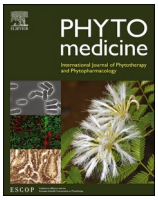
Phytomedicine 113 (2023) 154727

Contents lists available at ScienceDirect

Phytomedicine

journal homepage: www.elsevier.com/locate/phymed



# Effectiveness of Chengqi-series decoctions in treating severe acute pancreatitis: A Systematic review and meta-analysis

Juan Lin [a,#], Chenxia Han [a,#], Ning Dai [b], Siwei Bi [c], Dan Du [d,*], Qing Xia [a,**]

[a] West China Centre of Excellence for Pancreatitis, Institute of Integrated Traditional Chinese and Western Medicine, Sichuan Provincial Pancreatitis Centre and West China-Liverpool Biomedical Research Centre, West China Hospital, Sichuan University, Chengdu 610041, China
[b] Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing, 100010, China
[c] Department of Burn and Plastic Surgery, West China Hospital, Sichuan University, Chengdu 610000, Sichuan, China
[d] Advanced Mass Spectrometry Center, Research Core Facility, Frontiers Science Center for Disease-related Molecular Network, West China Hospital, Sichuan University, Chengdu 610041, China

ARTICLE INFO

*Keywords:*
Severe acute pancreatitis
Traditional Chinese medicine
Chengqi-series decoctions
Meta-analysis
Multiple organ dysfunction syndrome

ABSTRACT

*Background:* Evidence suggests that Dachengqi and its modified decoctions are effective for treating abdominal pain, multiple organ dysfunction syndrome (MODS) and inflammation in various disease conditions. We performed a meta-analysis to ascertain the effectiveness of a series of chengqi decoctions in patients with severe acute pancreatitis (SAP).

*Methods:* We searched Pubmed, Embase, Cochrane library, Web of Science, Chinese National Knowledge Infrastructure, Chinese Biomedical Literature, Wanfang database and China Science and Technology Journal Database before August 2022 to identify eligible randomized controlled trials (RCTs). Mortality and MODS were chosen as primary outcomes. Secondary outcomes included time until relief of abdominal pain, APACHE II score, complications, effectiveness, IL-6 and TNF-α levels. The risk ratio (RR) and standardized mean difference (SMD) with a 95% confidence interval (CI) were selected as effect measures. The quality of evidence was independently assessed by two reviewers using Grading of Recommendations Assessment Development and Evaluation (GRADE) system.

*Results:* Twenty-three RCTs ($n$ = 1865) were finally included. The results showed that, compared with routine therapies, chengqi-series decoctions (CQSDs) treatment groups were associated with lower mortality rate (RR: 0.41, 95%CI: 0.32 to 0.53, $p$ = 0.992) and incidence of MODS (RR: 0.48, 95%CI: 0.36 to 0.63, $p$ = 0.885). They also reduced remission time of abdominal pain (SMD: -1.66, 95%CI: -1.98 to -1.35, $p$ = 0.000), complications (RR: 0.52, 95%CI: 0.39 to 0.68, $p$ = 0.716), APACHE II score (SMD: -1.04, 95%CI:-1.55 to -0.54, $p$ = 0.003), IL-6 (SMD: -1.5, 95%CI: -2.16 to –0.85, $p$ = 0.000), TNF-α (SMD: -1.18, 95%CI: -1.71 to -0.65, $p$ = 0.000), and improved curative effectiveness (RR:1.22, 95%CI: 1.14 to 1.31, $p$ = 0.757). The certainty of the evidence for these outcomes was low to moderate.

*Conclusion:* CQSDs seem to be effective therapy for SAP patients with notable reductions in mortality, MODS and abdominal pain, with low quality evidence. Large-scale, multi-center RCTs that are more meticulous are advised in order to produce superior evidence.

*Abbreviations:* AP, acute pancreatitis; bid, twice a day; CNKI, Chinese National Knowledge Infrastructure; CQSDs, chengqi-series decoctions; CSCQD, Chaishao chengqi decoction; DCQD, Dachengqi decoction; IL-6, interleukin-6; GRADE, Grading of Recommendations Assessment Development and Evaluation; MODS, multiple organ dysfunction syndrome; NSAIDs, nonsteroidal anti-inflammatory drugs; P.O, oral treatments or infusion on gastric tube; P.R, enema treatments; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; qd, once a day; qid, four times a day; RCTs, randomized controlled trials; RR, risk ratio; RT, routine therapies; SAP, severe acute pancreatitis; SMD, standardized mean difference; tid, three times a day; TCM, Traditional Chinese Medicine; TNF-α, tumor necrosis factor-α; 95%CI, 95% confidence interval.

* Corresponding author at: Advanced Mass Spectrometry Center, Research Core Facility, Frontiers Science Center for Disease-related Molecular Network, West China Hospital, Sichuan University, Chengdu 610041, China.

** Corresponding author at: West China center of Excellence for Pancreatitis, Institute of Integrated Traditional Chinese and Western Medicine, Sichuan Provincial Pancreatitis center and West China-Liverpool Biomedical Research center, West China Hospital, Sichuan University, Chengdu 610041, China.

*E-mail addresses:* dudan1520@163.com (D. Du), Xiaqing@medmail.com.cn (Q. Xia).

# These authors contributed equally to this work.

https://doi.org/10.1016/j.phymed.2023.154727
Received 11 December 2022; Received in revised form 31 January 2023; Accepted 20 February 2023
Available online 2 March 2023

## Introduction

Acute pancreatitis (AP) is a pancreatic inflammatory illness that manifests suddenly with excruciating abdominal pain and has the potential to be life threatening (Lankisch et al., 2015). It is mostly caused by bile stones, excessive alcohol consumption and hyperlipidemia (Boxhoorn et al., 2020). With more than 270,000 admissions and expenses over 2.6 billion dollars annually in the United States, AP is one of the top 3 gastrointestinal illnesses that lead to hospitalization. (Peery et al., 2015). For the majority of patients, this disease takes a mild course, but around 20% patients experience a severe episode of AP, with a mortality rate ranges from 15% to 35% (van Santvoort, Bakker et al. 2011). According to the 2012 Revised Atlanta classification, severe acute pancreatitis (SAP) is defined as persistent organ failure (> 48 h) (Banks et al., 2013).

Multiple organ dysfunction syndrome (MODS) is the primary cause of mortality in SAP (Petrov et al., 2010). Respiratory failure is the commonest organ failure in this condition, followed by cardiovascular, hepatic and renal failures (Buchler et al., 2000). Distant organ damage or MODS could occur early within a few days of onset of AP, which is induced by pancreatitis per se, and could develop later due to infected pancreatic necrosis induced sepsis (Garg and Singh 2019). Elevated evidence suggested that, the small intestine and colon may contribute to bacterial translocation and infected necrosis due to its close proximity to the pancreas, and thus lead to systemic pathology (Garg and Singh 2019). Accumulated studies have pointed out that gastrointestinal tract is the main target organ of SAP (Ji et al., 2017; Shu et al., 1998). Clinical research has shown that in patients with SAP, the gastrointestinal tract's bacteria and endotoxins transfer into the lymph and blood after the gastrointestinal system's defense and protection mechanisms are damaged. This eventually results in systematic inflammation response syndrome and MODS (Ge et al., 2020; Landahl et al., 2015).Therefore, recovery of gastrointestinal function is a key intervention for patients with SAP.

SAP progression is caused by combines of manifold factors. However, current interventions still focus on goal-targeted treatments towards initial pathological events, which include local pancreatic injury, gastrointestinal dysfunction, hypoperfusion and systematic inflammation (Hines and Pandol 2019). The corresponding routine therapies involve analgesia, enteral and parenteral nutrition, fluid resuscitation, endoscopic retrograde cholangiopancreatography and prevention of infectious complications (Boxhoorn et al., 2020). Evidently, single-target medicines in SAP development lack clinical viability (Lee and Papachristou 2019), synthesized or synergetic treatment approaches may become a breakthrough for SAP.

Chinese herbal formulas, which upheld the holistic therapeutic philosophy, have been widely employed in clinical practices in many Asian nations and showed promise therapeutic impact in AP compared to western medicine, which often focuses on a single target (W et al., 2005). A previous meta-analysis of 16 randomized controlled trials (RCTs) involving 912 SAP patients indicated that *Rhei radix et rhizoma* (Dahuang) combined with trypsin inhibitor could decrease mortality, length of hospitalization, and abdominal pain duration (Hu et al., 2018). Clinical evidence showed that Chinese herbal formulas like Dachengqi and Qingyi decoctions were effective and safe treatments for non-biliogenic SAP (Lu et al., 2014), and the protective effect included reducing pro-inflammatory interleukin-6 (IL-6), IL-8, tumor necrosis factor-α (TNF-α) and IL-1 (Wang et al., 2022). However, there is no systematic review or meta-analysis for the effect of Dachengqi-derived decoctions on mortality, MODS, or complications in SAP patients.

Dachengqi decoction (DCQD), which consists of *Rhei radix et rhizoma* (Dahuang), *Natrii sulfas* (Mangxiao), *Aurantii fructus immaturus* (Zhishi) and *Magnoliae officinalis cortex* (Houpo), was first documented in *"Treatise on Cold Pathogenic Diseases"* by Zhang Zhongjing. It is a representative purgative for constipation treatment and could clear internal heat in the gastrointestinal tract. It has been used as a classical prescription in China to treat AP for more than three decades (Xia 2006). Clinical studies indicated that DCQD could protect the intestinal mucosal immune barrier and decrease the incidence of pancreatic infection and MODS (CHEN et al., 2010). Meanwhile, its derived formula Chaishao chengqi decoction (CSCQD) has been proved to improve intestinal dysfunction, inflammation, pancreatic infection and organ failure (Wang et al., 2007). Chengqi-series decoctions (CQSDs) mean a series of decoctions which are derived from DCQD, they also represent the modified DCQD. Numerous researches had suggested that DCQD or CQSDs may be able to relieve SAP-related symptoms (Wei, QIN et al. 2021). Most of these studies, however, lacked multi-center, thorough testing, the conclusion they came to were ambiguous, which result that the relationship between outcomes and disease severity was incomplete (CHEN et al., 2023; Ou et al., 2020; SUN et al., 2022). In order to provide high-quality data for therapeutic decision-making, we intended to analyze the effects of chengqi-series decoctions (CQSDs) in the treatment of patients with SAP using meta-analysis on mortality, MODS, relief time of abdominal pain, APACHE II score, complications, effectiveness as well as pro-inflammatory IL-6 and TNF-α.

## Methods

### *Search strategy*

This study was registered in Preferred Reporting Items for International prospective register of systematic reviews (PROSPERO, CRD42022333559). We conducted the meta-analysis following the guideline of the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)" (Page et al., 2021), "PRISMA extension for Chinese herbal medicines 2020″ (Tan et al., 2020) and *Cochrane Handbook 6.3* (Higgins et al., 2022). We searched databases, including Pubmed, Embase, Cochrane library, Web of Science, Chinese National Knowledge Infrastructure, Chinese Biomedical Literature, Wanfang database and China Science and Technology Journal Database before August 2022 for relevant studies. We searched MeSH heading, keyword, abstract or title: "acute pancreatitis", "chengqi decoction", "chengqi granules" or "chengqi tang". Besides, references from selected trials were manually added to the searched menu. There was no restriction on language. The detailed search strategies and screening process were provided in Supplementary Information 1.

### *Inclusion and exclusion criteria*

*Inclusion criteria were as follows:*

(1) Study population: SAP patients.

Diagnostic criteria of AP includes at least two of the below three manifestations: 1) unbearable acute abdominal pain; 2) serum amylase and/or lipase was three times or more than the upper normal limitation; 3) characteristic computed tomography imaging of AP.

SAP defines as patients meet the criteria above which combined with persistent organ failure (> 48 h) (Banks et al., 2013).

(2) Intervention and control:

Both groups received routine therapies (RT), the intervention group was supplemented with CQSDs (or granules) on top of RT.

RT mainly included gastrointestinal decompression (nasojejunal tube or nasgastric tube), acid suppression (proton pump inhibitors or H2 receptor antagonist), nutritional support (enteral nutrition, oral intake or total parenteral nutrition), enough fluid resuscitation (Ringer's lactate or saline) and electrolyte balance.

CQSDs include DCQD and a series of derived formulas based on it, the name of the formula should contain "chengqi", such as Chaiqin chengqi decoction, CSCQD, Zengye chengqi decoction and etc.

(3) Outcomes should at least contain all-cause mortality rate or MODS as primary outcomes. The secondary outcomes include time until relief of abdominal pain, APACHE II score, complications, effectiveness, IL-6 counts, or TNF-α counts. Definition of outcomes were provided in

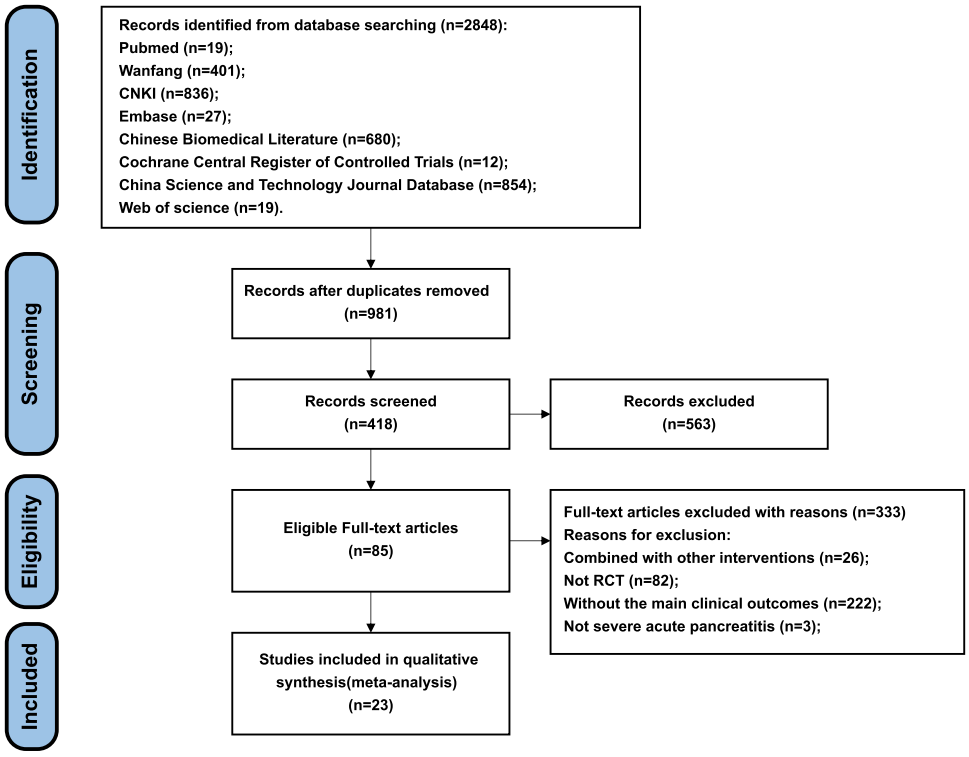



**Fig 1.** PRISMA flow diagram of study selection process
RCTs: randomized controlled trials CNKI: Chinese National Knowledge Infrastructure.

Supplementary information 2.

(4) Study: RCT

*Exclusion criteria were as follows:*

(1) The type of studies which are meta-analysis commentary articles, letters and the researches with full text unavailable;
(2) Target patients were diagnosed as mild or moderately severe AP, and patients with SAP were aged < 18;
(3) Complex interventions: CQSDs (or granules) combined with acupuncture, moxibustion, or external use of other medicines.

*Data extraction and assessment of risk of bias*

The study selection was finalized by two reviewers (JL and CXH) according to the inclusion and exclusion criteria, then they independently extracted data including the publication year, first author, province, sample size, age range, gender, intervention, herbal medicine information, duration of treatment, dosing schedules, primary and secondary outcomes. All data was cross-checked after extraction, and disagreements were resolved by the third reviewer (ND).

Meanwhile, the risk of bias for the included studies were assessed by two investigators independently according to the *Cochrane Handbook for the Systematic Review of interventions (*Higgins et al. , 2022*)* using Rob bias assessment tool. The assessments evaluated by Review Manager 5.4 included five aspects: (1) random sequence generation about selection bias; (2) allocation concealment concerning selection bias; (3) blinding of participants, outcome assessment and personnel; (4) incomplete outcome data; (5) selective reporting. Divergences were discussed with the third reviewer.

*Quality assessment*

The quality of evidence was independently evaluated by two authors with the Grading of Recommendations Assessment Development and Evaluation (GRADE) system. Summary of findings table for outcomes was made using GRADEpro3.2 (https://gdt.gradepro.org). We used the approach according to the GRADE system to assess the quality of evidence of each result. The quality could be evaluated for five reasons to downgrade (risk of bias, imprecision, inconsistency, indirectness, and publication bias) and upgrade for three reasons (large effect, dose response gradient, and plausible confounding). Divergences were discussed with the third investigator.

*Data analysis*

The risk ratio (RR) of the binary variable, the standardized mean difference (SMD) of the continuous variable and the 95% confidence interval (CI) were chosen to value the combined effect size using STATA software version 15.0 (Stata Corp, College Station, TX, USA). The $I^2$ test was used to measure statistical heterogeneity among the included studies and $p < 0.05$ or $I^2 > 50\%$ indicated significant heterogeneity. If significant heterogeneity was not observed, a fixed-effects model was used to make estimates, otherwise, a random-effects model was applied to statistical analysis. If significant heterogeneity was present and the number of included trials over 10, subgroup analysis or meta-regression was performed to discover the source of the heterogeneity. And the cutoff of sample size and treatment duration was designed as the medium of included studies' data. Meta regression would be preferred to find the causes of high heterogeneity according to the type of CQSDs depending on components, the sample size of each group ($\leq 30$ or $> 30$), the treatment duration ($\leq 7$ days or $> 7$ days) and the publication year (2015 before or not). Then subgroup analysis was further carried out to explain heterogeneous results depending on the variables above. Sensitivity analysis was used to test the stability of the results. Funnel plots and Egger's test were analyzed to find the source of publication bias. A $p < 0.05$ was considered statistical difference.

**Table 1**
Characteristics of the included studies.

| First author | Year | Province | Age (year)* | Sex (M/F) | Cases (T/C) | Intervention (T/C) | Duration | Decoction | Administration | Outcomes |
|---|---|---|---|---|---|---|---|---|---|---|
| Xiao,et al. | 2018 | Sichuan | 18–70 | NA | 34/34 | RT+ decoction/RT | 14d | DCQD | NA, qid, P. O | 1,3,4,5 |
| Guan | 2020 | Hainan | T:(52.14 ± 9.83) C:(51.36 ± 9.65) | T:17/15 C:16/16 | 32/32 | RT+ decoction/RT | 7d | DCQD | 1 dose/day, bid, P. O, P. R | 1,3,5,7,8 |
| Li,et al. | 2018 | Guangdong | T:(40.48 ± 8.26) C:(40.85 ± 9.21) | T:40/24 C:39/25 | 64/64 | RT+ decoction/RT | 7–14d | DHCQD | 1 dose/day, bid, P. O | 1,2,5,6,7,8 |
| Li,et al. | 2010 | Hunan | T:(39.8) C:(40.3) | T:28/12 C:29/11 | 40/40 | RT+ decoction/RT | 5–7d | Modified DCQD | 1 dose/day, bid, P.O or P. R | 1,2,4 |
| Zhang, et al. | 2019 | Jiangxi | T:(50.29 ± 10.26) C:(51.02 ± 9.99) | T:34/18 C:32/20 | 52/52 | RT+ decoction/RT | 30d | Modified DCQD | 1 dose/day, tid, P. O, P. R | 2,4,6 |
| Men,et al. | 2018 | Hebei | T:(46.5 ± 11.09) C:(50.91 ± 14.22) | T:19/11 C:18/12 | 30/30 | RT+ decoction/RT | NA | Modified DCQD | 1 dose/day, bid, P. O | 1,2,3,4,5,6 |
| Sun,et al. | 2017 | Zhejiang | T:(45.4 ± 5.6) C:(44.3 ± 4.9) | T:33/29 C:37/25 | 62/62 | RT+ decoction/RT | 14d | THCQD | 1 dose/day, bid, P. O | 1,2,3,5,6,7,8 |
| He,et al. | 2014 | Sichuan | T:(46.3 ± 10.1) C:(45.8 ± 9.7) | T:18/14 C:20/12 | 32/32 | RT+ decoction/RT | 7d | CSCQD | NA, qid, P. O | 1,3,4,6 |
| Zhao,et al. | 2019 | Shanxi | T:(44.01 ± 7.28) C:(42.73 ± 8.74) | T:28/20 C:24/19 | 48/43 | RT+ decoction/RT | 10d | Modified CSCQD | NA, NA, P. R | 1,3,4,6 |
| Ling,et al. | 2013 | Sichuan | T:(47.8 ± 15.4) C:(56.6 ± 15.3) | T:10/5 C:9/6 | 15/15 | RT+ decoction/RT | 7d | CSCQD | 1 dose/day, tid, P. O | 1,3,7 |
| Chen, et al. | 2019 | Hainan | T:(35.1 ± 2.9) C:(36.1 ± 3.2) | T:36/14 C:33/17 | 50/50 | RT+ decoction/RT | 7d | CSCQD | 1 dose/day, bid, P. O | 1,7 |
| Wang, et al. | 2015 | Hubei | T:(54 ± 2) C:(50.5 ± 3.1) | T:16/13 C:19/10 | 29/29 | RT+ decoction/RT | 7d | DHCQD | 1 dose/day, bid, P. O | 1,3,4,6 |
| Chen, et al. | 2007 | Sichuan | 21–80 | T:23/16 C:24/13 | 39/37 | RT+ decoction/RT | NA | ZYCQD | 1 dose/day, tid, P. O | 1,2 |
| Zhang, et al. | 2014 | Gansu | T:(46.2 ± 15) C:(44.6 ± 13.2) | T:32/ 12 C:28/14 | 44/42 | RT+ decoction/RT | 5–7d | QYCQD | NA, bid, P. O | 1,3,5 |
| Chen, et al. | 2010 | Beijing | NA | NA | 20/20 | RT+ decoction/RT | 7d | DCQD | 1 dose/day, bid, P. O | 1,2,5,7,8 |
| D.-l. Jiang, et al. | 2016 | Jiangsu | T:22–65 C:21–68 | T:25/16 C:21/15 | 41/36 | RT+ granules/ RT | 14d | Dachengqi granules | 4 bag/day, bid, P.O, P. R | 1 |
| Zhu,et al. | 2011 | Liaoning | T:(28–71) C:(29–72) | T:57/29 C:41/22 | 86/63 | RT+ decoction/RT+ saline | NA | Compound DCQD | NA, bid, P. R | 1,2 |
| Li,et al. | 2014 | Guangdong | T:(43.7 ± 14.2) C:(41.5 ± 13.2) | T:25/15 C:24/16 | 40/40 | RT+ decoction/RT | 7d | DCQD addition | 1 dose/day, tid, P. O | 2,3,5,7,8 |
| Yang | 2010 | Chongqing | T:(53 ± 21) C:(54 ± 22) | T:23/12 C:22/12 | 35/34 | RT+ decoction/RT | 5–7d | CSCQD | 1 dose/day, NA, P. O | 1,3,4,5 |
| Ma | 2008 | Zhejiang | T:(47 ± 2.01) C:(49 ± 2.84) | T:29/21 C:20/16 | 50/36 | RT+ decoction/RT | 30d | Modified DCQD | NA, bid, P. O | 1 |
| Yan | 2007 | Hebei | T:(44.7 ± 14.5) C:(45.1 ± 15.7) | T:22/10 C:20/11 | 32/31 | RT+ decoction/RT | 5–7d | DCQD | 1 dose/day, tid/qid, P. O | 1,3,4 |
| Yang | 2018 | Tianjin | T:(23–70) C:(22–63) | T:25/25 C:30/20 | 50/50 | RT+ decoction/RT | 7d | DCQD | 2 dose/day, qid, P.O | 1,4,6 |
| Li Jing, et a.l | 2014 | Tianjin | T:(43.7 ± 14.2) C:(41.5 ± 13.2) | T:24/9 C:25/10 | 49/19 | RT+ granules /RT+ placebo | 28d | Qingfei chengqi granules | 2 dose/day, bid, P. O, P. R | 1 |

M, male; F, female; C, control group; T, intervention group; NA, not available; RT, routine therapies; qd, once a day; bid, twice a day; tid, three times a day; qid, four times a day; P.O, oral treatments or infusion on gastric tube; P.R, enema treatments *, mean ± SD or range or mean; DCQD, Dachengqi decoction; DHCQD, Dahuang chengqi decoction; THCQD, Taohe chengqi decoction; CSCQD, Chaishao chengqi decoction; ZYCQD, Zengye chengqi decoction; QYCQD, Qingyi chengqi decoction; Outcomes 1: mortality rate; 2: multiple organ dysfunction syndrome (MODS); 3: time until relief of abdominal pain; 4: complications; 5: APACHE II score; 6: effectiveness; 7: serum level of IL-6; 8: serum level of TNF-α.

## Results

### *Literature retrieve and study characteristics*

A total of 2848 records were initially retrieved from the eight databases. After removing duplicates and screening the titles and abstracts, 418 studies were filtered out. About 333 studies were excluded for the reasons which combined with other interventions, not RCTs of study design, not for patients of SAP and the loss of main clinical outcomes after reading the full-text articles. Twenty-three RCTs with a total of 1865 participants were finally included in this study (Fig. 1). All these studies published between 2007 and 2020 were carried out in China. The sample size was ranged from 15 to 86, and the duration of treatment was 5–30 days. The control groups received RT, whereas the intervention group replenished with CQSDs. The characteristics were showed in Table 1. While information about components of prescriptions were presented in Table 2 and frequency in Table 3.

### *Risk of bias*

All the 23 RCTs were assessed for risk of bias (Fig. 2). Twelve RCTs referred to the generation of random sequence generation while the rest of them were not. But there was a lack of the information about allocation concealment, blinding of participants and personnel and blinding of outcome assessment. All the RCTs had a low risk of bias in incomplete outcomes data and selective reporting.

The blinding of outcome was unclear risk due to the index assessment like recovery time of abdominal pain was evaluated without blinding.

**Table 2**
Components of CQSDs.

| Decoction name | First author | Year | Main components | Modified part |
|---|---|---|---|---|
| CSCQD | Yang | 2010 | 10 g Aurantii fructus immaturus, 10 g Magnoliae officinalis cortex, 10 g Natrii sulfas, 15 g Rhei radix et rhizoma | 10 g Bupleuri radix, 10 g Paeoniae radix alba, 10 g Scutellariae radix |
| | Ling,et al. | 2013 | 10 g Magnoliae officinalis cortex, 10 g Aurantii fructus immaturus, 30 g Rhei radix et rhizoma, 30 g Natrii sulfas | 10 g Bupleuri radix, 10 g Paeoniae radix alba, 10 g Scutellariae radix |
| | He,et al. | 2014 | 10 g Aurantii fructus immaturus, 10 g Magnoliae officinalis cortex, 10 g Rhei radix et rhizoma | 10 g Bupleuri radix, 10 g Scutellariae radix, 10 g Natrii sulfas exsiccatus, 10 g Paeoniae radix alba |
| | Chen, et al. | 2019 | 10 g Magnoliae officinalis cortex, 10 g Aurantii fructus immaturus, 10 g Rhei radix et rhizoma | 10 g Bupleuri radix, 10 g Scutellariae radix, 10 g Paeoniae radix alba |
| Compound DCQD | Zhu,et al. | 2011 | 15 g Rhei radix et rhizoma, 20 g Magnoliae officinalis cortex, 10 g Natrii sulfas | 30 g Raphani semen, 15 g Aurantii fructus, 9 g Persicae sem, 15 g Paeoniae radix rubra |
| DCQD | Yan | 2007 | 10 g Aurantii fructus immaturus, 10 g Magnoliae officinalis cortex, 9–15 g Rhei radix et rhizoma, 9 g ,Natrii sulfas | 10 g Natrii sulfas exsiccatus, 10 g Bupleuri radix, 10 g Paeoniae radix alba, 10 g Scutellariae radix |
| | Chen, et al. | 2010 | 12 g Rhei radix et rhizoma, 6 g Natrii sulfas, 9 g Magnoliae officinalis cortex, 9 g Aurantii fructus immaturus | |
| | Yang | 2018 | 10 g Aurantii fructus immaturus, 10 g Magnoliae officinalis cortex, 10 g Rhei radix et rhizoma | 10 g Scutellariae radix, 10 g Bupleuri radix, 10 g Pinelliae rhizomea, 10 g Paeoniae radix alba, 10 g Natrii sulfas exsiccatus |
| | Xiao,et al. | 2018 | Rhei radix et rhizoma, Magnoliae officinalis cortex, Aurantii fructus immaturus, Natrii sulfas | |
| | Guan | 2020 | 12 g Rhei radix et rhizoma,12 g Aurantii fructus immaturus, 24 g Magnoliae officinalis cortex, 6 g Natrii sulfas | |
| Dachengqi granules | D.-l. Jiang, et al. | 2016 | modified Da Chengqi granules (11.2 g/bag (Jiangyin Tianjiang Pharmaceutical Co., Ltd. Wuxi, China)) | |
| DHCQD | Li,et al. | 2018 | 15 g Rhei radix et rhizoma, 10 g Natrii sulfas, 10 g Aurantii fructus immaturus, 10 g Magnoliae officinalis cortex | 6 g Glycyrrhizae radix et rhizoma, 15 g Bupleuri radix, 10 g Carthami flos, 10 g Astragali radix, 10 g Scutellariae radix, 10 g Paeoniae radix alba, 10 g Angelicae sinensis radix, 10 g Persicae sem |
| | Wang, et al. | 2015 | 10 g Magnoliae officinalis cortex, 10 g Aurantii fructus immaturus, 15 g Rhei radix et rhizoma, 10 g Natrii sulfas | 15 g Bupleuri radix, 10 g Scutellariae radix, 10 g Paeoniae radix alba |
| Modified CSCQD | Zhao, et al. | 2019 | 15 g Rhei radix et rhizoma, 15 g Magnoliae officinalis cortex, 15 g Aurantii fructus immaturus | 15 g Bupleuri radix, 15 g Scutellariae radix, 30 g Paeoniae radix alba, 4 g Notoginseng radix et rhizoma, 15 g Salviae miltiorrhizae radix rhizoma, 4 g Fritillariae thunbergii bulbus, 15 g Gall1 gigerii endothelium corneum, 8 g Citri reticulatae pericarpium, 15 g Sargentodoxae caulis, 9 g Nelumbinis folium, 6 g Glycyrrhizae radix et rhizome |
| DCQD addition | Li,et al. | 2014 | 15 g Aurantii fructus immaturus, 15 g Rhei radix et rhizoma, 15 g Natrii sulfas | 15 g Bupleuri radix, 15 g Gardeniae fructus, 15 g Raphani semen, 15 g Sophorae flavescentis radix, 15 g Corydalis rhizoma, 20 g Salviae miltiorrhizae radix rhizoma, 20 g Artemisiae scopariae herba, 30 g Paeoniae radix alba, 10 g Paridis rhizoma, 10 g Linderae radix, 10 g Glycyrrhizae radix et rhizoma |
| Modified DCQD | Ma | 2008 | 30 g Rhei radix et rhizoma, 15 g Natrii sulfas, 15 g Aurantii fructus immaturus, 15 g Magnoliae officinalis cortex | 30 g Artemisiae scopariae herba, 15 g Gardeniae fructus, 15 g Aucklandiae radix, 15 g Paeoniae radix alba, 15 g Corydalis rhizoma |
| | Li,et al. | 2010 | 30–60 g Rhei radix et rhizoma, 12 g Magnoliae officinalis cortex, 12 g Aurantii fructus immaturus, 15 g Natrii sulfas | 15 g Bupleuri radix, 12 g Aucklandiae radix, 20 g Corydalis rhizoma, 15 g Gardeniae fructus, 20 g Salviae miltiorrhizae radix rhizoma |
| | Zhang, et al. | 2019 | 10 g Magnoliae officinalis cortex, 10 g Aurantii fructus immaturus, 15 g Natrii sulfas, 15 g Rhei radix et rhizome | Modified according to situation. |
| | Men,et al. | 2018 | 15 g Rhei radix et rhizoma, 30 g Natrii sulfas, 15 g Magnoliae officinalis cortex, 15 g Aurantii fructus immaturus | 12 g Chuanxiong rhizoma, 10 g Persicae sem, 15 g Lonicerae japonicae flos, 15 g Scutellariae radix, 18 g Forsythiae fructus, 15 g Taraxaci herba, 12 g Bupleuri radix, 12 g Aucklandiae radix, 10 g Corydalis rhizoma |
| QYCQD | Zhang, et al. | 2014 | 30 g Rhei radix et rhizoma, 10 g Natrii sulfas, 10 g Aurantii fructus immaturus, 10 g Magnoliae officinalis cortex | 12 g Bupleuri radix, 10 gScutellariae radix, 10 g Paeoniae radix alba, 10 g Coptidis rhizoma, 20 g Salviae miltiorrhizae radix rhizoma |
| Qingfei chengqi granules | Li Jing, et al. | 2014 | Qingfei chengqi granules (11.2 g/bag (Jiangyin Tianjiang Pharmaceutical Co., Ltd. Wuxi, China)) | |
| THCQD | Sun,et al. | 2017 | 15 g Rhei radix et rhizoma, 8 g Natrii sulfas | 15 g Persicae sem, 8 g Cinnamomi ramulus, 8 g Glycyrrhizae radix et rhizoma |
| ZYCQD | Chen, et al. | 2007 | 20 g Rhei radix et rhizoma, 10 g Magnoliae officinalis cortex, 20 g Natrii sulfas | 15 g Scrophulariae radix, 20 g Ophiopogonis radix, 20 g Rehmanniae radix |

CSCQD, Chaishao chengqi decoction; DCQD, Dachengqi decoction; DHCQD, Dahuang chengqi decoction; THCQD, Taohe chengqi decoction; QYCQD, Qingyi chengqi decoction; ZYCQD, Zengye chengqi decoction.

**Table 3**
Usage frequency of single herb in included studies.

| Latin name (Pinyin) | Frequency | Frequency in 21 trials (%) |
|---|---|---|
| Rhei radix et rhizoma (Dahuang) | 21 | 100.0 |
| Magnoliae officinalis cortex (Houpo) | 19 | 90.5 |
| Aurantii fructus immaturus (Zhishi) | 18 | 85.7 |
| Natrii sulfas (Mangxiao) | 17 | 81.0 |
| Bupleuri radix (Chaihu) | 13 | 61.9 |
| Paeoniae radix alba (Baishao) | 12 | 57.1 |
| Scutellariae radix (Huangqin) | 11 | 52.4 |
| Corydalis rhizoma (Yanhusuo) | 4 | 19.0 |
| Persicae sem (Taoren) | 4 | 19.0 |
| Salviae miltiorrhizae radix rhizoma (Danshen) | 4 | 19.0 |
| Glycyrrhizae radix et rhizoma (Gancao) | 4 | 19.0 |
| Natrii sulfas exsiccatus (Xuanmingfen) | 3 | 14.3 |
| Gardeniae fructus (Zhizi) | 3 | 14.3 |
| Aucklandiae radix (Muxiang) | 3 | 14.3 |
| Raphani semen (Laifuzi) | 2 | 9.5 |
| Artemisiae scopariae herba (Yinchen) | 2 | 9.5 |
| Astragali radix (Huangqi) | 1 | 4.8 |
| Notoginseng radix et rhizoma (Sanqi) | 1 | 4.8 |
| Carthami flos (Honghua) | 1 | 4.8 |
| Linderae radix (Wuyao) | 1 | 4.8 |
| Angelicae sinensis radix (Danggui) | 1 | 4.8 |
| Aurantii fructus (Zhiqiao) | 1 | 4.8 |
| Gall1 gigerii endothelium corneum (Jineijin) | 1 | 4.8 |
| Sargentodoxae caulis (Daxueteng) | 1 | 4.8 |
| Nelumbinis folium (Heye) | 1 | 4.8 |
| Lonicerae japonicae flos (Jinyinhua) | 1 | 4.8 |
| Paeoniae radix rubra (Chishao) | 1 | 4.8 |
| Citri reticulatae pericarpium (Chenpi) | 1 | 4.8 |
| Fritillariae thunbergii bulbus (Zhebeimu) | 1 | 4.8 |
| Sophorae flavescentis radix (Kushen) | 1 | 4.8 |
| Paridis rhizoma (Chonglou) | 1 | 4.8 |
| Cinnamomi ramulus (Guizhi) | 1 | 4.8 |
| Scrophulariae radix (Xuanshen) | 1 | 4.8 |
| Ophiopogonis radix (Maidong) | 1 | 4.8 |
| Rehmanniae radix (Shengdi) | 1 | 4.8 |
| Taraxaci herba (Pugongyin) | 1 | 4.8 |
| Forsythiae fructus (Lianqiao) | 1 | 4.8 |
| Coptidis rhizoma (Huangliang) | 1 | 4.8 |
| Chuanxiong rhizoma (Chuanxiong) | 1 | 4.8 |
| Pinelliae rhizomea (Banxia) | 1 | 4.8 |

*Primary outcomes*

*Mortality rate*

A total of 21 studies reported the impact on mortality in 1681 patients (Fig. 3A). A significant reduction in mortality was observed in the CQSDs intervention group compared to control group (RR: 0.41, 95% CI: 0.32 to 0.53, $I^2 = 0.0\%$, $p = 0.992$). Sensitivity analysis was carried out and the results showed the reliability of our conclusion (Fig. 3B). Funnel plot and Egger's test revealed potential publication bias of these studies, with a *P*-value equals to 0.001 in Egger's test (Fig. 3C and 3D).

*MODS*

Nine RCTs comprising 841 patients (433 in CQSDs intervention group and 408 in control group) reported MODS as an outcome measure (Fig. 4). In this outcome, CQSDs displayed an advantage over control group in reducing MODS risk (RR: 0.48, 95%CI:0.36 to 0.63, $I^2 = 0.0\%$, $p = 0.885$).

*Secondary outcomes*

*Time until relief of abdominal pain*

Twelve RCTs reported the time until relief of abdominal pain (Fig. 5A). The results showed that CQSDs treatment shortened this parameter in 857 patients with SAP (SMD: −1.66, 95%CI: −1.98 to −1.35, Fig. 5B). Heterogeneity was high ($I^2 = 74.4\%$, $p = 0.000$), thus a random-effects model was used. The funnel plot and egger's test (Fig. 5C and 5D) indicated that there was no potential publication bias ($p = 0.198$).

*APACHE II score*

Four articles reported the information of APACHE II score (Fig. 6). The results revealed that CQSDs reduced APACHE II score at seventh day in 336 SAP patients (SMD: −1.04, 95%CI: −1.55 to −0.54). The random-effects model was utilized to evaluate the pooled effect size because of the high heterogeneity from Guan's study (Guan 2020) ($I^2 = 78.2\%$, $p = 0.003$).

*Complications*

Nine included studies involving 689 participants reported complications as an outcome (Fig. 7A). The pooled rates indicated that CQSDs significantly reduced the incidence of complications in SAP patients (RR: 0.52, 95%CI: 0.39 to 0.68;$I^2 = 0.00\%$, $p = 0.716$).

*Effectiveness*

Fig. 7B shows the result from the fixed-effects model combining the RR for SAP. Among the 23 studies, 7 trials showed significant improvement in effectiveness after treatment of CQSDs (RR: 1.22, 95% CI: 1.14 to 1.31;$I^2 = 0.0\%$, $p = 0.757$).

*IL-6*

IL-6 was reported in 7 studies involving 566 SAP patients (Fig. 7C). There was significant heterogeneity among these studies ($I^2 = 91.2\%$, $p = 0.000$) and a random-effects model was conducted. The results suggested that CQSDs effectively reduced this measure compared with control group (SMD: −1.5, 95%CI: −2.16 to −0.85). No source of heterogeneity was found.

*TNF-α*

To investigate the effect of CQSDs on TNF-α level in SAP patients, 5 studies involving 436 participants were included (Fig. 7D). Given that significant heterogeneity ($I^2 = 83.8\%$, $p = 0.000$) was observed among the studies, we applied a random-effects model. The combined result showed that intervention group was effective in decreasing the TNF-α counts (SMD: −1.18, 95%CI: −1.71 to −0.65). No source of heterogeneity was found.

*Meta regression*

The analyses regarding the relief time of abdominal pain met the situations to make meta regression. Among 4 variables, the type of decoctions had significant correlation with the heterogeneity. The conclusions of these indexes kept consistent with the results before subgroup analysis, which illustrated stable effect of CQSDs on relieving pain (Supplementary Table 1–2). At the same time, modified CSCQD showed advantage to shorten the time of abdominal pain than other decoctions (Supplementary Table 3).

*Quality assessment of evidence*

The summary of findings and the GRADE recommendations were illustrated in Table 4. Additionally, the certainty of the evidence for mortality rate, MODS, time until relief of abdominal pain, and APACHE II was low, while for complications, effectiveness, IL-6 and TNF-α was moderate.

## Discussion

*Summary of main findings*

This meta-analysis indicated that CQSDs, on top of RT, significantly reduced mortality rate (RR: 0.41, 95%CI: 0.32 to 0.53, low certainty

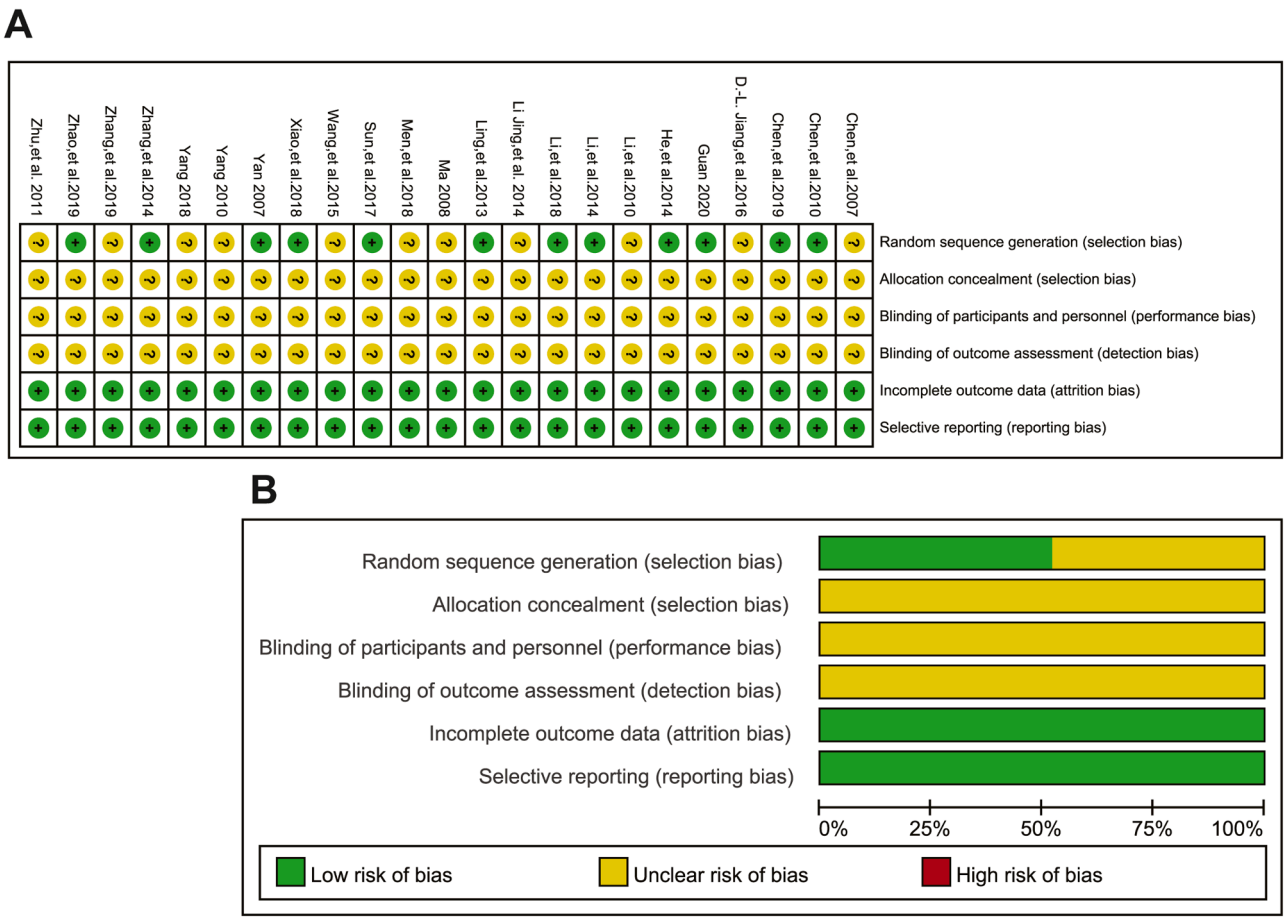



**Fig 2.** (A) Risk of bias summary. (B) Risk of bias graph.

evidence) and the incidence of MODS (RR: 0.48, 95% CI: 0.36 to 0.63, low certainty evidence) in patients with SAP. Besides, CQSDs showed advantages in reducing remission time of abdominal pain (SMD: −1.66, 95%CI: −1.98 to −1.35, low certainty evidence) and complications (RR:0.52, 95%CI: 0.39 to 0.68, moderate certainty evidence). The results also reported the improvements of therapeutic effectiveness (RR:1.22, 95%CI: 1.14 to 1.31, moderate certainty evidence) and APACHE II score (SMD: −1.04, 95%CI: −1.55 to −0.54, low certainty evidence). CQSDs, as supplement therapies, lowered the production of serum level of IL-6 (SMD: −1.50, 95%CI: −2.16 to −0.85, moderate certainty evidence) and TNF-α (SMD: −1.18, 95%CI: −1.71 to −0.65, moderate certainty evidence). Taken together, our results support the conclusion that application of CQSDs could alleviate the disease severity by preventing organ failure, reducing inflammatory mediators' level, and ameliorating pain in SAP patients.

*Strengths*

In Traditional Chinese Medicine (TCM) theories, the pathologies of AP mainly involve stagnation of qi and heat, which result in blockage of blood, and dysfunction of *zang-fu viscera*, finally lead to organ failure (Li et al., 2017; Yang et al., 2021). According to the differentiation of syndromes by eight principles of TCM theories, most AP pathology fit the syndrome of interior excess and heat, especially those develop to severe conditions. Thus, the treatments based on syndrome differentiation emphasis the principle of clearing purgation and heat, which is the key step to stop the process from mild AP to SAP, and this treating strategy exactly represents the action mechanism of DCQD. Indications of DCQD mainly focus on the syndrome of solid viscera of *Yangming*, which manifests as abdominal pain, constipation or intestine obstruction. A meta-analysis included 60 eligible RCTs reported that DCQD could significantly improve intestine obstruction (Yang et al., 2014). DCQD has been proved to attenuate intestinal vascular endothelial Injury in SAP mice (Pan et al., 2017), other action mechanisms of DCQD include ameliorating pancreas inflammation (Ma et al., 2020), recovering intestinal mucosal permeability (Chen, Li et al. 2010), reserving metabolism dysfunction (Li et al., 2015) and reducing ROS generation (Zhao et al., 2013). The sovereign drug of DCQD is *Rhei radix et rhizoma* (Dahuang) and emodin is the main active component, which has been proved to contribute to recover intestinal mucosa injury in experimental SAP via inhibitive mechanism on caspase-1 (Ning et al., 2017), and regulation toward miR-218a-5p expression (Zhang et al., 2020). Other studies confirmed that emodin could recover intestinal mucosal barrier injury by inflammatory and oxidative mechanisms (Qian et al., 2020; Shang et al., 2021), modulate microbiota by increasing the alpha- and beta-diversity of gut microbiota (Gao et al., 2021; Zhang et al., 2022), and simulate regulatory T-cell immune responses to trigger intestinal immunity (Mabwi et al., 2022).

The current study revealed the clinical value of recovering intestinal function in the managements of SAP and reducing MODS. It is well accepted that intestinal homeostasis plays an important role in the managements of SAP (Patel et al., 2021). When pancreas injury occurred as the first hit, gut became the place where the second hit happened. An animal study indicated that the application of the two-hit strategy could successfully induce SAP models accompanied by multiple organ failures with over 30% mortality (Yang et al., 2022). The deterioration of gut dysfunction has a close relationship with MODS in AP patients. Intestine is both victim and culprit of SAP. When AP-induced intestinal injury occurred, intestinal ischemia, reperfusion and barrier failure might participate in the formation of MODS (Flint and Windsor 2003). This

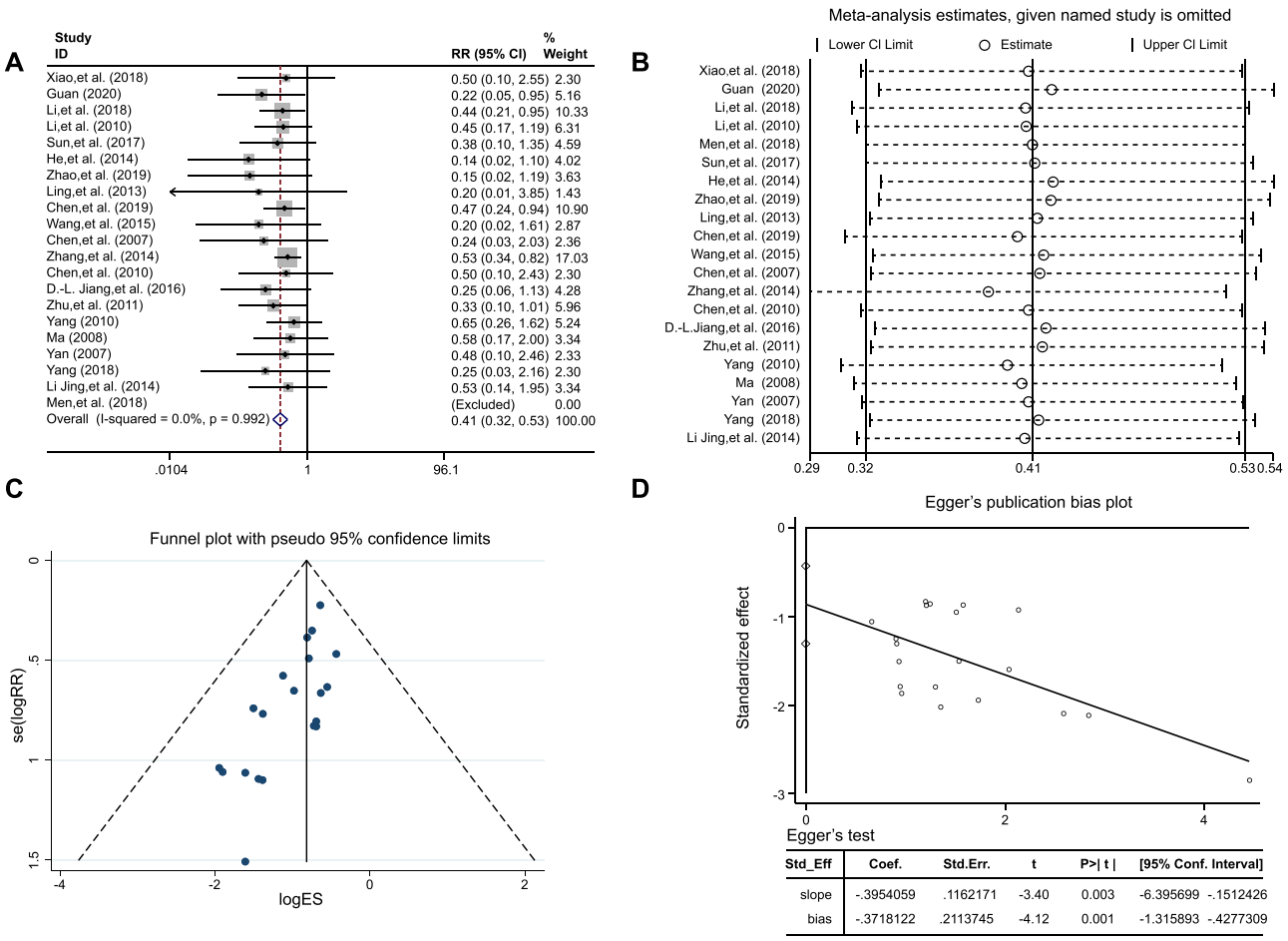



**Fig 3.** Meta-analysis of mortality rate in SAP patients after treating with CQSDs. (A) Forest plot showed mortality. (B) Sensitivity analysis demonstrated the reliability of CQSDs to affect mortality rate. (C) Filled funnel plot for the publication bias. (D) Egger's funnel plot analysis revealed potential publication bias.

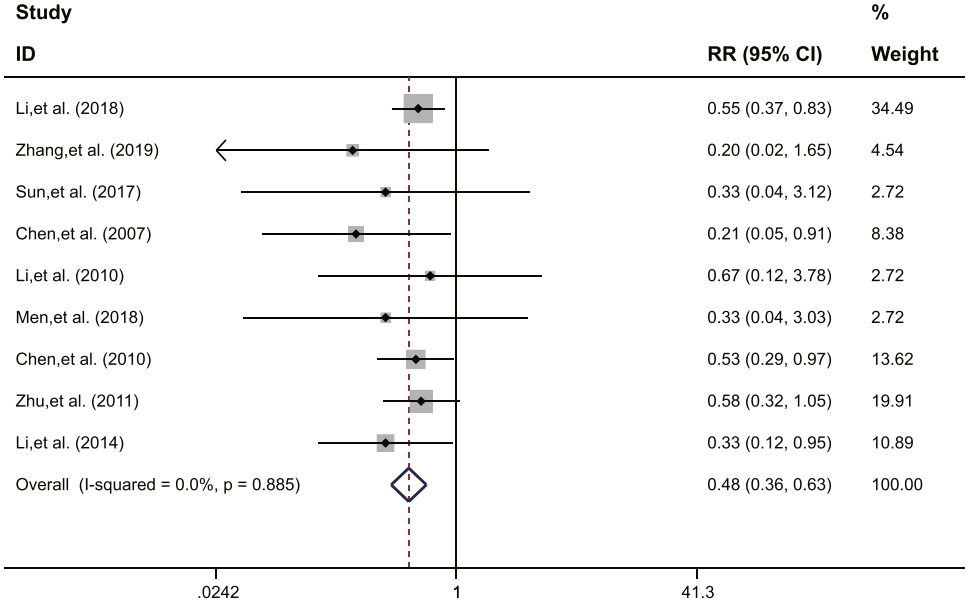



**Fig 4.** Forest plot showed MODS after CQSDs treatment.

process was initiated from decrease of gut motility, then developed to the translocation of gut bacteria, inflammatory amplification, microcirculatory disturbance, systematic inflammation response syndrome and finally organ failure. Besides, gut dysfunction could trigger gut-lymph inflammation amplification via mesenteric lymphatic flow to injury multiple organs (Landahl et al., 2015). Meanwhile, gut

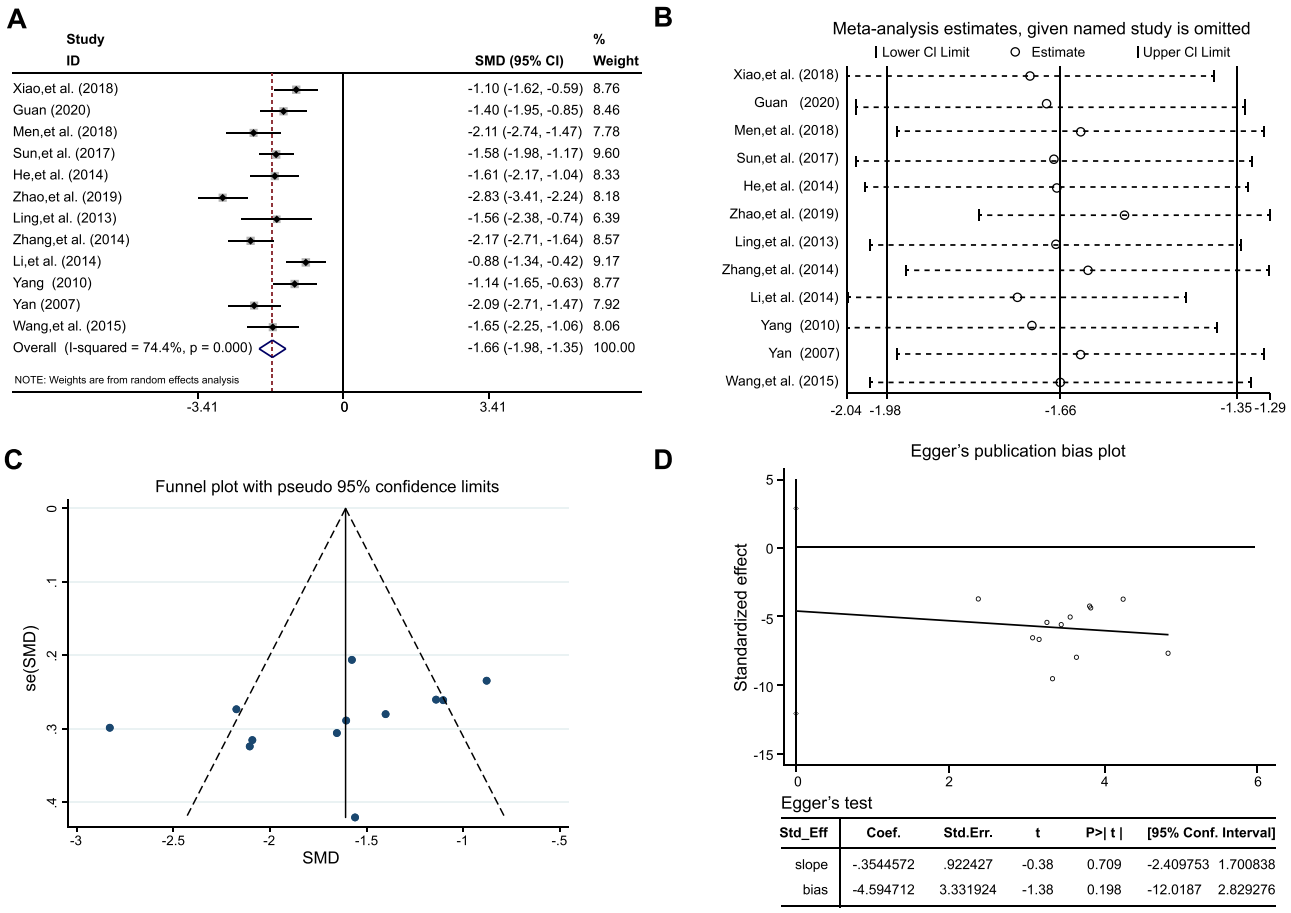



**Fig 5.** Meta-analysis of time until relief of abdominal pain in SAP patients after treating with CQSDs. (A) Forest plot showed remission time of abdominal pain after decoction treatments. (B) Sensitivity analysis illustrated the reliability of CQSDs treatment to affect the duration of abdominal pain. (C) Filled funnel plot for the publication bias. (D) Egger's funnel plot analysis revealed potential publication bias.

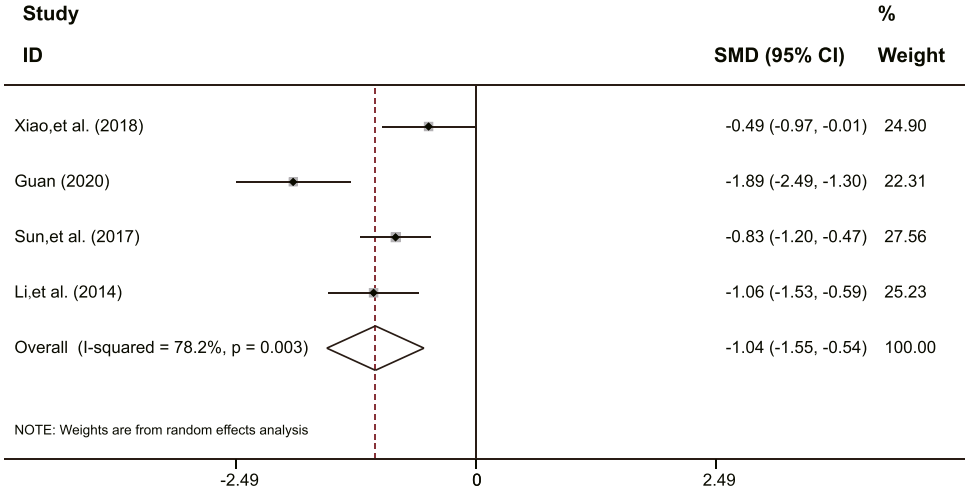



**Fig 6.** Forest plot showed APACHE II score after treating with CQSDs.

microbiome could protect SAP-induced lung injury by producing short-chain fatty acids (Wang et al., 2022). Thus, the dysfunction of intestine is implicated in the development of MODS and clinical mortality. The core therapeutic principle of CQSDs is consistent with their basic formula, purgation to clear the intestine, which could improve gut function. Several formulas modified from CQSDs could protect intestinal function and subsequently improve disease severity in SAP, including recovering intestinal mucosal barrier by lowering bacterial translocation of mesenteric lymph nodes (Qin et al., 2015), and increasing gut motility by regulating protein kinase C-mediated calcium release in colonic smooth muscle cells (Zhang et al., 2017). Our results indicated that, purgation method as the main strategy in TCM, which could effectively improve intestinal function, plays an important role in the treatment of SAP. In another word, the action mechanism of CQSDs to reduce MODS

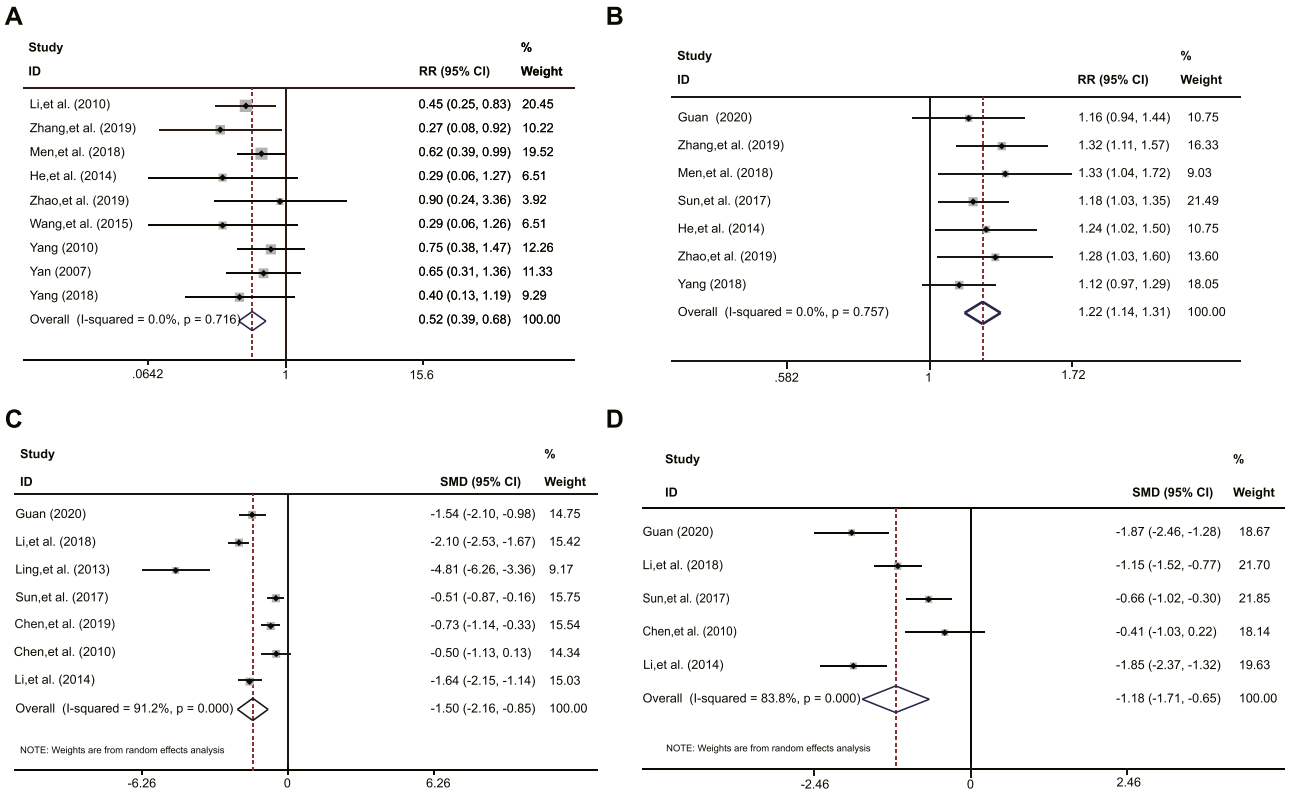



**Fig 7.** Forest plots showed (A) Complications, (B) Effectiveness, (C) Serum IL-6 and (D)Serum TNF-α after CQSDs treatment.

**Table 4**
Summary of findings for included studies.

| CQSDs plus routine therapies compared to routine therapies for severe acute pancreatitis patients<br>Patient or population: severe acute pancreatitis patients<br>Intervention: CQSDs plus routine therapies<br>Comparison: routine therapies | | | | | |
|---|---|---|---|---|---|
| Outcomes | Anticipated absolute effects* (95% CI)<br>Risk with RT | Relative effect (95% CI)<br>Risk with CQSDs plus RT | N° of participants (studies) | Certainty of the evidence (GRADE) | |
| Mortality Rate | 209 per 1000 | 86 per 1000 (67 to 111) | RR 0.41 (0.32 to 0.53) | 1681 (21 RCTs) | ⨁⨁◯◯ Low[a,b] |
| MODS | 262 per 1000 | 126 per 1000 (94 to 165) | RR 0.48 (0.36 to 0.63) | 841 (9 RCTs) | ⨁⨁◯◯ Low[a,b] |
| Time until relief of abdominal pain | – | SMD 1.66 SD lower (1.98 lower to 1.35 lower) | – | 857 (12 RCTs) | ⨁⨁◯◯ Low[a,c] |
| APACHE II score | – | SMD 1.04 SD lower (1.55 lower to 0.54 lower) | – | 336 (4 RCTs) | ⨁⨁◯◯ Low[a,c] |
| Complications | 314 per 1000 | 163 per 1000 (122 to 213) | RR 0.52 (0.39 to 0.68) | 689 (9 RCTs) | ⨁⨁⨁◯ Moderate[a] |
| Effectiveness | 767 per 1000 | 936 per 1000 (875 to 1000) | RR 1.22 (1.14 to 1.31) | 607 (7 RCTs) | ⨁⨁⨁◯ Moderate[a] |
| Serum IL-6 | – | SMD 1.5 SD lower (2.16 lower to 0.85 lower) | – | 566 (7 RCTs) | ⨁⨁⨁◯ Moderate[c] |
| Serum TNF-α | – | SMD 1.18 SD lower (1.71 lower to 0.65 lower) | – | 436 (5 RCTs) | ⨁⨁⨁◯ Moderate[c] |

CI: confidence interval; RR: risk ratio; SMD: standardised mean difference; RT: routine therapies; CQSDs: chengqi-series decoctions.
GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

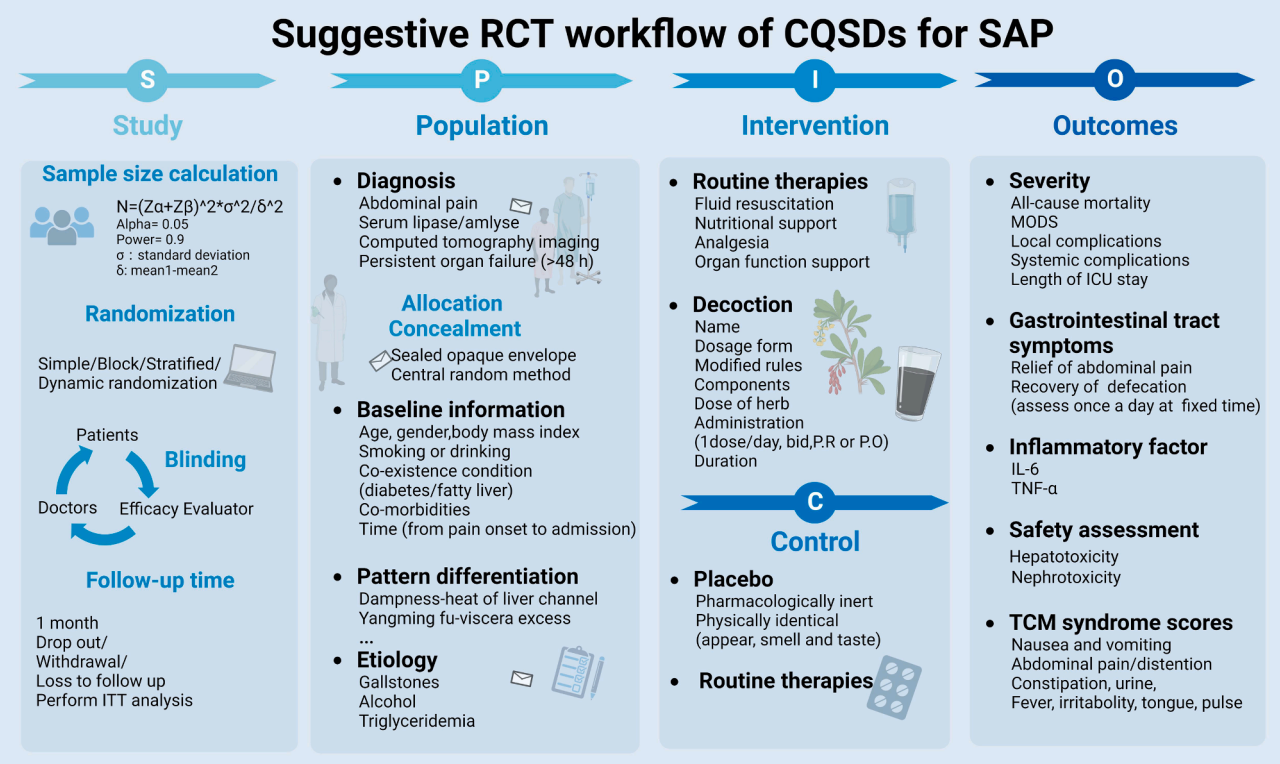



**Fig 8.** Suggestive randomized controlled trials workflow of chengqi-series decoctions for severe acute pancreatitis.

and death rate is mainly contributed by the effect of improving gut motility and removing the intestinal content.

Another notable finding of our research is the superior effect of modified CSCQD in pain relief of SAP patients. Pain, as an outward sign of the illness, also represents neurogenic inflammation that accelerates disease severity of AP (Liddle and Nathan 2004; Ramnath and Bhatia 2006). In this outcome, modified CSCQD as adjuvant treatment showed the best effect. CSCQD is composed by DCQD and *Bupleuri radix* (Chaihu), *Paeoniae radix alba* (Baishao), *Scutellariae radix* (Huangqin). In TCM theories, one of pathology of pain is stagnation of liver qi. *Bupleuri radix-Paeoniae radix alba* (Chaihu-Baishao) is a widely used drug pair to disperse stagnated liver-qi for relieving qi stagnation. *Scutellariae radix* (Huangqin) could clear the heat. The pain of SAP mainly feels like burning and stabbing. Thus, the addition of the 3 drugs exhibited a better effect in pain relief compared with other CQSDs formulas. Analgesia can not only improve the life quality of SAP patients, but also, which is more important, reduce neurogenic inflammation, an important pathology contributes to AP aggravation (Barreto et al., 2021). Clinical evidence suggested that, epidural anesthesia could significantly decrease the mortality in SAP patients (Jabaudon et al., 2018), and nonsteroidal anti-inflammatory drugs (NSAIDs) could reduce SAP incidence and serum IL-6 and TNF-α (Huang et al., 2020).

As we expected, mortality rate and APACHE II score showed significant improvements after CQSDs treatment. APACHE II score helps distinguish mild from SAP and to predict death. Along with our results, two meta-analysis which concerned add-on effect of *Rhei radix et rhizoma* (Dahuang) to RT (WMD −1.16; 95% CI −1.91 to −0.41,5 trials; MD = −1.37 95% CI (−1.92 to −0.81, 7 trails) in AP (LD 2020; Zhou et al., 2016). Our analysis illustrated that APACHE II score has reduced with decoction treatments after 7 days.

In addition, our results confirmed the inhibitive effect of CQSDs on serum IL-6 and TNF-α. Serum IL-6 is associated with respiratory failure in AP (Mayer et al., 2000; Minkov et al., 2015), it could trans-signaling phosphorylated the STAT3 pathways and result the neutrophil attractant CXCL1 to mediate lung damage (Scheller et al., 2014; Zhang et al., 2013). There is also a clear association between TNF-α and lung injury. Knockdown of this gene improved survival and reduced complications in rats (Hughes et al., 1996; Zhang et al., 2001). Large number of experiments and clinical studies showed the active components of CQSDs could reduce the production of inflammatory factors. For instance, emodin could adjust the balance of macrophage M1 and M2, and regulate cellular inflammatory pathways, suppressing the serum level of TNF-α, IL-6, IL-1β (Cui et al., 2020). Besides, *Magnoliae officinalis cortex (Houpo)* could regulate signaling cascades composition and generate an anti-inflammatory response (Poivre and Duez 2017). Thus, compared with single use of inflammatory factor inhibitor, decoctions possess the advantage of multi-targeting to confront the sophisticated pathological process involving immune, inflammation, and nervous system.

## Conclusions

Taken together, according to our study, CQSDs seem to be effective for SAP patients with notable reductions in mortality, MODS, APACHE II score and abdominal pain with low quality evidence; and improve complications, effectiveness, serum IL-6 and TNF-α levels with moderate quality evidence. Moreover, our research emphasized the key role of intestinal recovery in SAP.

## Limitations and future perspectives

There are several limitations in this meta-analysis. Firstly, the poor methodological quality of included trials and the inadequate information about the botanical material led to the infallible results and heterogeneity. Secondly, our findings may not be applicable to other broader populations since all the included trials were performed in China. Thirdly, subgroup analysis is not deep enough due to the limited number of trials included in each outcome. Finally, publication bias would be resulted from inaccurate reports of negative outcomes.

We propose that future RCTs of CQSDs in treating SAP should aim at recruiting larger cohorts from multi-center, which contain sufficient

statistic power to examine their efficacy. A well-designed RCT should follow the principles of random allocation, blinding and follow-up (Fig. 8). The study subject should not be limited to Chinese people alone, and detailed information regarding their baseline information, etiology, severity levels and Chinese pattern differentiation are required. Regarding to the control group and the intervention group, routine therapies including fluid resuscitation, analgesia use, nutritional support, and organ function support should be given; the CQSDs intervention group need to additionally provide the constitutive medicinal plant materials, treatment dose, administration route and duration. It is worth noting that the choice of outcome indicators is also critical. Mortality, MODS, complications, and length of ICU stay are possible choices for the main outcome measure of severity. Other secondary outcomes might be chosen from gut tract symptoms, inflammatory factors, side effect and TCM symptom scores. In addition, we recommended that CQSDs should be employed in the early stage of SAP. Evidence showed that taking CQSDs orally combined with enema administration in early stage of AP could be clinically effective on gastrointestinal symptoms (WEI et al., 2021). According to the studies we included, CQSDs were effective when be given twice with one dose a day for oral or enema administration in most cases.

## Declaration of Competing Interest

None.

*Acknowledgments*

The study was supported by National Natural Science Foundation of China (No. 82104598, Chenxia Han).

*CRediT authorship contribution statement*

Qing Xia and Dan Du conceived and designed the review. Juan Lin, Chenxia Han, and Ning Dai conducted the search and screening of articles. Juan Lin and Chenxia Han extracted the data. Juan Lin, Chenxia Han, Ning Dai and Siwei Bi evaluated the methodological quality of each RCT, the evidence quality and conducted the statistical analysis. Chenxia Han and Juan Lin drafted the manuscript and revised the manuscript. All authors reviewed and approved the final manuscript.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.phymed.2023.154727.

## References

Banks, P.A., Bollen, T.L., Dervenis, C., Gooszen, H.G., Johnson, C.D., Sarr, M.G., Tsiotos, G.G., Vege, S.S., 2013. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. Gut 62 (1), 102–111.

Barreto, S.G., Habtezion, A., Gukovskaya, A., Lugea, A., Jeon, C., Yadav, D., Hegyi, P., Venglovecz, V., Sutton, R., Pandol, S.J., 2021. Critical thresholds: key to unlocking the door to the prevention and specific treatments for acute pancreatitis. Gut 70 (1), 194–203.

Boxhoorn, L., Voermans, R.P., Bouwense, S.A., Bruno, M.J., Verdonk, R.C., Boermeester, M.A., van Santvoort, H.C., Besselink, M.G., 2020. Acute pancreatitis. Lancet 396 (10252), 726–734.

Buchler, M.W., Gloor, B., Muller, C.A., Friess, H., Seiler, C.A., Uhl, W., 2000. Acute necrotizing pancreatitis: treatment strategy according to the status of infection. Ann. Surg. 232 (5), 619–626.

CHEN, H., LI, F., JIA, J.-g., DIAO, Y.-p., LI, Z.-x., SUN, J.-b., 2010. Effects of traditional Chinese medicine on intestinal mucosal permeability in early phase of severe acute pancreatitis. Chin. Med. J. 123 (12), 1537–1542.

CHEN, T., GAO, J., BAI, D., LIU, R., ZHANG, H., 2023. Meta-analysis on the Effectiveness and Safety of Chaiqin Chengqi Decoction Combined with Western Medicine in the Treatment of Acute Pancreatitis. Guangming Tradit Chin Med 38 (02), 212–217.

Cui, Y., Chen, L.J., Huang, T., Ying, J.Q., Li, J., 2020. The pharmacology, toxicology and therapeutic potential of anthraquinone derivative emodin. Chin J Nat Med 18 (6), 425–435.

Flint, R.S., Windsor, J.A., 2003. The role of the intestine in the pathophysiology and management of severe acute pancreatitis. HPB (Oxford) 5 (2), 69–85.

Gao, R., Wang, C., Han, A., Tian, Y., Ren, S., Lv, W., Chen, A., Zhang, J., 2021. Emodin Improves Intestinal Health and Immunity through Modulation of Gut Microbiota in Mice Infected by Pathogenic Escherichia coli O(1). Animals (Basel) 11 (11).

Garg, P.K., Singh, V.P., 2019. Organ Failure Due to Systemic Injury in Acute Pancreatitis. Gastroenterology 156 (7), 2008–2023.

Ge, P., Luo, Y., Okoye, C.S., Chen, H., Liu, J., Zhang, G., Xu, C., Chen, H., 2020. Intestinal barrier damage, systemic inflammatory response syndrome, and acute lung injury: a troublesome trio for acute pancreatitis. Biomed. Pharmacother. 132, 110770.

Guan, W., 2020. Effects of Dachengqi Decoction with Traditional Chinese Medicine Enema on Prognosis of Patients with Severe Acute Pancreatitis. J Hubei Univ Chin. Med. 22 (01), 64–67.

Higgins J.P.T., Thomas J., Chandler J., Cumpston M., Li T., Page M.J. and W.V. (editors), 2022. Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). Cochrane. Available from www.training.cochrane.org/handbook.

Hines, O.J., Pandol, S.J., 2019. Management of severe acute pancreatitis. BMJ 367, l6227.

Hu, J., Li, P., Zhang, T., 2018. Rhubarb combined with trypsin inhibitor for severe acute pancreatitis: a systematic review and meta-analysis. Phytother. Res. 32 (8), 1450–1458.

Huang, Z., Ma, X., Jia, X., Wang, R., Liu, L., Zhang, M., Wan, X., Tang, C., Huang, L., 2020. Prevention of Severe Acute Pancreatitis With Cyclooxygenase-2 Inhibitors: a Randomized Controlled Clinical Trial. Am. J. Gastroenterol. 115 (3), 473–480.

Hughes, C.B., Grewal, H.P., Gaber, L.W., Kotb, M., El-din, A.B., Mann, L., Gaber, A.O., 1996. Anti-TNFalpha therapy improves survival and ameliorates the pathophysiologic sequelae in acute pancreatitis in the rat. Am. J. Surg. 171 (2), 274–280.

Jabaudon, M., Belhadj-Tahar, N., Rimmele, T., Joannes-Boyau, O., Bulyez, S., Lefrant, J. Y., Malledant, Y., Leone, M., Abback, P.S., Tamion, F., Dupont, H., Lortat-Jacob, B., Guerci, P., Kerforne, T., Cinotti, R., Jacob, L., Verdier, P., Dugernier, T., Pereira, B., Constantin, J.M., Azurea, N., 2018. Thoracic Epidural Analgesia and Mortality in Acute Pancreatitis: a Multicenter Propensity Analysis. Crit. Care Med. 46 (3), e198–e205.

Ji, Y.-.F., Zhang, X.-.M., Mitchell, D.G., Li, X.-.H., Chen, T.-.W., Li, Y., Bao, Z.-.G., Wei Tang, W., Xiao, B., Huang, X.-.H., Yang, L., 2017. Gastrointestinal tract involvement in acute pancreatitis: initial findings and follow-up by magnetic resonance imaging. Quant Imaging Med Surg 7 (6), 641–653.

Landahl, P., Ansari, D., Andersson, R., 2015. Severe Acute Pancreatitis: gut Barrier Failure, Systemic Inflammatory Response, Acute Lung Injury, and the Role of the Mesenteric Lymph. Surg. Infect. (Larchmt) 16 (6), 651–656.

Lankisch, P.G., Apte, M., Banks, P.A., 2015. Acute pancreatitis. Lancet 386 (9988), 85–96.

LD, C.X.D.L.H.H.W., 2020. A meta-analysis of the efficacy of enteral nutrition combined with rhubarb in the treatment of severe acute pancreatitis. Jiangxi Med. J. 55 (05), 55–558.

Lee, P.J., Papachristou, G.I., 2019. New insights into acute pancreatitis. Nat. Rev. Gastroenterol. Hepatol. 16 (8), 479–496.

Li, J., Zhang, S., Zhou, R., Zhang, J., Li, Z.F., 2017. Perspectives of traditional Chinese medicine in pancreas protection for acute pancreatitis. World J. Gastroenterol. 23 (20), 3615–3623.

Li, J., Zhu, S.F., Zhao, X.L., Liu, Y.X., Wan, M.H., Guo, H., Liu, Y.L., Gong, H.L., Chen, G. Y., Tang, W.F., 2015. Metabolomic profiles illuminate the efficacy of Chinese herbal Da-Cheng-Qi decoction on acute pancreatitis in rats. Pancreatology 15 (4), 337–343.

Liddle, R.A., Nathan, J.D., 2004. Neurogenic inflammation and pancreatitis. Pancreatology 4 (6), 551–559 discussion 559-560.

Lu, X., Xiao, W., Kang, X., Yu, J., Fan, Z., 2014. The effect of Chinese herbal medicine on non-biliogenic severe acute pancreatitis: a systematic review and meta-analysis. J. Ethnopharmacol. 155 (1), 21–29.

Ma, X., Jin, T., Han, C., Shi, N., Liang, G., Wen, Y., Yang, J., Fu, X., Lan, T., Jiang, K., Nunes, Q.M., Chvanov, M., Criddle, D.N., Philips, A.R., Deng, L., Liu, T., Windsor, J. A., Sutton, R., Du, D., Huang, W., Xia, Q., 2020. Aqueous extraction from dachengqi formula granules reduces the severity of mouse acute pancreatitis via inhibition of pancreatic pro-inflammatory signalling pathways. J. Ethnopharmacol. 257, 112861.

Mabwi, H.A., Lee, H.J., Hitayezu, E., Mauliasari, I.R., Pan, C.H., Mwaikono, K.S., Komba, E.V.G., Lee, C.G., Cha, K.H., 2022. Emodin modulates gut microbial community and triggers intestinal immunity. J. Sci. Food Agric.

Mayer, J., Rau, B., Gansauge, F., Beger, H.G., 2000. Inflammatory mediators in human acute pancreatitis: clinical and pathophysiological implications. Gut 47 (4), 546–552.

Minkov, G.A., Halacheva, K.S., Yovtchev, Y.P., Gulubova, M.V., 2015. Pathophysiological mechanisms of acute pancreatitis define inflammatory markers of clinical prognosis. Pancreas 44 (5), 713–717.

Ning, J.W., Zhang, Y., Yu, M.S., Gu, M.L., Xu, J., Usman, A., Ji, F., 2017. Emodin alleviates intestinal mucosal injury in rats with severe acute pancreatitis via the caspase-1 inhibition. Hepatobiliary Pancreat. Dis. Int. 16 (4), 431–436.

Ou, Z., Li, L., Wang, J., Yi, Z., Chen, G., Yuan, T., 2020. Meta-analysis of Dachengqi Decoction on Severe Acute Pancreatitis. J Emerg in Tradit Chin Med 29 (08), 1370–1373.

Page, M.J., Moher, D., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E., Chou, R., Glanville, J., Grimshaw, J.M., Hróbjartsson, A., Lalu, M.M., Li, T., Loder, E.W., Mayo-Wilson, E., McDonald, S., McGuinness, L.A., Stewart, L.A., Thomas, J., Tricco, A.C., Welch, V.A., Whiting, P., McKenzie, J.E., 2021. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ 372, n160.

Pan, L.Y., Chen, Y.F., Li, H.C., Bi, L.M., Sun, W.J., Sun, G.F., Zhang, X.F., Xu, K., Feng, D. X., 2017. Dachengqi Decoction Attenuates Intestinal Vascular Endothelial Injury in Severe Acute Pancreatitis in Vitro and in Vivo. Cell. Physiol. Biochem. 44 (6), 2395–2406.

Patel, B.K., Patel, K.H., Bhatia, M., Iyer, S.G., Madhavan, K., Moochhala, S.M., 2021. Gut microbiome in acute pancreatitis: a review based on current literature. World J. Gastroenterol. 27 (30), 5019–5036.

Peery, A.F., Crockett, S.D., Barritt, A.S., Dellon, E.S., Eluri, S., Gangarosa, L.M., Jensen, E. T., Lund, J.L., Pasricha, S., Runge, T., Schmidt, M., Shaheen, N.J., Sandler, R.S., 2015. Burden of Gastrointestinal, Liver, and Pancreatic Diseases in the United States. Gastroenterology 149 (7), 1731-1741 e1733.

Petrov, M.S., Shanbhag, S., Chakraborty, M., Phillips, A.R.J., Windsor, J.A., 2010. Organ failure and infection of pancreatic necrosis as determinants of mortality in patients with acute pancreatitis. Gastroenterology 139 (3), 813–820.

Poivre, M., Duez, P., 2017. Biological activity and toxicity of the Chinese herb Magnolia officinalis Rehder & E. Wilson (Houpo) and its constituents. J Zhejiang Univ Sci B 18 (3), 194–214.

Qian, J., Li, G., Jin, X., Ma, C., Cai, W., Jiang, N., Zheng, J., 2020. Emodin protects against intestinal and lung injury induced by acute intestinal injury by modulating SP-A and TLR4/NF-kappaB pathway. Biosci. Rep. 40 (9).

Qin, D.P., Wei, X., Fang, G.D., Yang, F., Lai, D.P., 2015. [Intervention Effect of Modified Dachengqi Decoction on Intestinal Mucosal Barrier of Severe Acute Pancreatitis Model Rats]. Chin. J. Integr. Tradit. West. Med. (Chin. Ed.). 35 (12), 1482–1489.

Ramnath, R.D., Bhatia, M., 2006. Substance P treatment stimulates chemokine synthesis in pancreatic acinar cells via the activation of NF-kappaB. Am. J. Physiol. Gastrointest. Liver Physiol. 291 (6), G1113–G1119.

Scheller, J., Garbers, C., Rose-John, S., 2014. Interleukin-6: from basic biology to selective blockade of pro-inflammatory activities. Semin. Immunol. 26 (1).

Shang, L., Liu, Y., Li, J., Pan, G., Zhou, F., Yang, S., 2021. Emodin Protects Sepsis Associated Damage to the Intestinal Mucosal Barrier Through the VDR/Nrf2 /HO-1 Pathway. Front. Pharmacol. 12, 724511.

Shu, Z., Li, W., Wang, X., Wang, Z., Wang, S., Wang, L., Du, J., Li, J., 1998. Gastrointestinal tract complications in severe acute pancreatitis. World J. Gastroenterol. 4 (Suppl2), 122.

SUN, Y., WEl, L., YANG, D., WANG, Z., WANG, Y., YANG, K., 2022. Meta-analysis of the Efficacy of Chaiqin Chengqi Decoction in the Treatment of Severe AcutePancreatitis. Pract Tradit Chin Intern Med 36 (10), 7-10+146-148.

Tan, Y., Zhang, W., Wu, H.Y., Xia, J., Zhang, H.B., Liu, M.W., Qian, C.Y., 2020. Effects of emodin on intestinal mucosal barrier by the upregulation of miR-218a-5p expression in rats with acute necrotizing pancreatitis. Int. J. Immunopathol. Pharmacol. 34, 2058738420941765.

van Santvoort, H.C., Bakker, O.J., Bollen, T.L., Besselink, M.G., Ali, U.Ahmed, Schrijver, A.M., Boermeester, M.A., van Goor, H., Dejong, C.H., van Eijck, C.H., van Ramshorst, B., Schaapherder, A.F., van der Harst, E., Hofker, S., Nieuwenhuijs, V.B., Brink, M.A., Kruyt, P.M., Manusama, E.R., van der Schelling, G.P., Karsten, T., Hesselink, E.J., van Laarhoven, C.J., Rosman, C., Bosscha, K., de Wit, R.J., Houdijk, A.P., Cuesta, M.A., Wahab, P.J., Gooszen, H.G., Dutch Pancreatitis Study, G., 2011. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. Gastroenterology 141 (4), 1254–1263.

W, Q., W, Y., Y, J., G, T., G, Z., Pengcheng, Z., 2005. Chinese medicinal herbs for acute pancreatitis. Cochrane Database Syst. Rev. (1), CD003631

Wang, C., Zhou, X.-h., Yin, Y.-x., Li, J., 2007. Study of chaishao chengqi Decoction in treating sever Acute Pancreatitis with Gastrointestinal Function Failure. Chin. Youjiang Med. J. (03), 240–242.

Wang, G., Shang, D., Zhang, G., Zhang, S., Jiang, N., Liu, H., Chen, H., 2022a. Effects of QingYi decoction on inflammatory markers in patients with acute pancreatitis: a meta-analysis. Phytomedicine 95, 153738.

Wang, Z., Liu, J., Li, F., Luo, Y., Ge, P., Zhang, Y., Wen, H., Yang, Q., Ma, S., Chen, H., 2022b. The gut-lung axis in severe acute Pancreatitis-associated lung injury: the protection by the gut microbiota through short-chain fatty acids. Pharmacol. Res. 182, 106321.

WEI, X., QIN, D., WANG, Y., YANG, Q., CHEN, J., 2021. Effect of Chengqi Decoction Series on Intestinal Function and Prognosis of Severe AcutePancreatitis: network Meta-analysis. J. Tradit. Chin. Med. 62 (20), 1827–1836.

Xia, Q., 2006. Yi-Huo-Qing-Xia method as the main therapy in integrated traditional Chinese and western medicine on severe acute pancreatitis: a report of 1161 cases. Chin J TCM WM Crit Care 13, 131–134.

Yang, B., Xu, F.Y., Sun, H.J., Zou, Z., Shi, X.Y., Ling, C.Q., Tang, L., 2014. Da-cheng-qi decoction, a traditional Chinese herbal formula, for intestinal obstruction: systematic review and meta-analysis. Afr J Tradit Complement Altern Med 11 (4), 101–119.

Yang, C., Wang, T., Chen, J., He, J., Li, Y., Chen, C., Lu, G., Chen, W., 2021. Traditional Chinese Medicine Formulas Alleviate Acute Pancreatitis: pharmacological Activities and Mechanisms. Pancreas 50 (10), 1348–1356.

Yang, J., Tang, X., Wu, Q., Ren, P., Yan, Y., 2022. A Severe Acute Pancreatitis Mouse Model Transited from Mild Symptoms Induced by a "Two-Hit" Strategy with L-Arginine. Life (Basel) 12 (1).

Zhang, C.L., Lin, Z.Q., Luo, R.J., Zhang, X.X., Guo, J., Wu, W., Shi, N., Deng, L.H., Chen, W.W., Zhang, X.Y., Bharucha, S., Huang, W., Sutton, R., Windsor, J.A., Xue, P., Xia, Q., 2017. Chai-Qin-Cheng-Qi Decoction and Carbachol Improve Intestinal Motility by Regulating Protein Kinase C-Mediated Ca(2+) Release in Colonic Smooth Muscle Cells in Rats with Acute Necrotising Pancreatitis. Evid Based Complement Alternat Med, 5864945, 2017.

Zhang, H., Neuhöfer, P., Song, L., Rabe, B., Lesina, M., Kurkowski, M.U., Treiber, M., Wartmann, T., Regnér, S., Thorlacius, H., Saur, D., Weirich, G., Yoshimura, A., Halangk, W., Mizgerd, J.P., Schmid, R.M., Rose-John, S., Algül, H., 2013. IL-6 trans-signaling promotes pancreatitis-associated lung injury and lethality. J. Clin. Invest. 123 (3), 1019–1031.

Zhang, M., Lian, B., Zhang, R., Guo, Y., Zhao, J., He, S., Bai, Y., Wang, N., Lin, Y., Wang, X., Liu, Q., Xu, X., 2022. Emodin Ameliorates Intestinal Dysfunction by Maintaining Intestinal Barrier Integrity and Modulating the Microbiota in Septic Mice. Mediators Inflamm. 2022, 5026103.

Zhang, Q., Ni, Q., Cai, D., Zhang, Y., Zhang, N., Hou, L., 2001. Mechanisms of multiple organ damages in acute necrotizing pancreatitis. Chin. Med. J. 114 (7), 738–742.

Zhang, X., Tan, R., Lam, W.C., Yao, L., Wang, X., Cheng, C.W., Liu, F., Chan, J.C., Aixinjueluo, Q., Lau, C.T., Chen, Y., Yang, K., Wu, T., Lyu, A., Bian, Z., 2020. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Extension for Chinese Herbal Medicines 2020 (PRISMA-CHM 2020). Am. J. Chin. Med. 48 (6), 1279–1313.

Zhao, J., Tang, W., Wang, J., Xiang, J., Gong, H., Chen, G., 2013. Pharmacokinetic and pharmacodynamic studies of four major phytochemical components of Da-Cheng-Qi decoction to treat acute pancreatitis. J. Pharmacol. Sci. 122 (2), 118–127.

Zhou, Y., Wang, L., Huang, X., Li, H., Xiong, Y., 2016. Add-on effect of crude rhubarb to somatostatin for acute pancreatitis: a meta-analysis of randomized controlled trials. J. Ethnopharmacol. 194, 495–505.