	7d
Tan 2022a[41]	T 55.32±5.72 C 55.73±5.42	T 32/25 C 30/27	114 (57/57)	compound Danshen injection 20 ml+250 ml normal saline, QD, iv drip+WM	WM	①②⑦	14d
Tan 2022b[42]	T 45.10±5.41 C 44.36±5.23	T 22/19 C 23/18	82 (41/41)	Wendan Decoction and Dachengqi Decoction, oral and enema+WM	WM	①②⑧	7d
Wang 2019[43]	T 43.7±5.8 C 42.6±5.8	T 33/22 C 34/21	110 (55/55)	Radix et Rhizoma Rhei, 200 ml, tid, *via* nasogastric tube+WM	WM	①②	7d
Wang 2022[44]	T 50±11 C 48±11	T 25/15 C 23/17	80 (40/40)	Radix et Rhizoma Rhei, 150 ml, enema+colonic dialysis +WM	WM+colonic dialysis	②⑦	7d
Wang and Feng 2019[45]	T 42.26±7.55 C 41.55±6.96	T 21/10 C 20/9	60 (31/29)	Chaishao Chengqi Decoction, 150 ml, bid, *via* nasogastric tube+WM	WM	②⑦	7d
Wu 2015a[46]	T 40.2±17.8 C 38.2±19.5	T 17/13 C 16/14	60 (30/30)	Da Chaihu Decoction, 100 ml, bid, *via* nasogastric tube+WM	WM	①②	7d
Wu 2015b[47]	T 44.3±12.6 C 43.5±13.1	T 32/8 C 30/8	78 (40/38)	Da Chaihu Decoction + compound rhubarb enema liquid, 300 ml, QD, enema+Mirabilite, external application+WM	WM	①②③⑦	5d
Wu 2020[11]	40.74± 4.65	T 44/17 C 48/16	125 (64/61)	Modified Sini powder, 100 ml, qid/tid, *via* nasogastric tube+WM	WM	①②⑤⑥	14d
Xie 2013[48]	T 48.8±12 C 48.6±11	T 18/14 C 19/13	64 (32/32)	Tongfu mixture, 200 ml, bid, enema+Mirabilite, external application+WM	WM	④⑤⑥⑦	NR
Xiong 2016[49]	41.2±9.0	48/15	63 (32/31)	Zhu She Yong Dan Shen Duofen Suan Yan 200 mg+250 ml 5%glucose injection, QD+WM	WM	①②⑦	NR

Table continued

Table I. ***(Continued).*** The characteristics of the 50 eligible studies.

Study	Age (years)	Sex (M/F)	Sample (T/C)	Intervention		Outcomes	Duration (Days)
				T	C		
Xu 2011[50]	48.1±14.5	32/22	54 (30/24)	Fufang Dachengqi Tang, 150-200 ml, Tid, *via* nasogastric tube+WM	WM	①②③⑦	3-5d
Xu 2018[51]	T 42.58±2.04 C 43.14±1.06	T 12/11 C 13/10	46 (23/23)	Chaishao Chengqi Decoction, 200 ml, bid, *via* nasogastric tube +100 ml, enema, QD+WM	WM	①②⑥⑦	7-14d
Yan 2015[52]	T 46.68±4.35 C 47.13±4.42	T 7/12 C 8/11	38 (19/19)	Traditional Chinese medicine apozem (based on symptoms): 1) Qingyi Xianxiong Decoction 2) Da Chengqi Decoction 3) Qingyi Decoction/Qingyi Chengqi Decoction 4) Xiangsha Liu Junzi Decoction 5) Shenling Baizhu San 6) Gexia Zhuyu Decoction 7) Bazhen Decoction, 200 ml, *via* nasogastric tube/oral, 2-4 times a day+WM	WM	①②③⑦	7d
Yan 2020[53]	T 40.6±15.3 C 41.2±15.4	T 22/8 C 24/6	60 (30/30)	Qingyi Tongfu Decoction, 200 ml, enema, bid+25 ml, *via* nasogastric tube, 4–8 times a day+WM	WM	①	7d
Yang 2013[57]	45.5±14.25	T 10/12 C 11/12	45 (22/23)	Da Chaihu Decoction, one dose a day, bid, *via* nasogastric tube/oral+Mirabilite, external application+Danshen injection, 20 ml, QD, iv drip+WM	WM	②③④⑦	7d
Yang 2017[58]	T 49.5±6.5 C 49.5±8.5	T 23/20 C 21/22	86 (43/43)	Qingyi Decoction, 200 ml, *via* nasogastric tube/oral, QD + alprostadil+WM	WM + alprostadil	①③	7d
Yang 2018[56]	38.2±8.0	38/22	60 (30/30)	Da Chaihu Decoction, enema/oral+Radix et Rhizoma Rhei and Mirabilite, external application+WM	WM	②⑦	NR

Table continued

Table I. ***(Continued).*** The characteristics of the 50 eligible studies.

Study	Age (years)	Sex (M/F)	Sample (T/C)	Intervention		Outcomes	Duration (Days)
				T	C		
Yang 2019[55]	T 37.35±4.33 C 38.01±4.42	T 31/26 C 33/24	114 (57/57)	Qingyi Decoction, 100 ml, *via* nasogastric tube, bid+WM	WM+SST 250 μg.h/1, continuous infusion	①②⑤⑥⑦	14d
Yang 2021[54]	T 45.68±3.59 C 47.17±3.25	T 18/15 C 15/17	65 (33/32)	Qingjie Huagong Decoction, 200 ml, bid, oral+WM	WM	①⑥	7d
Yu 2015[59]	41.98±6.59	34/30	64 (32/32)	Danshen injection, 20 ml, iv drip, QD+alprostadil + WM	WM+alprostadil	②⑤⑥⑦	10-14d
Yuan 2016[60]	T37.19±14.59 C 38.11±14.89	T 18/15 C 18/14	65 (33/32)	Shenxiong glucose injection, 100 ml, iv drip, QD + hemofiltration + WM	WM+hemofiltration	①⑤	7d
Zhang 2014[62]	T 34.3±15.1 C 37.2±16.3	T 29/7 C 32/4	72 (36/36)	Da Chaihu Decoction, 200 ml, *via* nasogastric tube, bid+Dachengqi Decoction, enema, QD+WM	WM	①②③⑥⑧	7d
Zhang 2022[61]	T 65.1±3.74 C 64.6±3.92	T 15/15 C 16/14	60 (30/30)	Qingyi Decoction, 150 ml, *via* nasogastric tube, bid+WM	WM	①	7d
Zhao 2020[63]	T 39.04±10.58 C 39.87±9.67	T 18/5 C 20/3	46 (23/23)	Tongfu Huoxue granules, 50 ml, *via* nasogastric tube, bid+WM	WM	①②	7d
Zhou 2016[64]	T 52.8±8.05 C 52.5±8.10	T 14/16 C 17/13	60 (30/30)	Danshen injection, 20 ml+5% glucose injection, 250-500 ml, QD, iv drip+WM	WM	②⑦	7d
Zhou 2019[65]	T 39.8±10.1 C 40.2±9.8	T 21/9 C 23/7	60 (30/30)	Da Chaihu Decoction and Erchen Decoction, 200 ml, oral, bid+WM	WM	①②⑦	14d

T: the experimental group; C: the control group; M: male; F: female; NR: not reported; WM: Western medicine treatment; SST: somatostatin; ① total effective rate; ② duration of symptom resolution; ③ recovery time for plasma amylase; ④ recovery time for plasma triglyceride; ⑤ mortality; ⑥ the complication rate; ⑦ length of hospital stay; ⑧ adverse reactions.

All studies included in this analysis were RCTs. Of these studies, 27 reported appropriate methods of random sequence generation (random number table method)[6,8,11,23,24,26-28,32,33,37-39,41,42,44,45,49,51,53], 20 solely focused on randomization[7,9,10,25,29-31,34-36, 40,43,46-48,50,52,57,60,65], and three were grouped according to the time or order of admission[58,64,66]. Blinding and allocation concealment were not mentioned in any of the articles, resulting in an unclear risk of potential bias in selection, detection, and performance. All the studies included had designed precise inclusion and exclusion criteria, performed statistical analysis, and presented comprehensive outcomes. At baseline, the two groups were comparable in age, gender, disease course, and severity. Only one article reported the duration of follow-up, with a mean of 15 months[66]. Figures 2 and 3 delineated the risk of bias in the studies included.

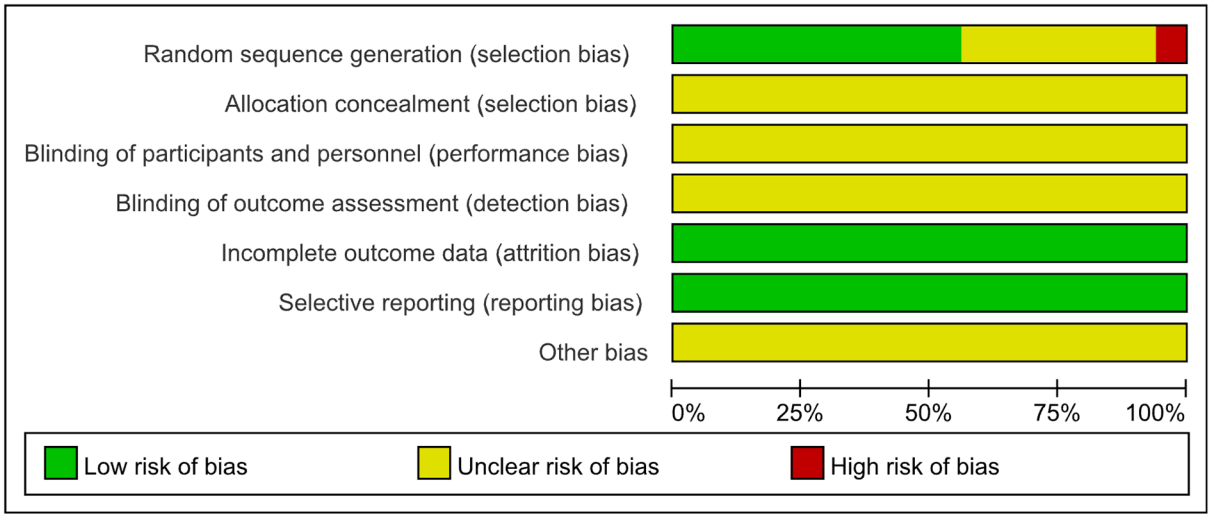

Figure 2. Methodological quality graph.

Efficacy of the Combined CHM Therapy

Total effective rate

A total of 39 trials reported the total effective rate (n=2,888)[6-11,23,24,26-33,35,36,38-43,46,47,49-55,58,60-63,65]. No significant heterogeneity was detected among the trials, and a fixed-effects model was utilized (p=0.61, I^2=0%). The results demonstrated a statistically significant difference in total effective rate between the combined CHM treatment group and the control group [RR: 1.19; 95% CI: (1.16, 1.23) p<0.00001; Figure 4].

Duration of Symptom Resolution

Abdominal pain relief time

A total of 30 studies expounded on the abdominal pain relief time (n = 2,256)[7,9,11,23,25-27,29-31,35-39,41,42,45-47,49]. The random-effects model was utilized for substantial heterogeneity among the studies (p<0.00001, I^2=96%). A significant difference was revealed between the combined CHM group and the Western medicine treatment group in shortening abdominal pain time, as evidenced by an MD of -1.68 [95% CI: (-2.04, -1.31); p<0.00001; Figure 5].

Abdominal distension relief time

Abdominal distension relief time was reported in 14 studies (n=1,128)[11,23,26,27,29-31,36,39,44,45,47,63,65]. The random-effects model was utilized to examine the data of the studies based on substantial heterogeneity (p<0.00001, I^2=86%). As shown in Figure 6A, the meta-analysis revealed the high efficacy of the combined CHM treatment in shortening the abdominal distension relief time in HLAP patients in comparison to the control group [MD: -1.58; 95% CI: (-1.86, -1.29); p < 0.00001; Figure 6A].

Recovery time for anal defecation/exhaust

17 studies[11,25,30-32,36,37,40,41,43,45-47,51,52,56,63] explored the recovery time for anal defecation/exhaust (n=1,311). Due to obvious heterogeneity, the random-effects model was used to analyze the data (p<0.00001, I^2=85%). According to the meta-analysis, the combined CHM therapy can decrease recovery time for anal defecation/exhaust to a considerable extent [MD: -1.59; 95% CI: (-1.86, -1.33); p < 0.00001; Figure 6B].

Recovery time for plasma amylase

A total of 15 studies[7,26,29-31,35,36,40,47,50,52,57,58,62,66] expounded on the recovery time for plasma amylase (n=1,083). A random-effects model was applied to analyze data due to statistically significant heterogeneity (p<0.00001, I^2=90%). According to the results of the meta-analysis, the combined CHM therapy reduced the recovery time of serum amylase dramatically compared with the group of Western medicine [MD: -1.65; 95% CI: (-2.06, -1.23); p<0.00001; Figure 7A].

Recovery time for plasma triglyceride

Three studies[40,48,57] described the recovery time for plasma triglyceride (n=161). The fixed-effects model was applied due to minimal heterogeneity among the studies (p=0.18, I^2=42%). As shown

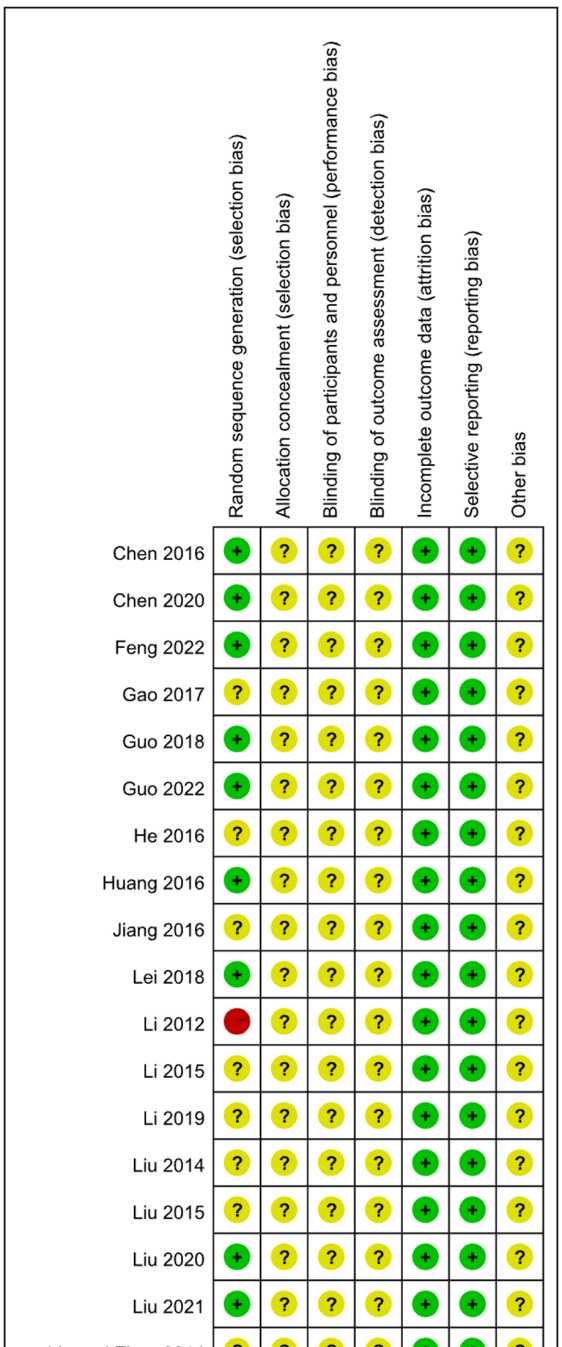

Figure 3. Methodological quality summary. +: L (low risk of bias); ?: U (unclear risk of bias); −: H (high risk of bias).

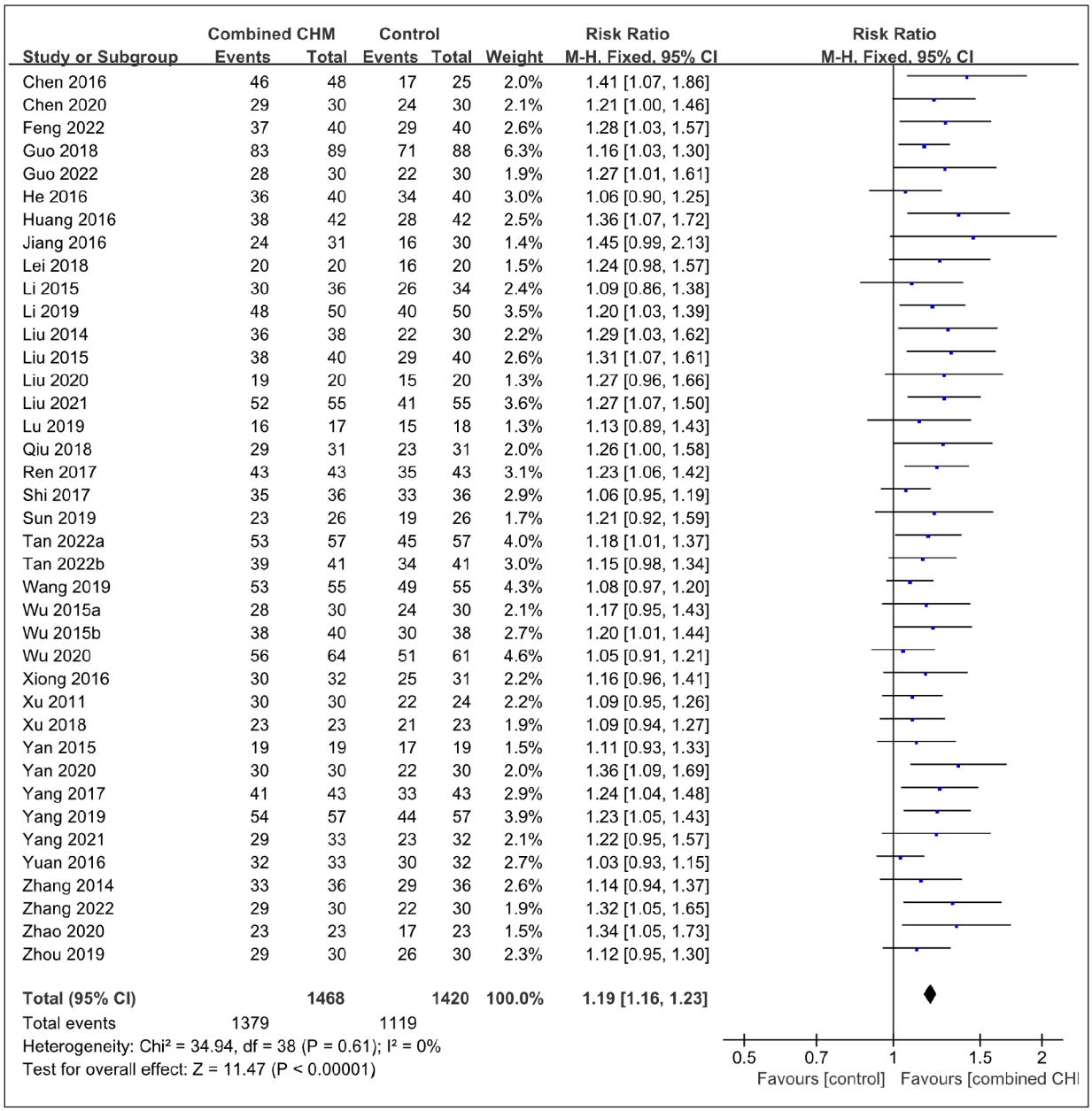

Figure 4. Forest plot of total effective rate.

in the forest plot, the combined CHM therapy can shorten the recovery time of serum triglyceride dramatically compared with the control group [MD: -1.38; 95% CI: (-1.70, -1.05); p<0.00001; Figure 7B].

Mortality

Mortality data were available from 10 trials (n=812)[6,8-11,34,48,55,59,60]. The fixed-effects model was employed because of low heterogeneity among the studies (p=1.00, I^2=0%). According to the meta-analysis, compared to the control group, the combined CHM treatment sharply decreased the risk of mortality in HLAP patients [RR: 0.28; 95% CI: (0.14, 0.56); p=0.0003; Figure 8A].

Complication Rate

Complication rates were reported in 14 studies (n=1,045)[6-11,34,35,48,51,54,55,59,62]. A fixed-effects model was used to conduct the analysis according to the heterogeneity test (p=0.74, I^2=0%). The forest plot demonstrated the high efficacy of the combined CHM treatment in reducing the complication rate compared to the control group [RR: 0.40; 95% CI: (0.31, 0.52); p<0.00001; Figure 8B].

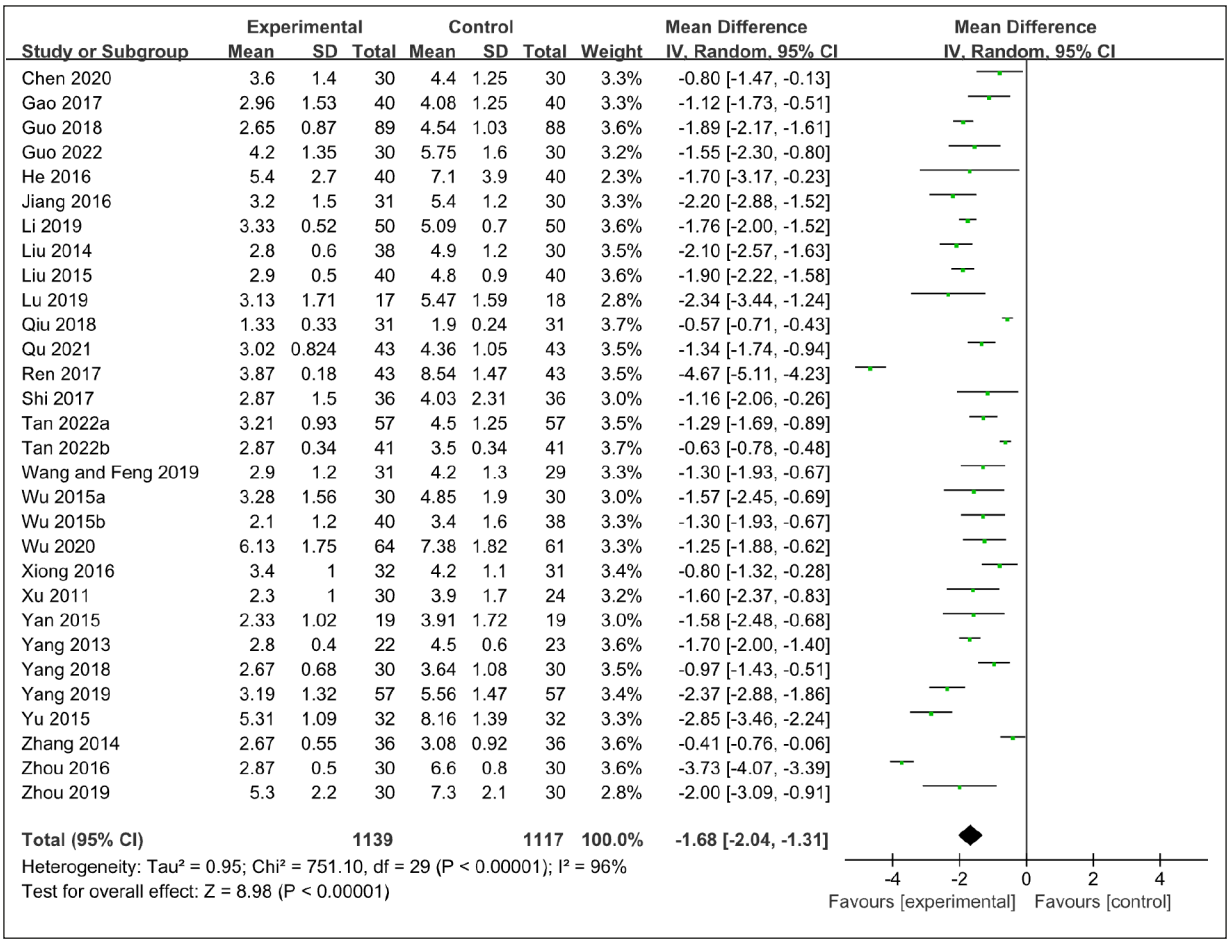

Figure 5. Forest plot of abdominal pain relief time.

Length of Hospital Stay

The effect of the combined CHM treatment on the length of hospital stay in HLAP patients was evaluated in 22 studies (n=1,483)[9,23,24,34,36,39,41,44,45,47-52,55-57,59,64-66]. Due to significant variability among the studies, the random-effects model was adopted for data analysis (p<0.00001, I^2=92%). The meta-analysis results indicated a substantial difference in the length of hospital stay between the combined CHM group and the Western medicine group. In other words, the combined CHM treatment shortened the length of hospital stay of HLAP patients dramatically [MD: -3.96; 95% CI: (-4.76, -3.16); p < 0.00001; Figure 9A].

Adverse Reactions

The adverse reactions were reported in six trials (n = 583)[24,26,32,36,42,62]. The data was analyzed using a fixed-effects model based on the heterogeneity test (p=0.80, I^2=0%). As shown in Figure 9B, no significant difference existed in adverse reactions between the combined CHM group and the Western medicine group [RR: 0.78; 95% CI: (0.31, 1.99); p=0.61].

Sensitivity Analysis

Significant heterogeneity was observed in the following five outcome indicators: abdominal pain relief time, abdominal distension relief time, recovery time for anal defecation/exhaust, recovery time for plasma amylase, and length of hospital stay. Therefore, a sensitivity analysis was carried out through the study-by-study exclusion method. The results showed the meta-analysis was low sensitivity, and the results were stable and robust (Figure 10).

Publication Bias

According to the funnel plot of the publication bias test based on the total effective rate, the left-right distribution of the points representing single studies was asymmetrical (Figure 11A). Based on

the Egger linear regression plot, the 95% CI did not include 0, and the intercept α corresponded to the situation when $p<0.05$. Therefore, there was a publication bias in the included studies [95% CI: (1.92,3.65); $p = 0.000$; Figure 11B].

Discussion

This systematic review and meta-analysis of 50 randomized controlled trials (RCTs) comprising 3,635 patients was conducted to evaluate the efficacy of combined CHM treatment for HLAP. First of all, the findings indicated a 19% increase in the total effective rate among HLAP patients receiving combined CHM treatment compared to those receiving Western medicine treatment. Secondly, combined CHM therapy could rapidly improve clinical symptoms and promote the recovery of amylase and triglyceride. Finally, we also found the combined CHM treatment was associated with shorter hospital stays and lower mortality and complication rates in patients with HLAP. The findings were robust according to

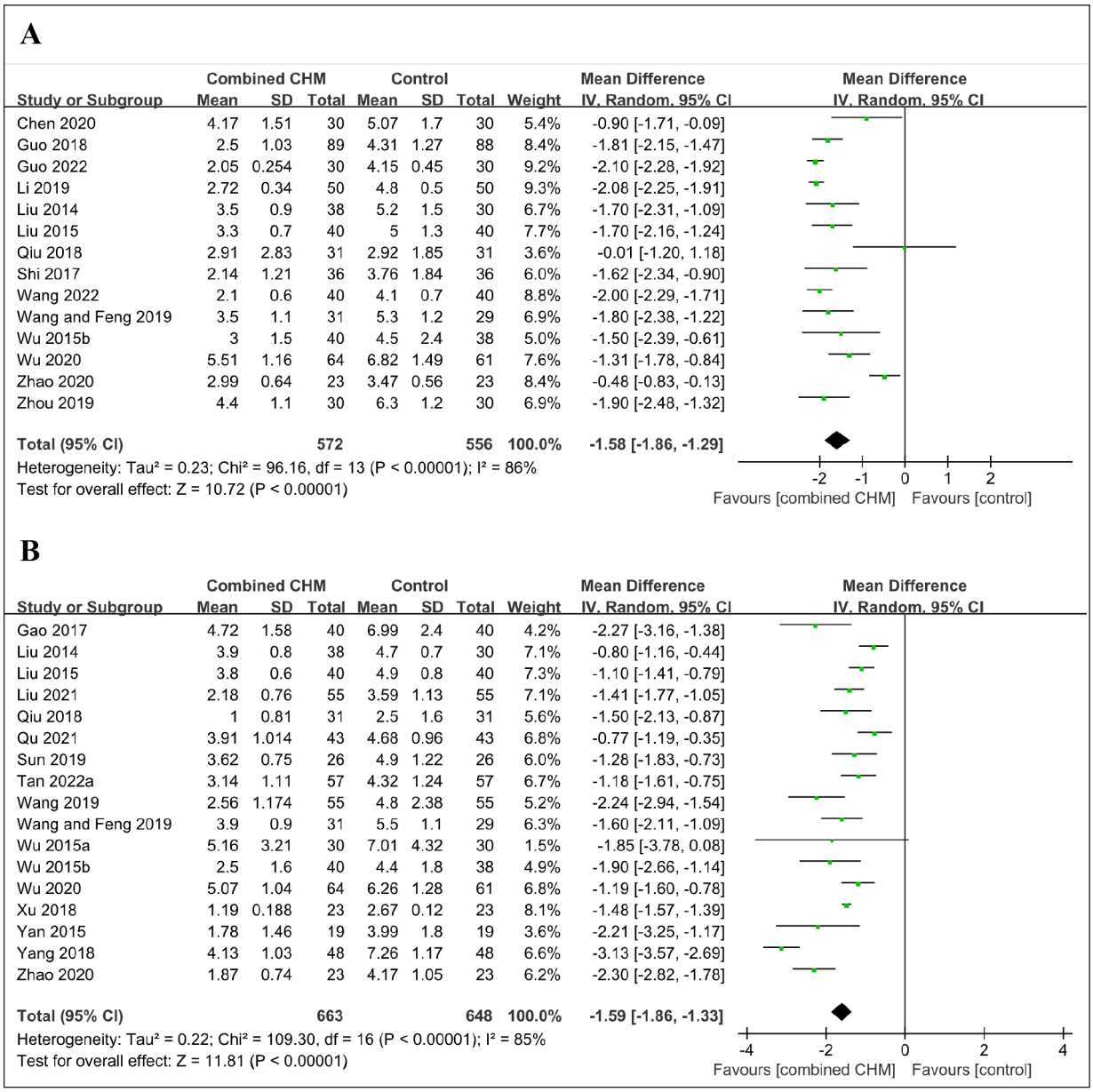

Figure 6. Forest plot of abdominal distension relief time and recovery time for anal defecation/exhaust. **A**, Abdominal distension relief time. **B**, Recovery time for anal defecation/exhaust.

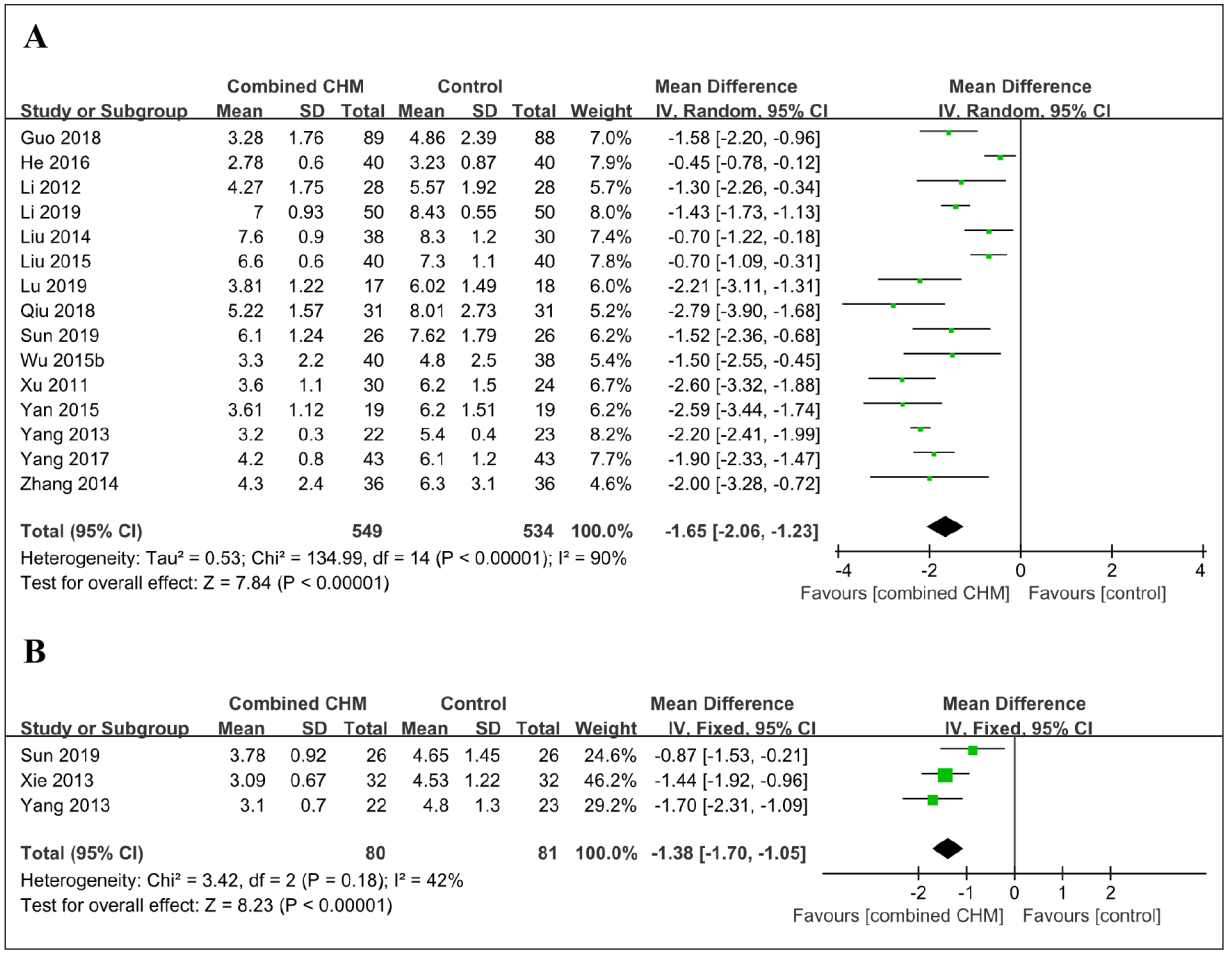

Figure 7. Forest plot of recovery time for plasma amylase and triglyceride. **A**, Recovery time for plasma amylase. **B**, Recovery time for plasma triglyceride.

the sensitivity analysis, and the adverse reactions were similar between groups. All of the above validated the efficacy of the combined CHM treatment. However, the methodological quality of the evidence was considered low to moderate, and there was a potential publication bias. Therefore, the conclusions should be interpreted with caution, and further research is required to confirm the efficacy of the combined CHM therapy.

At present, the potential pathogenesis of HLAP is not fully understood. As a widely accepted mechanism model, the Havel theory[67] holds that TG in and around the pancreas can be hydrolyzed by pancreatic lipase exuded from acinar cells, thus resulting in a high concentration of free fatty acids (FFA). Increased levels of FFA and TG induce blood viscosity, block pancreatic blood circulation, and cause ischemia and acidosis. FFA has been proven cytotoxic to pancreatic acini and vascular endothelial cells. In addition, FFA activates trypsinogen in an acidic environment, causing pancreatic autodigestion and triggering AP. Therefore, reducing TG levels and rapidly improving microcirculation disorders are essential in the treatment of HLAP. On this basis, there are also other mechanisms such as inflammatory mediators-cytokine damage, pancreatic cell calcium overload, microcirculation disorder, oxidative stress, and gene polymorphism worth attention.

The major clinical manifestations of AP include acute severe upper abdominal pain, abdominal distension, abnormal anal exhaust and defecation, nausea, vomiting, and fever. According to traditional Chinese medicine (TCM) theory, it is located in the spleen, which shares a close relationship with the liver, gallbladder, and stomach. It can be categorized as “abdominal pain”, “spleen ache”, “Spleen Dan”, and “stomach ache”.

The basic pathogenesis of AP is the Qi stagnation in the liver and spleen and the disorder of ascending and descending in the spleen and stomach. Such symptoms can be attributed to overeating, excessive drinking, obstruction of insect accumulation, emotional depression, etc. These triggering factors further lead to the production of damp-heat, phlegm, food accumulation, blood stasis, and other products in the body, resulting in "the obstruction of Fu Qi and a stagnated physical condition leading to pain"[68]. Hyperlipemia falls into the category of phlegm turbidity and congestion[69]. In HLAP patients, the condition is more complicated and severer because the accumulation of phlegm and blood stasis will lead to severer damp-heat within the body. Consequently, the circulation of Qi and blood is further obstructed. The treatment of HLAP mainly relies on regulating the movement of Qi in the liver and spleen, restoring ascending and descending in the spleen and stomach, and dissipating phlegm, damp-heat, and blood stasis.

In this meta-analysis, approximately 30% of the studies focused on Da Chaihu Decoction, 20% on Da Chengqi Decoction, and 8% on both for their therapeutic effect in HLAP patients. Da Chaihu

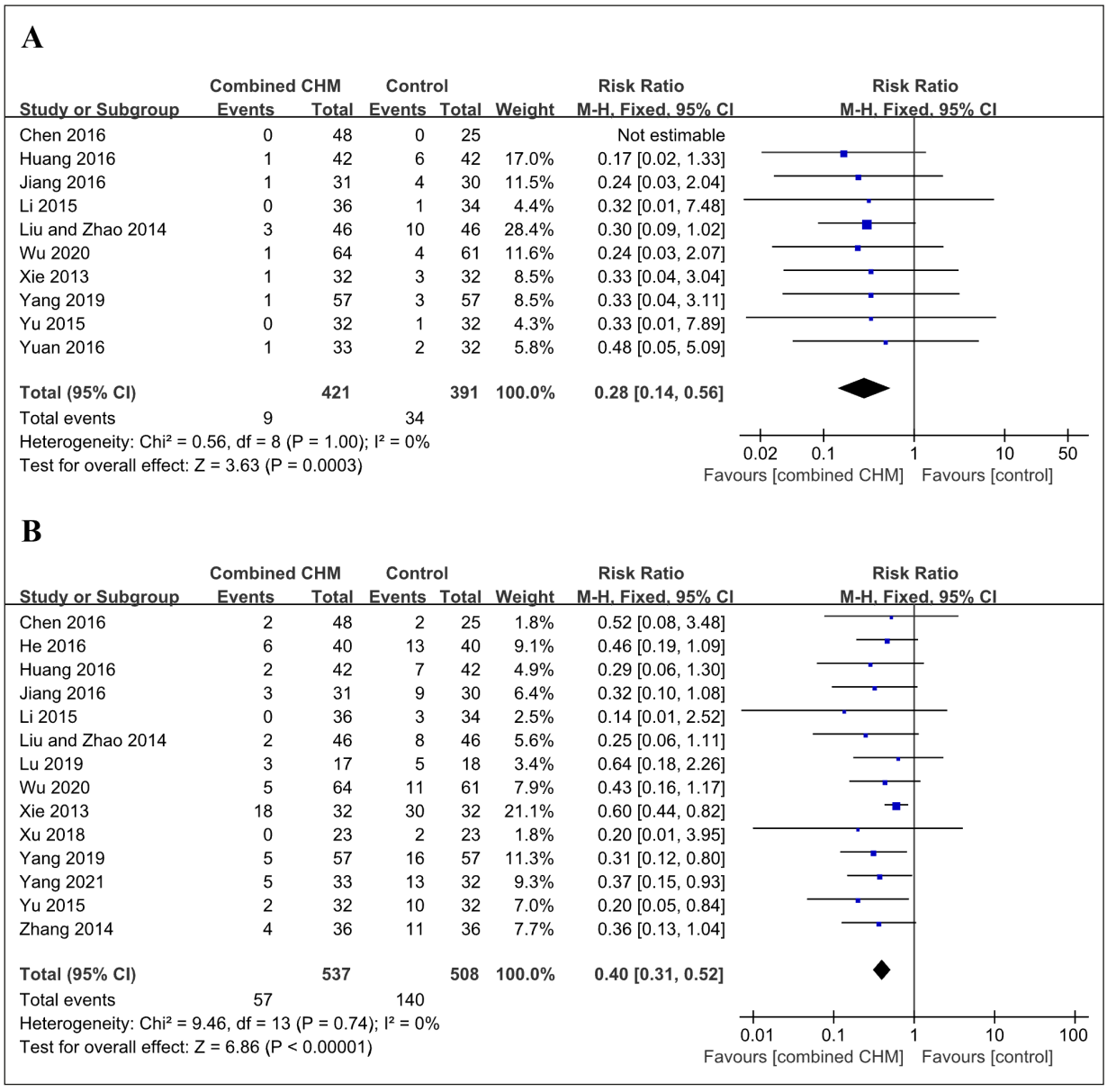

Figure 8. Forest plot of mortality and the complication rate. **A**, Mortality. **B**, The complication rate.

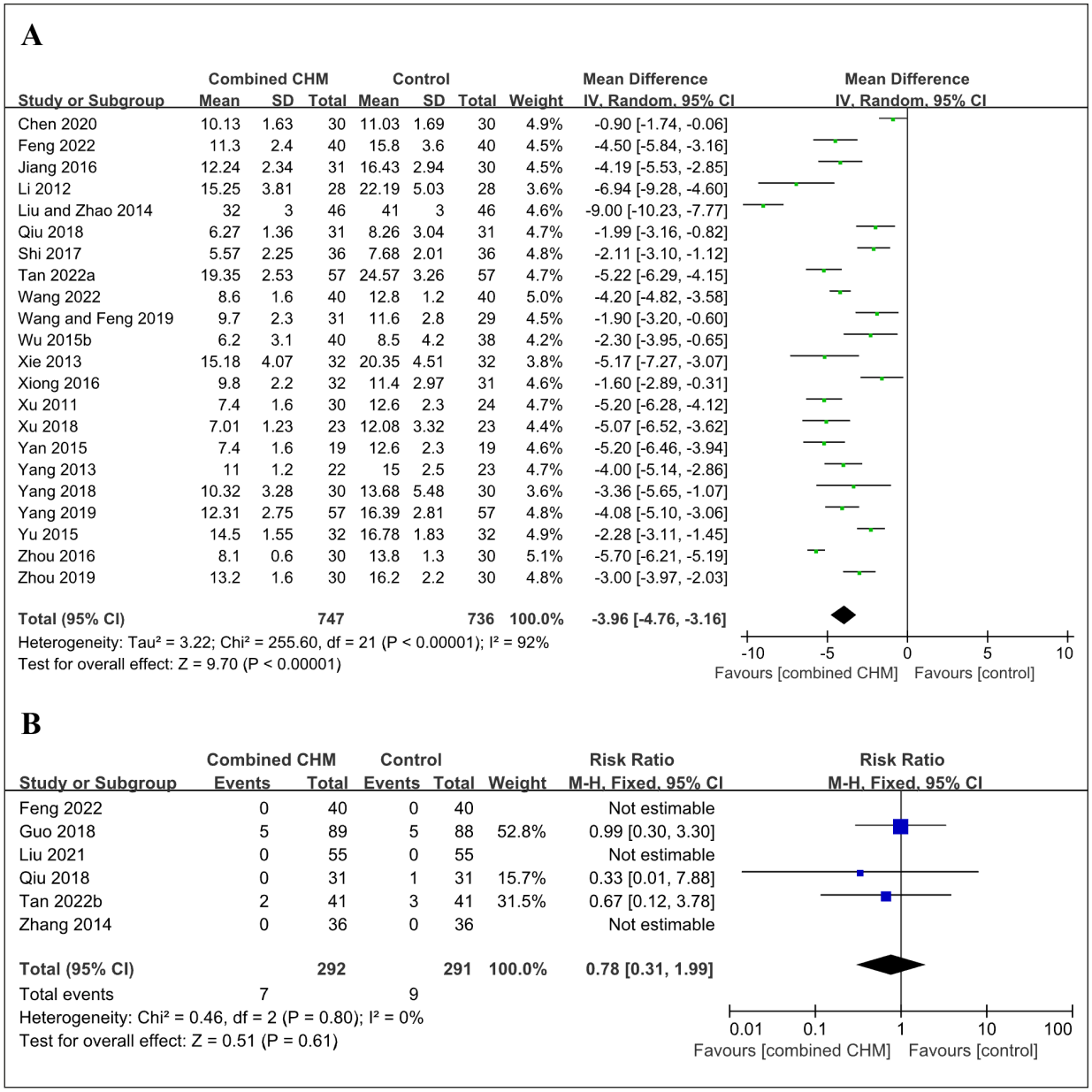

Figure 9. Forst plot of the length of hospital stay and adverse reactions. **A**, The length of hospital stay. **B**, Adverse reactions.

Decoction is administered mainly through a nasogastric tube, while Da Chengqi Decoction is mainly used for enemas, both of which are traditional herbal formulas from Shang Han Lun (Treatise on Febrile Diseases) in the Eastern Han Dynasty. Da Chaihu Decoction includes Chaihu (*Bupleuri radix*), Baishao (*Paeoniae radix alba*), Huangqin (*Scutellariae radix*), Banxia (*Pinelliae rhizoma*), Dahuang (*Rhei radix et rhizoma*), Zhishi (*Aurantii fructus immaturus*), Dazao (*Jujubae fructus*), and Shengjiang (*Zingiberis rhizoma recens*). It functions to smooth the movement of Qi in the liver and dissipate phlegm, congestion, and heat accumulation in stool through diarrhea. Clinical studies[24] have shown that the treatments in combination with Da Chaihu Decoction can lower serum low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), and triglyceride (TG). It can also prevent the formation of inflammatory mediators such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and high-sensitivity C-reactive protein (hs-CRP). Meanwhile, it accelerates the recovery of gastrointestinal function, shortens the course of the disease, reduces

the length of hospital stay, and improves the clinical symptoms and APACHE-II scores of HLAP patients[28,46].

Da Chengqi Decoction, a famous prescription for catharsis, includes Dahuang (*Rhei radix et rhizoma*), Houpo (*Magnoliae officinalis cortex*), Zhishi (*Aurantii fructus immaturus*), and Mangxiao (*Natrii sulfas*). Houpu and Zhishi can promote the downward movement of Qi, enhance the function of intestinal excretion, facilitate intesti-

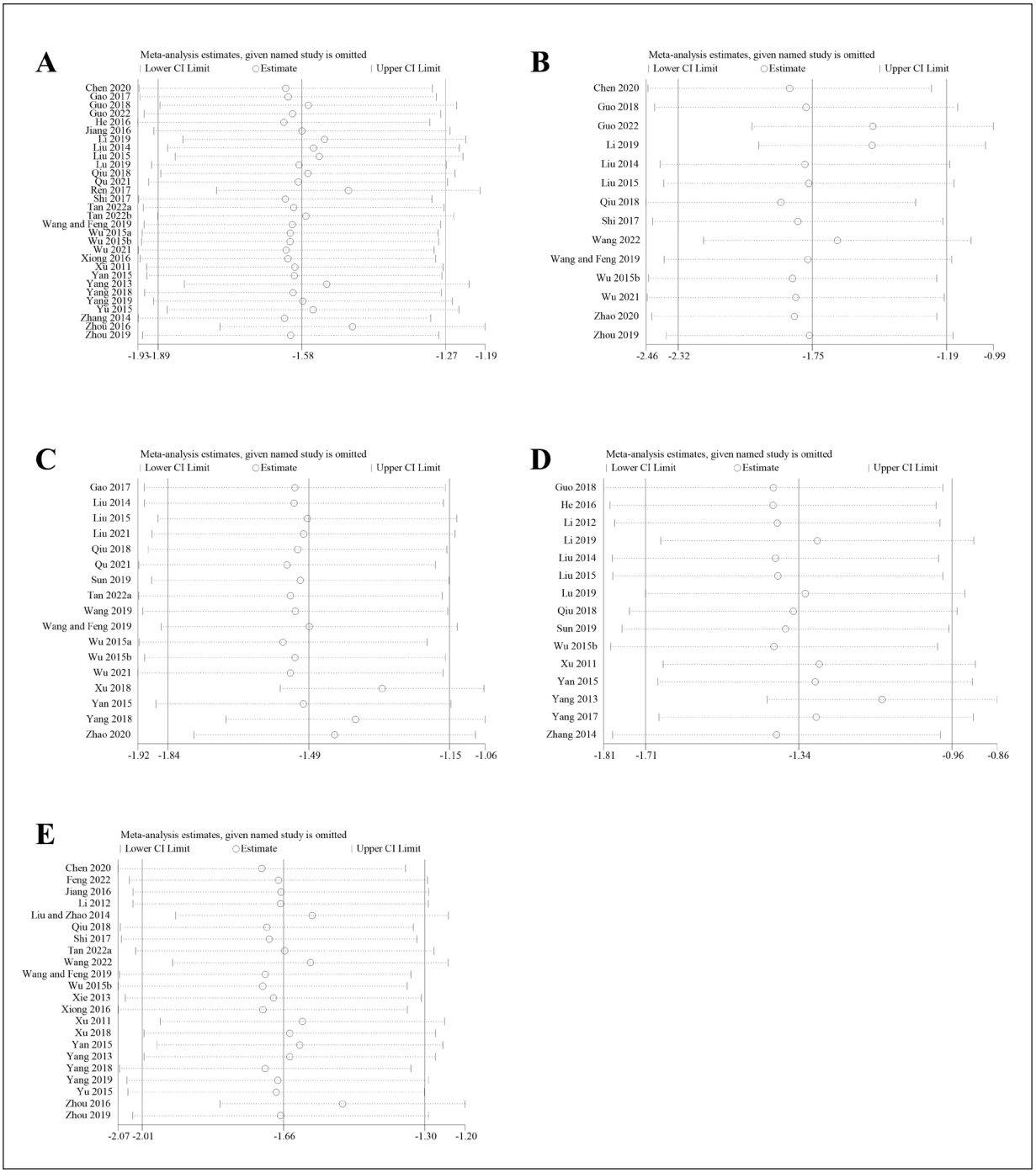

Figure 10. Sensitivity analysis. **A**, Abdominal pain relief time. **B**, Abdominal distension relief time. **C**, Recovery time for anal defecation/exhaust. **D**, Recovery time for plasma amylase. **E**, Length of hospital stay.

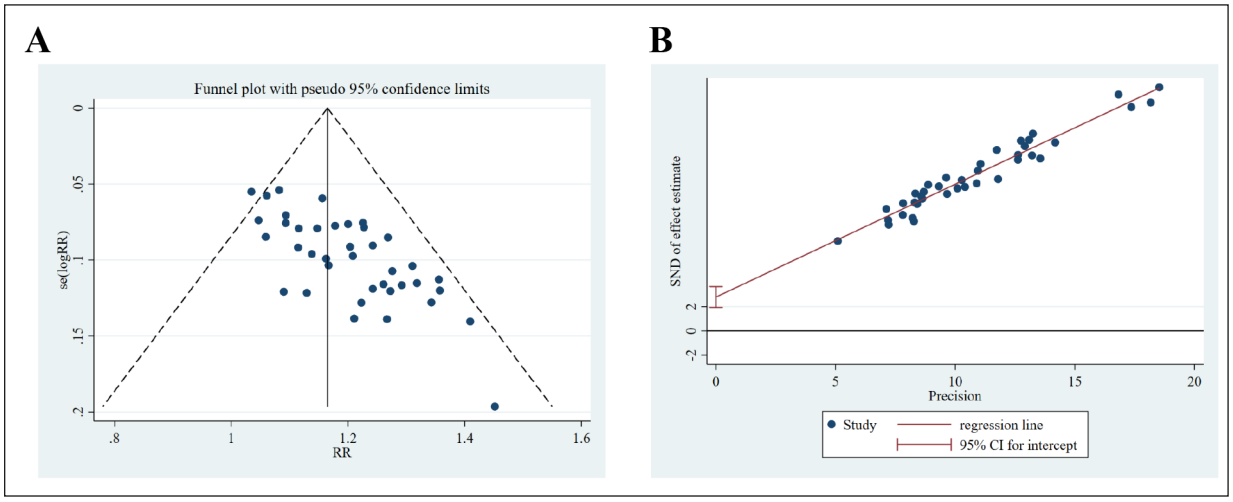

Figure 11. Publication Bias based on the total effective rate. **A**, Funnel plot. **B**, Egger linear regression plot.

nal peristalsis, and relieve abdominal distension. Dahuang has a direct cathartic effect due to its "cold" nature from the TCM philosophy. Hence, it helps clear the intestinal damp-heat, phlegm, food sludge, and other garbage within the body, and promotes the discharge of massive intestinal bacteria and toxic substances. Mangxiao can increase the moisture of the intestine and soften visible food and fecal mass in the intestine, which combines to facilitate excretion[70]. Modern pharmacological studies[32,66] have demonstrated that Dachengqi Decoction can alleviate inflammatory factors, inhibit oxidative stress, lower lipid levels, and improve TCM syndromes and symptoms in patients. Furthermore, it encourages restoration of intestinal function, safeguards the intestinal mucosal barrier, and prevents tissue necrosis caused by local blood stasis and Qi stagnation arising from obstruction.

Approximately 20% of the studies included explored injectable formulations of Danshen (*Salviae miltiorrhizae radix et rhizoma*) extracts, such as compound Danshen injection, Danshen injection, Salvianolate injection, and Salviae Miltiorrhizae and Ligustrazine Hydrochloride injection. Clinical trials[49,64] have shown that Danshen has effects of promoting microcirculation, scavenging oxygen free radicals, lipid-lowering, and anti-inflammatory. Clinical signs of HLAP can be significantly improved when a high-dose compound Danshen injection is given[6].

In addition, a modified Qingyi Decoction was investigated in 14% of the studies. Qingyi Decoction contains the following eight Chinese herbs: Chaihu (*Bupleuri radix*), Huangqin (*Scutellariae radix*), Dahuang (*Rhei radix et rhizoma*), Mangxiao (*Natrii sulfas*), Huhuanglian (*Picrorhizae rhizoma*), Muxiang (*Aucklandiae radix*), Yanhusuo (*Corydalis rhizoma*), and Baishao (*Paeoniae radix alba*). It can regulate Qi, soothe the liver, clear heat, and wipe out toxins. Yang et al[55] have demonstrated that Qingyi Decoction can bring significant benefits to HLAP patients by enhancing cellular immune function, improving blood hypercoagulability, reducing serum inflammatory markers, and promoting the recovery of pancreatic function.

Limitations

Studies included in the meta-analysis had some limitations. Firstly, the methodological quality of the studies reviewed was low to moderate. Although 54% of the studies (27/50) reported appropriate methods of random sequence generation, none of them mentioned the use of allocation concealment and blinding. Such problems may result in bias in selectivity, implementation, and measurement. Because of the specificity of herbal dosage forms, it is challenging to match an appropriate placebo, thus limiting the use of the blinding method. Secondly, since hypertriglyceridemia is a chronic disease, there is a high possibility for HLAP to recur. However, there was little information on the follow-up and recurrence rate in the included studies. Thirdly, publication bias is another limitation of this meta-analysis. Only one of the 50 studies was reported in English, and the remaining 49 were published in Chinese. CHM is the national treasure of China. We expect more well-designed RCTs to be published in multiple languages to

demonstrate the efficacy of CHM in improving people's health worldwide.

Conclusions

The combined CHM therapy is more effective than the Western medicine treatment in HLAP patients, as evidenced by the systematic review and meta-analysis in this study. However, in consideration of the low to moderate quality of the studies included, the findings must be interpreted with caution. Therefore, double-blind and well-designed RCTs with a larger sample size are called for to validate this conclusion in the future.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Authors' Contributions

Conceptualization: Xiaoguang Lu. Data curation: Wenxiu Guo and Yi Song. Formal analysis: Xiaoguang Lu and Libin Zhan. Funding acquisition: Xiaoguang Lu. Investigation: Wenxiu Guo. Methodology: Wenxiu Guo. Project administration: Wenxiu Guo and Yi Song. Resources: Wenxiu Guo and Yi Song. Software: Wenxiu Guo. Supervision: Yi Song. Validation: Yi Song. Visualization: Wenxiu Guo. Writing – original draft: Wenxiu Guo. Writing – review & editing: Wenxiu Guo, Xiaoguang Lu, Libin Zhan, and Yi Song.

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Informed Consent

Not applicable.

Ethics Approval

Not applicable.

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Availability of Data and Materials

All relevant data were within the manuscript.

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