Phytomedicine 138 (2025) 156393

Contents lists available at ScienceDirect

Phytomedicine

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

Original Article

Traditional Chinese medicine Chaiqinchengqi decoction for patients with acute pancreatitis: A randomized clinical trial

Lihui Deng [a], Zhiyao Chen [a], Tao Jin [a], Fei Cai [a], Yanqiu He [a], Yuxin Shen [a], Shihang Zhang [a], Jia Guo [a], Xiaonan Yang [a], Lin Yang [b], Huimin Lu [a,c], Chunhui Wang [a,d], Wenfu Tang [a], Ziqi Lin [a], Lan Li [a], Qingyuan Tan [a], Ping Zhu [a,e], Xiaoxin Zhang [a], Na Shi [a], Cheng Hu [a], Zixing Huang [f], Dan Du [g], Wei Huang [a], Zhongwei Zhang [h], Shu Zhang [i], Qing Xia [a,*], for the CAP Investigators

[a] *West China Centre of Excellence for Pancreatitis, Institute of Integrated Traditional Chinese and Western Medicine, West China Hospital, Sichuan University, Chengdu, PR China.*
[b] *Department of Clinical Pharmacology, West China Hospital, Sichuan University, Chengdu, PR China.*
[c] *Department of Pancreatic Surgery, West China Hospital, Sichuan University, Chengdu, PR China.*
[d] *Department of Gastroenterology, West China Hospital, Sichuan University, Chengdu, PR China.*
[e] *Department of Clinical Research Management, West China Hospital, Sichuan University, Chengdu, PR China.*
[f] *Department of Radiology, West China Hospital, Sichuan University, Chengdu, PR China.*
[g] *Mass Spectrometry Platform, Frontiers Science Centre for Disease-related Molecular Network, West China Hospital, Sichuan University, Chengdu, PR China.*
[h] *Department of Critical Care Medicine, West China Hospital, Sichuan University, Chengdu, PR China.*
[i] *Department of Emergency, West China Hospital, Sichuan University, Chengdu, PR China.*

ARTICLE INFO

Keywords:
acute pancreatitis
acute gastrointestinal injury
Chinese medicines
randomized clinical trial
respiratory failure

ABSTRACT

Background: Chaiqinchengqi decoction, a traditional Chinese medicine, has shown promising effects in in vitro, animal and preliminary small human studies for acute pancreatitis, but evidence of clinical practice is limited.
Purpose: To investigate whether Chaiqinchengqi decoction could improve clinical outcomes in patients with acute pancreatitis.
Study Design: Prospective, pragmatic, randomized controlled trial. (Chictr.org.cn registration number: ChiCTR2000034325)
Methods: This trial was conducted at West China Hospital of Sichuan University, China. Patients with acute pancreatitis were randomly assigned to receive either Chaiqinchengqi decoction or placebo by oral and rectal enemas in addition to guideline-directed administrations using a 1:1 ratio. The intervention of Chaiqinchengqi and placebo was determined by the grading of acute gastrointestinal injury. Patients were assessed within 24 and 48 hours, and on 3, 5, and 7 days after admission, or organ failure normalized. Survivors were followed up at 1, 3, and 6 months after discharge. Primary outcome was the duration of respiratory failure to 28 days after

Abbreviations: ACS, abdominal compartment syndrome; AGI, acute gastrointestinal injury; BISAP, Bedside Severity Index Score for Acute Pancreatitis; CI, confidence intervals; CRP, C-reaction protein; CRRT, continuous renal replacement therapy; EPIC, extrapancreatic inflammation computed tomography score; GCS, modified Glasgow Score; HAPS, Harmless Acute Pancreatitis Score; HPLC, High Performance Liquid Chromatography; HR, hazard ratio; IAH, intra-abdominal hypertension; ICU, intensive care unit; IMV, invasive mechanical ventilation; IQR, interquartile; ITT, intention-to-treat population; LOS, Length of hospital stay; MCTSI, modified computed tomography severity index; MMS, modified Marshall score; NIPPV, non-invasive positive pressure ventilation; QoL, quality of life; SD, standard deviation; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment; PASS, pancreatitis activity scoring system; VAS, visual analogue scale.

* **Correspondence author at** West China Centre of Excellence for Pancreatitis, West China Hospital, Sichuan University, No. 37 Wainan Guoxue Alley, Chengdu 610041, PR China

E-mail addresses: denglihui@scu.edu.cn (L. Deng), zhiyao_chen@wchscu.cn (Z. Chen), jintao@wchscu.cn (T. Jin), caifeiscu@163.com (F. Cai), 962087094@qq.com (Y. He), shenyuxin2021@stu.scu.edu.cn (Y. Shen), 2022224020188@stu.scu.edu.cn (S. Zhang), guojia4120@wchscu.cn (J. Guo), yangxiaonan@wchscu.cn (X. Yang), hxyyyl@yeah.net (L. Yang), hm.lu@scu.edu.cn (H. Lu), wangch@scu.edu.cn (C. Wang), tangwenfu@wchscu.cn (W. Tang), linziqi@wchscu.cn (Z. Lin), lilan@wchscu.cn (L. Li), tanqingyuan@wchscu.cn (Q. Tan), zhuping@wchscu.cn (P. Zhu), zhangxiaoxin@wchscu.cn (X. Zhang), nashi@scu.edu.cn (N. Shi), hucheng@wchscu.cn (C. Hu), zixinghuang@hotmail.com (Z. Huang), dudan@wchscu.cn (D. Du), dr_wei_huang@scu.edu.cn (W. Huang), zhangzhongwei@wchscu.cn (Z. Zhang), zhangs@wchscu.cn (S. Zhang), xiaqing@medmail.com.cn (Q. Xia).

https://doi.org/10.1016/j.phymed.2025.156393
Received 3 October 2024; Received in revised form 26 December 2024; Accepted 12 January 2025
Available online 23 January 2025

enrollment. Secondary outcomes included other organ failure, local complications, 6-month all-cause mortality, inflammatory indicators, and related interventions.
Results: Among 248 patients enrolled, Chaiqinchengqi decoction shortened the duration of respiratory failure compared with the placebo (median [IQR], 1.0 [0.0 to 5.0] vs 3.0 [1.0-8.0] days; median difference, -1.0; 95% CI, -2.0 to 0.0, P=.001). There were significant differences in the duration of circulatory failure, the incidence of new-onset respiratory and cardiovascular and failure, the incidence of new organ failure, severity, intensive care unit need, pain visual analogue scale, pancreatitis activity scoring system, and EQ-5D-5L.
Conclusion: Chaiqinchengqi decoction as an adjunctive therapy significantly reduced the duration of respiratory failure and improved 6-month clinical outcomes of acute pancreatitis in addition to guideline-directed treatments. Further study is needed to elucidate the mechanism of action.

Introduction

Acute pancreatitis is a potential life-threatening condition with substantial morbidity and an increasing incidence worldwide (Forsmark et al., 2016; Peery et al., 2019). Approximately 60% of patients with acute pancreatitis present with a mild clinical course and recovery within a few days with supportive care, but moderately severe or severe disease develops in 35% of patients with acute pancreatitis. Despite the in-depth research on the pathogenesis of the disease in recent years, there is a lack of internationally recognized effective drugs. Patients with moderately severe or severe acute pancreatitis still face high risks of mortality (Schepers et al., 2019; Shi et al., 2020).

Gastrointestinal injury is a common complication in patients with acute pancreatitis. The inflammatory state of acute pancreatitis triggers a cascade of pancreatic and intestinal injury with paralytic ileus and gastric dilatation, visceral edema, acute peripancreatic fluid collections, and ascites resulting in intra-abdominal hypertension (IAH). Liquid resuscitation (causing pulmonary edema, abdominal hypertension syndrome), non-selective positive inotropic drugs (leading to visceral ischemia), antibiotic therapy (aggravating the imbalance of intestinal flora) are the critical factors leading to IAH and abdominal compartment syndrome (ACS), which resulting in organ failure with a mortality of 49% (Siebert et al., 2021; Kirkpatrick et al., 2013; Wang et al., 2003; Wu et al., 2014).

Chaiqinchengqi decoction, a traditional Chinese medicine compound, is composed of multiple herbs and miner modified from

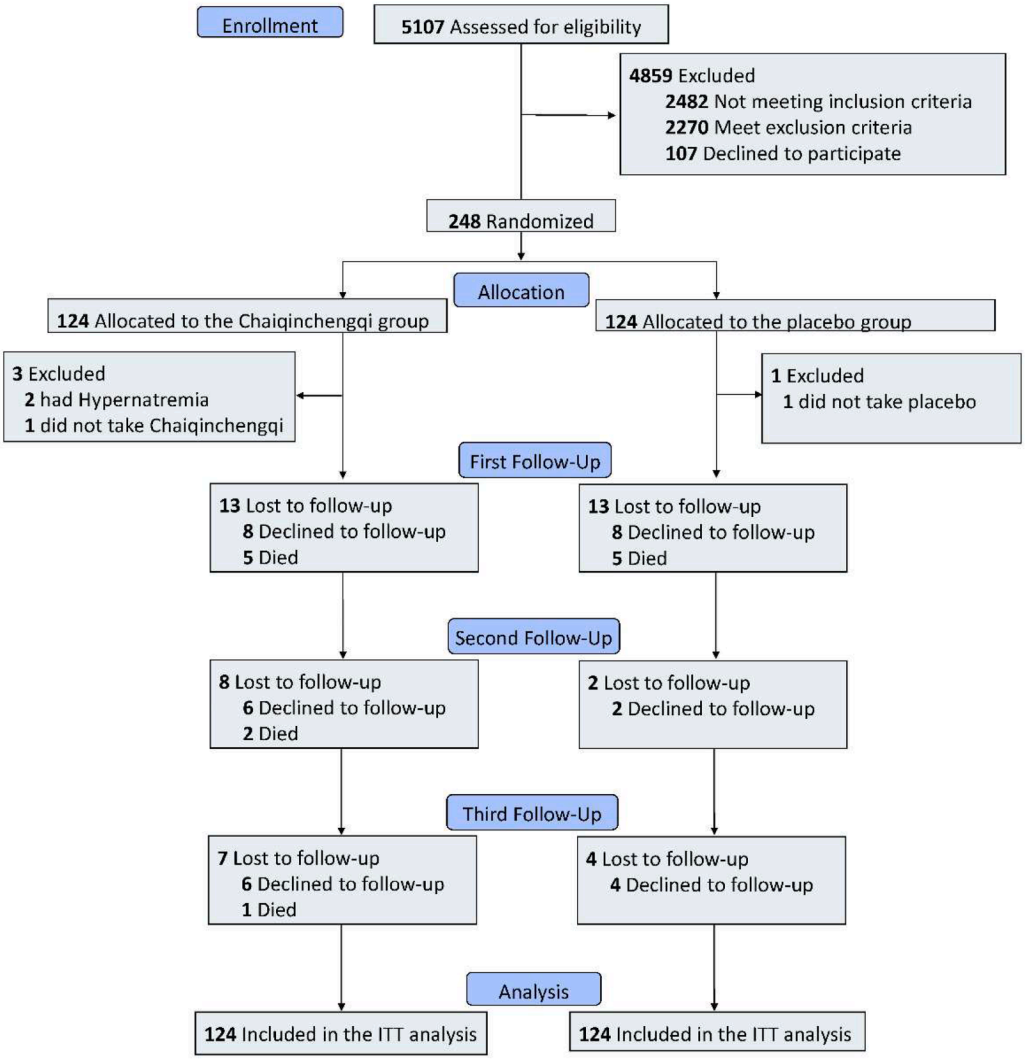

Fig. 1. Study Flowchart of Screening, Enrollment, Randomization, and Follow-up. ITT, intention-to-treat population.

Dachengqi decoction and Dachaihu decoction. Although the active ingredients and the exact mechanism of action remain unclear, our previous studies in vitro and in vivo showed that Chaiqinchengqi decoction inhibited the inflammation (Huang et al., 2012; Xue et al., 2014; Wu et al., 2016), antagonize oxidative stress injury (Du et al., 2018; Wen et al., 2020), improved intestinal motility and reduced lung renal injury (Zhang et al., 2017; Cao et al., 2024; Yang et al., 2020). Recent studies suggested that Chaiqinchengqi regulates the metabolic trajectory of pancreatic tissue in acute pancreatitis animals (Huang et al., 2022). Meta-analysis showed Chengqi-series compound reduce the mortality, hospitalization time, and surgery rate of severe acute pancreatitis (Qiong et al., 2005). Nevertheless, there is lacking of high-quality evidence on the efficacy of Chaiqinchengqi decoction.

We conducted this randomized controlled trial to assess the efficacy and safety of Chaiqinchengqi decoction as adjunctive therapy for the treatment of patients with acute pancreatitis with a range of severity of disease.

Methods

Study population and protocol

Chaiqinchengqi for acute pancreatitis trial was a randomized double-blind controlled trial conducted at the West China Hospital of Sichuan University (Chengdu, China). Details of the trial design have been published (Chen et al., 2022). Eligible patients were randomized at a 1:1 ratio to Chaiqinchengqi or placebo group (Fig. 1) in addition to guideline-directed therapies of acute pancreatitis. The study protocol (Supplement 1) was approved by the Biomedical Research Ethics Committee of West China Hospital of Sichuan University on June 22, 2020 (Ethics No. 2020107), passed the China Clinical Research Registration (Chictr.org.cn identifier: ChiCTR2000034325), and was conducted in accordance with the Declaration of Helsinki. The trial adhered to the recommendations of the Consolidated Standards of Reporting Trials.

Consecutive patients were eligible for enrollment if they were aged between 18 and 75 years, presented within 72 hours of symptoms onset with a diagnosis of acute pancreatitis according to the Revised Atlanta Classification. Exclusion criteria included pregnant or lactating women, sequential organ failure assessment (SOFA) score of any organ>3, harmless acute pancreatitis score> 2, concomitant any malignancy or history of radiotherapy within 6 months, gastrointestinal conditions that unsuitable for oral enemas of traditional Chinese medicines, chronic pancreatitis, history of tumors of the duodenum and biliopancreatic system, history of pancreatic resection, or involvement in other interventional clinical trials. The complete exclusion criteria are listed in the study protocol in Supplement 1. Written informed consent was provided by all participants or their legal representatives before randomization.

Study herbal formulation

Chaiqinchengqi formula has 13 components: Rhei Radix et Rhizoma, Natrii Sulfas, Magnoliae Officinalis Cortex, Gardeniae Fructus, Bupleuri Radix, Scutellariae Radix, Corydalis Rhizoma, Aurantii Fructus Immaturus, Auklandiae Radix, Paeonia Radix Rubra, Chuanxiong Rhizoma, Carthami Flos, and Glycyrrhizae Radix et Rhizoma.

Due to the absence of a positive control for acute pancreatitis in worldwide and the difficulty of preparing a placebo for the decoction solution, we utilized a low-dose administration of 10% Chaiqinchengqi decoction and caramel coloring to mimic the experimental drug as a control (Zhou et al., 2014).

The raw drugs used in the trial were guaranteed to have consistent batches and passed the quality inspection. More information about Chaiqinchengqi, such as compound preparation, preservation, qualification of research drugs are available at Supplement 1. High Performance Liquid Chromatography (HPLC) fingerprint analysis and chemometric methods have demonstrated that Chaiqinchengqi decoction among multiple batches have similarity of more than 96%, indicating the 28 ingredients of Chaiqinchengqi decoction are stable and controllable (Supplement 2).

Randomization and blinding

Eligible patients were randomly assigned to receive Chaiqinchengqi or placebo group with the use of a computer-generated randomization system using a 1:1 ratio (Fig. 1). Two research assistants who were not involved in medical care and outcome assessment were assigned to allocate the eligible patients. The patients, physicians, nurses, outcome assessors, data collectors, and statisticians were blinded to treatment assignments.

Study procedures

Administration of Chaiqinchengqi or placebo was guided by acute gastrointestinal injury (AGI) (Reintam et al., 2012), which has been described previously (Chen et al., 2022). If the patients had Bedside Severity Index Score for Acute Pancreatitis (BISAP)(Wu et al., 2008) or modified Glasgow Score (GCS)(Imrie et al., 1978) score <2 points, they were given Chaiqinchengqi or placebo orally and enema (200 ml/three times daily); if patients were evaluated by BISAP or GCS score≥2 points, their intra-abdominal pressure were monitored for every 4 hours and they were administrated by: oral (200ml, 3 times daily) and enema (200ml, 3 times daily) Chaiqinchengqi or placebo for AGI gradeI; oral (100ml, every 6 hours daily) and enema (200ml, every 6 hours daily) Chaiqinchengqi or placebo for AGI gradeII; oral (100ml, every 4 hours daily) and enema (200ml, every 4 hours daily) Chaiqinchengqi or placebo for AGI gradeIII; oral (50ml, every 2 hours daily, via nasogastric tube) and enema (200ml, every 2 hours daily, via rectal canal) Chaiqinchengqi or placebo for AGI IV. Chaiqinchengqi or placebo administration was discontinued if the AGI grade isIfor 2 consecutive days, or if the patient refeeded without food intolerance. For more information about on the AGI-guided Chaiqinchengqi or placebo algorithm, see Supplement 1.

Conventional standardized treatments were directed by the American Pancreatic Association Guidelines for the management of patients with acute pancreatitis (Crockett et al., 2018; Tenner et al., 2013), with uniformity across the study between the groups (Section 6 Conventional treatment regimen in Supplement 1). Not applicable to other herbal medicines and alternative therapies in this study. Drugs that inhibit gastrointestinal motility and prokinetics were not routinely used. In the interests of patients' care, contaminant treatments were decided by the attending physicians in consultation with the principal investigator and were recorded in the case report form.

Study outcomes

Each patient enrolled in the study was evaluated by clinical characteristics, laboratory tests, severity scores including systemic inflammatory response syndrome (SIRS), GCS, BISAP, SOFA, and modified Marshall score (MMS) within 24 and 48 hours, and on 3, 5, and 7 days after admission. Relevant indicators of organ failure were followed up to normalization. The modified computed tomography severity index was evaluated for local complications. Patient quality of life (QoL) was evaluated weekly by the five-level EuroQol five-dimensional (EQ-5D-5L) health scale (Zhou et al., 2021). Survivors were followed up at 1, 3, and 6 months after discharge (study schedule and study schedule flowchart are provided in Supplement 1).

Primary outcome was the duration of respiratory failure within 28 days of enrollment, defined as the number of persistent days alive with failure of respiration organ systems. An individual SOFA score of 2 or more was defined as organ failure.

Secondary outcomes included the incidence of circulatory and renal failure, new-onset organ failure; duration of SIRS, IAH, ACS, and AGI-

related treatment; organ supportive therapy; length of hospital and intensive care unit (ICU) stay; hospital cost; localized pancreatic complications and their related interventions; severity; mortality; patient self-reported QoL. The incidence of adverse events was compared. Definitions for each outcome are listed in Supplement 1.

Statistical analysis

Assuming a reduction of 2 days in the duration of respiratory failure in the Chaiqinchengqi group and the standard deviation for each group was 4 days based on previous reports (Schepers et al., 2019; Chen et al., 2015) and an estimated dropout rate of 10%, a total of 248 patients would be required with 124 in each group (PASS statistic software, version 11.0.7, NCSS; significance level of 0.05 and 80% power, 2-sided α=.05 and β=0.20).

Continuous variables were presented as means with standard deviations (SD) or medians with interquartile (IQR) ranges. Intergroup comparisons were performed using the 2-tailed *t* test, Mann-Whitney *U* test (between 2 groups) or the Kruskal-Wallis H test (between 3 groups) as appropriate. Categorical variables were expressed as frequencies and percentages, and analyzed using the chi-square test or Fisher's exact test. The incidences of adverse events and serious adverse events were analyzed between the 2 groups using the $\chi 2$ test or Fisher exact test.

We performed analyses in the intention-to-treat (all randomized participants) and per-protocol (excluding those who had major protocol deviations, did not complete 14-day follow-up, or did not achieve at least 80% adherence) populations. Exploratory subgroup analysis was performed based on age (<60, 60-75, >75), sex (male, female), body mass index (≤28, >28), onset-to-arrival time (≤24 hours, >24 hours) and severity (mild, moderately severe, severe). Kaplan-Meier methods were used to show curves to onset of respiratory failure and new-onset respiratory failure within 28 days after enrollment. A log-rank *P*-test was used to test the equality of the estimated survival curves. A Cox proportional hazards model was used to estimate cause specific hazard ratios (HR).

Statistical analyses were performed using SPSS software, version 21.0 (IBM, Armonk, New York, USA). Two-sided test $P < 0.05$ was considered statistically significant. Full details of the statistical methods are available in Supplement 1.

Results

Participants and baseline characteristics

From August 1, 2020 and July 12, 2023, a total of 5107 patients were screened and 248 were enrolled. Patients were randomly assigned to receive either Chaiqinchengqi or placebo decoction (124 patients in each group) and were included in the intention-to-treat population (Fig. 1). Three patients in the Chaiqincehngqi group and one patient in the control group had safety data (eTable1 in Supplement 3).

The characteristics of the patients were well balanced between the two groups at baseline before treatment (Table 1). The mean age of the enrolled patients was 44.2 years and 72.2% were male. The median onset-to-arrival intervals were 38 hours. Hyperlipidemia (43.5%) and biliary stone (23.4%) were the first two etiologies.

Primary and secondary outcomes

Respiratory failure occurred in 90 patients (72.6%) in the Chaiqinchengqi group and 99 (79.8%) in the control group. The duration of respiratory failure was significantly lower in the Chaiqinchengqi group than in the control group (median [IQR], 1.0 [0.0 to 5.0] vs 3.0 [1.0-8.0]; median difference, -1; 95% CI, -2 to 0, *P*=.001) (Table 2). There was significant difference in the probability of respiratory failure (HR, 0.67; 95% CI, 0.5 to 0.9; *P*=.002) between the two groups with Kaplan-Meier curves (Fig. 2). The per-protocol analysis showed similar results.

Table 1
Baseline Characteristics of the Study Population

Variables	Chaiqinchengqi (n = 124)	Placebo (n = 124)
Age, mean (SD), y	44.1 (12.1)	44.2 (12.8)
Sex, n (%)		
Female	35 (28.2)	34 (27.4)
Male	89 (71.8)	90 (72.6)
Onset-to-arrival, median (IQR), h	40 (25 to 53)	37 (24 to 51)
BMI, median (IQR), kg/m^2	26.5 (24.3 to 28.9)	27.1 (25.2 to 29.3)
Etiologies, n (%)		
Hypertriglycemia	59 (47.6)	49 (39.5)
Gallstones	31 (25.0)	27 (21.8)
Idiopathic	21 (16.9)	29 (23.4)
Alcohol	13 (10.5)	18 (14.5)
Drug-related	0	1 (0.8)
Charlson Comorbidity Index, median (IQR)	1 (0 to 1)	0 (0 to 1)
Laboratory tests		
Hematocrit, mean (SD), %	46.0 (6.0)	46.0 (6.0)
White blood cell, median (IQR), ×10^{9}cells/L	13.7 (11.0 to 17.7)	13.39 (10.6 to 18.1)
Total bilirubin, median (IQR), umol/L	16.9 (11.7 to 29.0)	18.2 (13.2 to 30.6)
Direct bilirubin, median (IQR), umol/L	5.1 (2.8 to 10.3)	5.6 (3.2 to 10.8)
Alanine aminotransferase, median (IQR), umol/L	22.0 (15.3 to 33.0)	25.0 (16.0 to 48.3)
Aspartate aminotransferase, median (IQR), umol/L	33.0 (23.0 to 49.0)	33.5 (22.0 to 56.8)
Albumin, mean (SD), g/L	36.4 (5.6)	35.8 (5.9)
Glucose, median (IQR), mmol/L	12.0 (8.9 to 16.6)	11.4 (8.2 to 16.8)
Urea nitrogen, median (IQR), mmol/L	5.1 (3.7 to 7.5)	5.0 (3.4 to 7.2)
Creatinine, median (IQR), mmol/L	71.5 (58.3 to 101.8)	74.0 (56.0 to 91.8)
Triglycerides, median (IQR), mmol/L	7.9 (2.7 to 15.5)	5.3 (1.5 to 16.1)
Alkaline phosphatase, median (IQR), IU/L	75.0 (58.3 to 95.8)	70.5 (58.3 to 89.0)
Lactate dehydrogenase, median (IQR), IU/L	405.5 (283.5 to 604.0)	458.0 (268.0 to 598.8)
Pancreatic amylase, median (IQR), U/L	323.5 (154.0 to 660.0)	376.5 (170.0 to 778.0)
Amylase, median (IQR), IU/L	352.0 (172.0 to 716.8)	498.5 (223.3 to 872.0)
Lipase, median (IQR), IU/L	567.5 (272.0 to 1252.8)	748.0 (374.0 to 1524.5)
Sodium, median (IQR), mmol/L	133.1 (129.6 to 136.2)	133.8 (129.8 to 137.3)
Potassium, median (IQR), mmol/L	3.9 (3.5 to 4.4)	3.9 (3.5 to 4.4)
Calcium ion, mean (SD), mmol/L	1.9 (0.3)	1.9 (0.3)
C-reactive protein, median (IQR), mg/L	288.5 (187.0 to 399.8)	285.0 (155.8 to 388.0)
Procalcitonin, median (IQR), ng/L	1.9 (0.5 to 4.8)	1.1 (0.4 to 3.0)
Clinical scoring		
MMS score, median (IQR)	2 (0 to 2)	1 (0 to 2)
SOFA score, median (IQR)	2 (0 to 2)	1 (0 to 2)
HAPS score, median (IQR)	1 (1 to 2)	1 (1 to 1)
BISAP score, median (IQR)	2 (1 to 2)	2 (1 to 2)
GCS score, median (IQR)	2 (2 to 3)	2 (2 to 3)
MCTSI score, median (IQR)	6 (4 to 6)	6 (4 to 6)
EPIC score, median (IQR)	5 (3 to 5)	5 (3 to 6)

Abbreviations: SD, standard deviation; IQR, interquartile range; MMS, modified Marshall score; SOFA, Sequential Organ Failure Assessment; HAPS, Harmless Acute Pancreatitis Score; BISAP, Bedside Severity Index Score for Acute Pancreatitis; GCS, modified Glasgow Score; MCTSI, modified computed tomography Severity Index score; EPIC, extrapancreatic inflammation computed tomography score.

For the secondary outcomes (Table 2), the duration of circulatory failure, the incidence of circulatory failure, new-onset of organ failure, multi-organ failure, and the utilization of inotropic agents (3.2% vs 12.1%, P=.009), the incidence of acute peripancreatic fluid and catheter

Table 2
Primary and secondary outcomes

Variables	Chaiqinchengqi (n=124)	Placebo (n=124)	Between-group difference (95% CI)	*P* value
Primary outcome				
Duration of respiratory failure, median (IQR)	1 (0 to 5)	3 (1 to 8)	-1 (-2 to 0)	.001
Secondary outcomes				
Duration of circulatory failure, median (IQR)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	.008
Duration of renal failure, median (IQR)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	.540
New-onset of organ failure, n (%)				
Any single organ	32 (25.8)	57 (46.0)	-20.2 (-31.8 to -8.5)	.001
Respiratory	30 (24.2)	50 (40.3)	-16.1 (-27.6 to -4.7)	.007
Circulatory	2 (1.6)	15 (12.1)	-10.5 (-16.6 to -4.3)	.001
Renal	2 (1.6)	6 (4.8)	-3.2 (-7.6 to 1.2)	.280
Multi-organ failure, n (%)	1 (0.8)	8 (6.5)	-5.7 (-10.3 to -1.0)	.040
Organ supportive treatment, n (%)				
NIPPV	48 (38.7)	59 (47.6)	-8.9 (-21.1 to 3.4)	.158
IMV	10 (8.1)	17 (13.7)	- 5.7 (-13.4 to 2.1)	.154
Inotropic agents	4 (3.2)	15 (12.1)	- 8.9 (-15.4 to 2.3)	.009
CRRT	7 (5.6)	9 (7.3)	-1.6 (-7.7 to 4.5)	.605
AGI grading, n (%)				.008
I	60 (48.4)	40 (32.3)	16.1 (4.1 to 28.2)	
II	17 (13.7)	19 (15.3)	-1.6 (-10.4 to 7.2)	
III	39 (31.5)	51 (41.1)	-9.7 (-21.6 to 2.2)	
IV	8 (6.5)	14 (11.3)	-4.8 (-11.9 to 2.2)	
Duration of AGI, median (IQR), d	2 (0 to 5)	4 (0 to 7)	-1 (-3 to 0)	.001
Duration of IAH, median (IQR), d	1 (0 to 4)	3 (0 to 5)	0 (-1 to 0)	.040
Duration of fasting, median (IQR), d	5 (4 to 8)	7 (5 to 9)	-1 (-2 to -1)	.001
Anal tube, n (%)	11 (8.9)	30 (24.2)	-15.3 (-24.4 to -6.3)	.001
Gastrointestinal decompression, n (%)	66 (53.2)	73 (58.9)	-5.7 (-18.0 to 6.7)	.370
Duration of gastrointestinal decompression, median (IQR), d	1 (0 to 3)	1 (0 to 4.75)	0 (-1 to 0)	.077
Prokinetic agents, n (%)	23 (18.5)	38 (30.6)	-12.1 (-22.7 to 1.5)	.027
Local complications, n (%)	98 (79.0)	103 (83.1)	-4.0 (-13.8 to 5.7)	.418
Acute peripancreatic fluid	80 (64.5)	95 (76.6)	-12.1 (-23.3 to -0.9)	.037
Pancreatic/ peripancreatic necrosis	61 (49.2)	64 (51.6)	-2.4 (-14.9 to 10.0)	.703
Walled-off necrosis	5 (4.0)	6 (4.8)	-0.8 (-5.9 to 4.3)	.758
Pseudocyst	3 (2.4)	1 (0.8)	1.6 (-1.5 to 4.7)	.610
Infected pancreatic necrosis	8 (6.5)	10 (8.1)	-1.6 (-8.1 to 4.8)	.620
Catheter drainage or necrosectomy, n (%)	11 (8.9)	24 (19.4)	-10.5 (-19.1 to -1.9)	.018
Severity, n (%)				.004
Mild	15 (12.1)	10 (8.1)	4.0 (-3.5 to 11.5)	
Moderately severe	47 (37.9)	29 (23.4)	14.5 (3.2 to 25.9)	
Severe	62 (50.0)	85 (68.5)	-18.6 (-30.6 to -6.5)	
6-month all-cause mortality, n (%)	8 (6.5)	7 (5.6)	0.8 (-5.1 to 6.7)	.790
ICU need, n (%)	5 (4.0)	14 (11.3)	-7.3 (-13.8 to -0.7)	.030
LOS, median (IQR), d	11 (8 to 16)	12 (9 to 17)	-1 (-3 to 0)	.080
Costs, median (IQR), $	2,950 (1,945 to 5,363)	3,818 (2,135 to 5,841)	- 431 (-979 to 67)	.070
Duration of SIRS, median (IQR), d	6 (3 to 10)	9 (4 to 13)	-2 (-4 to -1)	.001
28-d cumulative CRP, median (IQR), mg	1,011 (789 to 1,284)	1,172 (796 to 1,498)	-114 (-237 to 10)	.070
Procalcitonin, median (IQR), ng/L				
3-d (n = 245)	0.7 (0.3 to 1.6)	0.6 (0.3 to 1.6)	0.0 (-0.1 to 0.2)	.920
5-d (n = 195)	0.4 (0.2 to 0.7)	0.4 (0.2 to 0.9)	0.0 (-0.1 to 0.1)	.876
7-d (n = 198)	0.3 (0.2 to 0.5)	0.3 (0.1 to 0.6)	0.0 (-0.1 to 0.1)	.650
14-d (n = 83)	0.2 (0.1 to 0.3)	0.1 (0.1 to 0.4)	0.0 (-0.0 to 0.1)	.389
Interleukin 6, median (IQR), pg/L				
3-d (n = 245)	52.0 (30.7 to 83.2)	79.7 (36.9 to 120.8)	-20.0 (-33.7 to -7.9)	.001
5-d (n = 229)	44.5 (21.8 to 80.8)	51.6 (29.5 to 106.0)	-9.7 (-21.0 to 0.2)	.054
7-d (n = 197)	39.9 (18.3 to 76.8)	37 (14.3 to 75.1)	1.2 (-8.2 to 10.6)	.520
14-d (n = 83)	26.3 (16.8 to 52.2)	19.0 (11.1 to 56.4)	4.3 (-5.0 to 13.1)	.358
Albumin, median (IQR), pg/L				
3-d (n = 247)	34.1 (31.7 to 37.0)	33.2 (30.8 to 36.4)	0.7 (-0.2 to 1.7)	.134
5-d (n = 232)	34.5 (32.5 to 37.5)	33.6 (33.6 to 36.7)	1.2 (0.2 to 2.4)	.028
7-d (n = 198)	33.9 (31.2 to 36.4)	34.0 (31.5 to 36.8)	-0.3 (-1.4 to 0.9)	.674
14-d (n = 85)	34.7 (31.7 to 37.4)	35.7 (33.1 to 38.2)	-1.1 (-2.9 to 0.5)	.206
Neutrophil count, median (IQR), pg/L				
3-d (n = 245)	8.8 (6.7 to 11.4)	8.3 (6.5 to 11.3)	0.2 (-0.7 to 1.0)	.731
5-d (n = 232)	9.8 (6.8 to 13.9)	10.2 (6.7 to 14.4)	-0.2 (-1.5 to 1.1)	.763
7-d (n = 198)	13.6 (9.3 to 18.2)	12.8 (8.9 to 17.6)	0.5 (-1.4 to 2.5)	.583
14-d (n = 85)	9.5 (5.8 to 11.9)	8.3 (6.5 to 14.1)	-0.6 (-2.6 to 1.5)	.535
VAS, median (IQR)				
1-d (n = 248)	3 (2 to 5)	4 (3 to 6)	-1 (-1 to 0)	.008
2-d (n = 248)	3 (2 to 4)	3 (2 to 5)	-1 (-1 to 0)	.001
3-d (n = 247)	2 (1 to 3)	3 (1 to 4)	0 (-1 to 0)	.090
4-d (n = 241)	2 (0 to 3)	2 (0 to 3)	0 (0 to 0)	.689
5-d (n = 233)	1 (0 to 3)	2 (0 to 3)	0 (0 to 0)	.641
6-d (n = 211)	1 (0 to 2)	1 (0 to 3)	0 (0 to 0)	.870

(*continued on next page*)

Table 2 (*continued*)

Variables	Chaiqinchengqi (n=124)	Placebo (n=124)	Between-group difference (95% CI)	*P* value
7-d (*n* = 200)	1 (0 to 2)	1 (0 to 3)	0 (0 to 0)	.944
PASS, median (IQR)				
1-d (*n* = 248)	180 (105 to 230)	210 (135 to 265)	-30 (-55 to -10)	.028
2-d (*n* = 248)	135 (80 to 229)	203 (105 to 278)	-40 (-70 to -15)	.002
3-d (*n* = 247)	115 (75 to 200)	183 (91 to 254)	-40 (-65 to -15)	.001
4-d (*n* = 241)	100 (65 to 205)	158 (74 to 220)	-25 (-55 to 0)	.025
5-d (*n* = 233)	105 (65 to 170)	135 (75 to 236)	-30 (-60 to -5)	.008
6-d (*n* = 211)	80 (50 to 165)	120 (65 to 234)	-25 (-50 to 0)	.045
7-d (*n* = 200)	90 (55 to 140)	110 (50 to 210)	-15 (-40 to 5)	.197
Mean EQ-5D-5L score, median (IQR)				
7-d (*n* = 198)	0.83 (0.5 to 0.9)	0.73 (0.2 to 0.9)	0.06 (0.0 to 0.2)	.039
6-w (*n* = 226)	1.0 (1.0 to 1.0)	0.94 (0.9 to 1.0)	0.06 (0.0 to 0.1)	<.001

Abbreviations: SD, standard deviation; IQR, interquartile range; CI, confidence intervals; NIPPV, non-invasive positive pressure ventilation; IMV, invasive mechanical ventilation; CRRT, continuous renal replacement therapy; AGI, gastrointestinal injury; IAH, intra-abdominal hypertension; ACS, abdominal compartment syndrome; ICU, intensive care unit; LOS, Length of hospital stay; SIRS, systemic inflammatory response syndrome; CRP, C-reaction protein; VAS, visual analogue scale; PASS, pancreatitis activity scoring system.

drainage or necrosectomy were significantly lower in Chaiqinchengqi group than in control group. The duration of SIRS (6.0 [3.0 to 10.0] vs 9.0 [4.0 to 13.0]; median difference, -2; 95% CI, -4 to -1, *P*=.001) and 3-day interleukin 6 (52.0 [30.7 to 83.2] vs 79.7 [36.9 to 120.8]; median difference, -20.0; 95% CI, -33.7 to -7.9, *P*=.001) were significantly lower in the Chaiqinchengqi group than in the control group. Compared with the placebo group, 5-day albumin (34.5 [32.5 to 37.5] vs 33.6 [33.6 to 36.7]; median difference, 1.2; 95% CI, 0.2 to 2.4, *P*=.028) was higher in the Chaiqinchengqi group.

There was no significant difference in 6-month all-cause mortality, the length of hospital stays and costs. The need of ICU admission was significantly lower in the Chaiqinchengqi group than in the control group (4.0% vs 11.3%, *P*=.032). Patients in the Chaiqinchengqi group had higher proportion of mild and moderately severe form, however, the placebo group had higher proportion of moderately and severe forms (*P*=.004). As for patient self-reported quality of life, Chaiqinchengqi group reported better quality of life in mobility, self-care, usual activities on 1-week after enrollment (*P*=.039).

The duration of IAH (1.0 [0 to 4.0] vs 3.0 [0 to 5.0]; median difference, 0; 95% CI, -1 to 0, *P*=.048), the composition ratio of AGI grading (P=.008), the days of AGI duration (2.0 [0 to 5.0] vs 4.0 [0 to 7.0]; median difference, -1; 95% CI, -3 to 0, *P*=.040), and the days of fasting (5.0 [4.0 to 8.0] vs 7.0 [5 to 9.0]; median difference, -1; 95% CI, -2 to -1, *P*=.001) were significantly lower in the Chaiqinchengqi group than in the control group. Accordingly, the adherence of the Chaiqinchengqi group to receive the research drug treatment orally was comparable, and the time of use and the dosage of the Chaiqinchengqi group patients receiving the subject drug orally and by enema were lower than those of the control group (both $P < .001$).

As for contaminant medications, the cumulative 28-day doses of

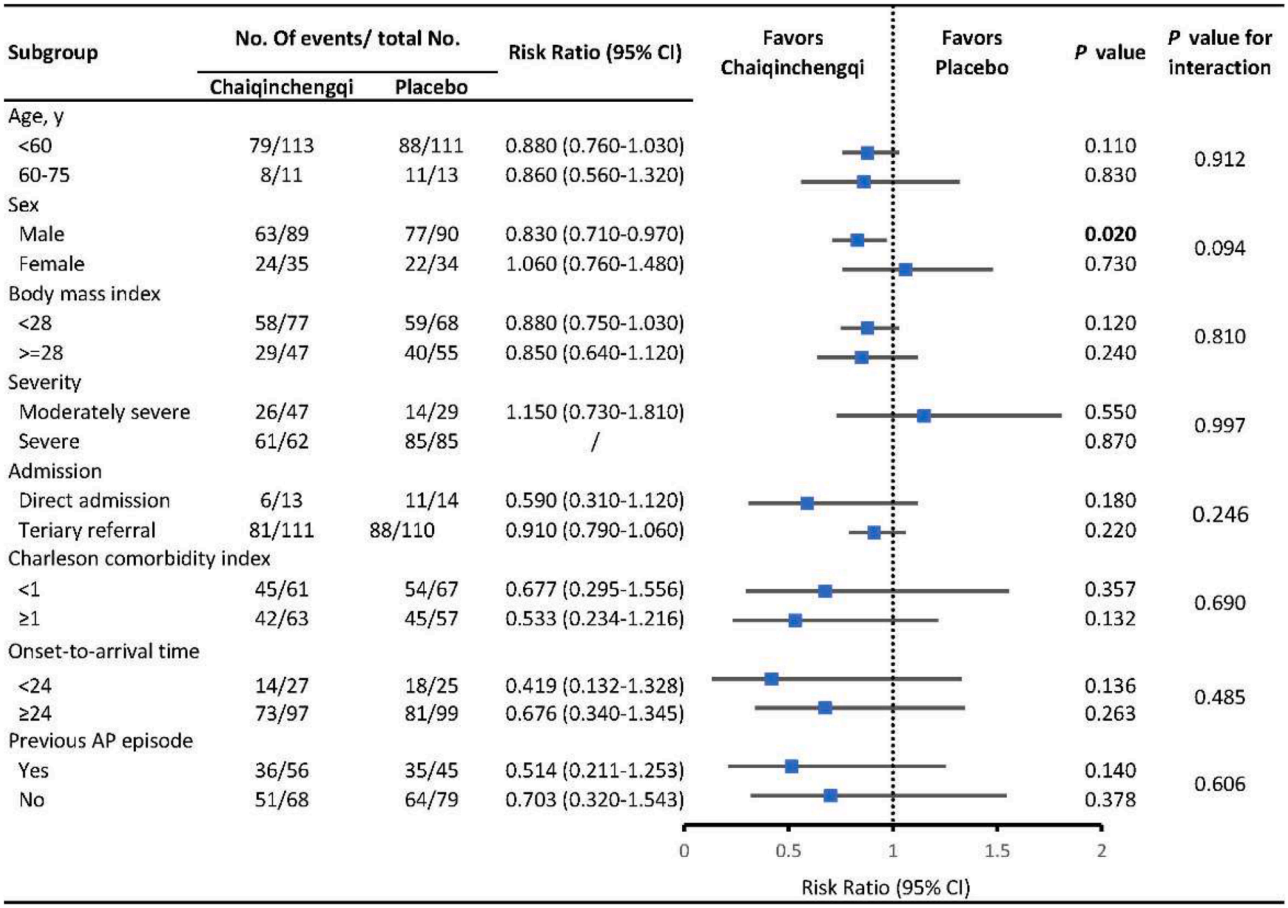

Fig. 2. Subgroup analysis for respiratory failure.

neostigmine, dulcolax, and gastrofibromyalgia was not significantly different between the two groups (eTable 2 in Supplement 3). The catheterization of anal tube (8.9% vs 24.2%, P=.001) was significantly lower in the Chaiqinchengqi group, but the utilization of gastrointestinal decompression was not significantly different. Compared with the placebo group, VAS scores on 1 and 2 days and the cumulative dosage of analgesics in the Chaiqinchengqi group was significantly lower than in the control group.

Subgroup analysis for respiratory failure within 28 days

In the subgroup analyses stratified based on age, sex, etiology, severity, intervals from onset to admission, and referral, Chaiqinchengqi was associated with a lower risk of respiratory failure among male patients (Fig. 2). Moreover, Chaiqinchengqi was associated with a lower risk of new-onset respiratory failure among patients aged < 60 years, male, body mass index < 28, severe form, with Charlson comorbidity index <1, with admission intervals <24h and first episode of acute pancreatitis (eFig. 1 in Supplement 3).

Time to respiratory failure resolution by day 28 in the chaiqinchengqi and placebo group

As compared with the placebo group, the Chaiqinchengqi group had a lower cumulative incidence of respiratory failure resolution from enrollment to day 28, with a significant reduction as well after the 3-day landmark point (HR, 0.64 [95% CI, 0.42 to 0.96]; Fig. 3).

Adverse events

Nonfatal serious adverse events occurred in 31 patients (25.0%) in the Chaiqinchengqi group and 29 (23.4%) in the placebo group (P = .767), mainly driven by symptoms in the digestive system such as diarrhea and nausea. The adverse drug reactions of hypernatremia that required treatment occurred in 24 patients (19.4%) in the Chaiqinchengqi group and 5 patients (0.4%) in the placebo group, respectively. Specific adverse events are listed in eTable 3 in Supplement 3.

Discussion

To the best of our knowledge, this is the first large randomized clinical trial to demonstrate the safety and efficacy of Chaiqinchengqi decoction with 89.9% of the patients presenting moderately severe to severe acute pancreatitis. In this randomized clinical trial of Chinese patients with acute pancreatitis, Chaiqinchengqi decoction as an adjunctive therapy in addition to guideline-directed treatment reduced the duration of 28-day respiratory failure, as well as secondary outcomes of circulatory failure, severity, gastrointestinal injuries, and new-onset organ failure. The Kaplan-Meier analysis consolidated the primary findings. This study provides important insights into the decision-making around Chaiqinchengqi decoction in patients with acute pancreatitis.

This trial proved Chaiqinchengqi can reduce gastrointestinal failure, promote the recovery of intestinal function, and ameliorates the acute deterioration of new-onset or existing organ failure. In the early stage of the disease, gastrointestinal injury and IAH are considered as the "trigger point" for severe acute pancreatitis (Uhl et al., 1996; Wang et al., 2003; Wu et al., 2014), which leading to the development of acute respiratory distress syndrome and acute lung injury. Our study showed a two-day reduction in the duration of respiratory failure, accompanying with the duration of IAH in the Chaiqinchengqi group being reduced by two days in comparison to the placebo group. In the theory of traditional Chinese medicine, the lung and the large intestine have an exterior-interiorly relationship. Our previous clinical study demonstrated traditional Chinese medicines alleviated the duration of intestinal obstruction and restore gastrointestinal function (Chen et al., 2015). The meta-analysis showed that the combination of rhubarb may facilitate the restoration of gut function and alleviate disease severity in patients with severe acute pancreatitis (Chen et al., 2020). In the theory of traditional Chinese medicine, the lung and the large intestine have an exterior-interiorly relationship. The potential explanation for these findings was that Chaiqinchengqi decoction could reduce IAH, purge the intestines and remove the detoxification, thereby alleviating respiratory failure. Both groups were treated with the standard conventional treatment, but the duration and dosage of the contaminant drugs, including somatostation, octreotide and neostigmine, in the Chaiqinchengqi group were lower than those in the placebo group. It can be stated with certainty that the improvement in clinical outcomes was owing to the effect of Chaiqinchengqi decoction.

In this trial, the patients were followed up until 6 months from the discharge, and the EQ-5D-5L questionnaire was used to assess the quality of life in patients. The results indicated EQ-5D-5L score in Chaiqinchengqi group was significantly higher compared with the placebo group within 6 weeks after discharge. Chaiqinchengqi decoction administration also effectively improve the health behavior ability of acute pancreatitis patients, relieve the pain and anxiety of acute

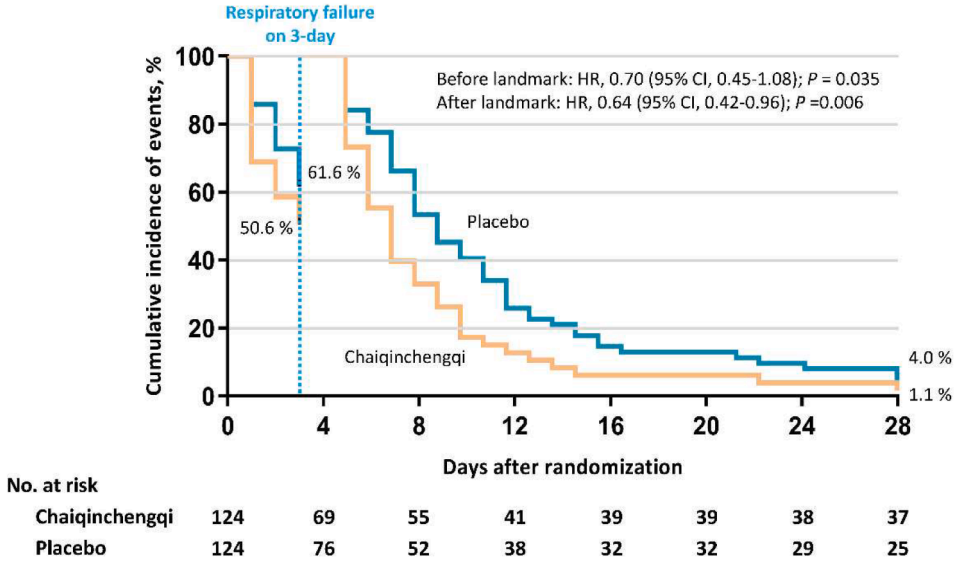

Fig. 3. Kaplan-Meier curves for the cumulative incidence of respiratory failure within 28 days. HR, hazard ratio.

pancreatitis patients, shorten the time to return to normal life, help patients return to normal work faster and improve the quality of life of patients, and have greater social value.

Concerns have been raised regarding the safety of herbal medicine. No severe adverse events were observed that were likely to be related to Chaiqinchengqi decoction. Some potential safety signals remained, as Chaiqinchengqi decoction may increase stool volume and frequency, as well as the risk of hypokalemia. However, the increase in stool and hypokalemia resolved upon cessation of Chaiqinchengqi decoction and with the administration of symptomatic treatment. It is our contention that the increase in stool volume was indicative of enhanced intestinal motility.

In this study, pragmatic approach was conducted to meet the practical needs of a heterogeneous population and the complex interventions, considering the internal authenticity in addition to the external authenticity of the study design. The AGI algorithm was proposed to guide appropriate use of traditional Chinese medicine, but AGI grading standard is a basic guidance. The use of research drugs was based on the patient's conditions and their wishes and the decision-making of medical experts. This study may serve as a model for future clinical trials to evaluate the safety and efficacy of Chinese medicinal decoction for critical disease.

Limitations

There are several limitations of this study. First, the Chaiqincehngqi decoction is a traditional Chinese compound of multiple plant and mineral products. Despite the clinical efficacy demonstrated in this trial, the active ingredients and the exact mechanisms remain to be determined. Second, this is a single-center study, and the clinical practices in relation to the patients with acute pancreatitis might vary among other healthcare settings. Third, the placebo of decoction solution has always been a difficulty in clinical trials due to the lack of uniform standards, and the use of low-dose of Chaiqinchengqi decoction as a placebo is an obstacle that restricts the clinical research of Chinese medicine for acute pancreatitis.

Conclusion

The findings of the study provide compelling evidence that the use of Chaiqinchengqi decoction as an adjunctive therapy in addition to guideline-directed therapies significantly reduces the duration of respiratory failure and improved clinical outcomes within 6 months. Multicenter, randomized controlled trial is warranted to strengthen the evidence of safety and efficacy of Chaiqinchengqi decoction in the management of acute pancreatitis.

Group information

A complete list of the CAP trial investigators is shown in Supplement 4.

Funding

This study is supported by the New Zealand-China Strategic Research Alliance 2016 Award, Ministry of Science and Technology, China (Grant No. 2016YFE0101800), Project of Sichuan Provincial Administration of Traditional Chinese Medicine (Grant No. 2020ZD004), Project of Sichuan Provincial Administration of Traditional Chinese Medicine Innovation Research Team (Grant No. 2023ZD04) and Projects of Sichuan Provincial Science and Technology (Grant No. 2023YFS0283).

CRediT authorship contribution statement

Lihui Deng: Writing – original draft, Project administration, Investigation, Conceptualization. **Zhiyao Chen:** Writing – original draft, Methodology, Investigation, Data curation. **Tao Jin:** Methodology, Investigation, Conceptualization. **Fei Cai:** Investigation. **Yanqiu He:** Investigation. **Yuxin Shen:** Investigation. **Shihang Zhang:** Investigation. **Jia Guo:** Investigation. **Xiaonan Yang:** Investigation. **Lin Yang:** Resources, Investigation. **Huimin Lu:** Investigation. **Chunhui Wang:** Investigation. **Wenfu Tang:** Investigation. **Ziqi Lin:** Investigation, Conceptualization. **Lan Li:** Investigation. **Qingyuan Tan:** Investigation. **Ping Zhu:** Software, Formal analysis. **Xiaoxin Zhang:** Investigation. **Na Shi:** Investigation. **Cheng Hu:** Investigation. **Zixing Huang:** Investigation. **Dan Du:** Validation, Investigation. **Wei Huang:** Writing – review & editing, Funding acquisition, Conceptualization. **Zhongwei Zhang:** Resources, Investigation. **Shu Zhang:** Resources, Investigation. **Qing Xia:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

We would like to acknowledge all the patients who participated in this study and all the staffs from multidisciplinary team for acute pancreatitis at West China Hospital of Sichuan University.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.phymed.2025.156393.

References

Cao, F., Xiang, J., Wang, Y., Chen, X., Lu, X., Xu, X., Chen, L., Fan, Y., Yuan, C., Dong, X., Zhu, Q., Han, C., Lu, G., Xia, Q., Chen, W., 2024. Chaiqin chengqi decoction alleviates acute pancreatitis by targeting gasdermin D-mediated pyroptosis. J. Ethnopharmacol. 318 (Pt A), 116920.

Chen, W., Yang, X., Huang, L., Xue, P., Wan, M., Guo, J., Zhu, L., Jin, T., Huang, Z., Chen, G., Tang, W., Xia, Q., 2015. Qing-Yi decoction in participants with severe acute pancreatitis: a randomized controlled trial. Chin. Med. 10, 11.

Chen, X., Yang, K., Jing, G., Yang, J., Li, K., 2020. Meta-analysis of efficacy of rhubarb combined with early enteral nutrition for the treatment of severe acute pancreatitis. JPEN. J. Parenter. Enteral. Nutr. 44 (6), 1066–1078.

Chen, Z., Yang, X., Guo, J., Jin, T., Lin, Z., Zhu, P., Li, J., Li, L., Sun, X., Du, D., Jiang, K., He, Y., Cai, F., Li, L., Hu, C., Tan, Q., Huang, W., Deng, L., Xia, Q., 2022. AGI grade-guided chaiqin chengqi decoction treatment for predicted moderately severe and severe acute pancreatitis (CAP trial): study protocol of a randomised, double-blind, placebo-controlled, parallel-group, pragmatic clinical trial. Trials 23, 933.

Crockett, S.D., Wani, S., Gardner, T.B., Falck-Ytter, Y., Barkun, A.N., 2018. American Gastroenterological Association Institute Guideline on Initial Management of Acute Pancreatitis. Gastroenterology 154, 1096–1101.

Du, D., Yao, L., Zhang, R., Shi, N., Shen, Y., Yang, X., Zhang, X., Jin, T., Liu, T., Hu, L., Xing, Z., Criddle, D.N., Xia, Q., Huang, W., Sutton, R., 2018. Protective effects of flavonoids from Coreopsis tinctoria Nutt. on experimental acute pancreatitis via Nrf-2/ARE-mediated antioxidant pathways. J. Ethnopharmacol. 224, 261–272.

Forsmark, C.E., Vege, S.S., Wilcox, C.M, 2016. Acute Pancreatitis. N. Engl. J. Med. 375, 1972–1981.

Huang, L., Wang, M.H., Cheng, Z.Y., Xue, P., Jin, T., Yang, X.N., Xia, Q., 2012. Effects of Chai-Qin-Cheng-Qi decoction on acute pancreatitis-associated lung injury in mice with acute necrotizing pancreatitis. Chin. J. Integr. Med. 2012. Sep 21.

Huang, Y., Wen, Y., Wang, R., Hu, L., Yang, J., Yang, J., Pu, Q., Han, C., Cai, W., Peng, Y., Wang, Y., Jiang, H., Hong, J., Phillips, A.R., Fu, X., Huang, W., Xia, Q., Du, D., 2022. Temporal metabolic trajectory analyzed by LC-MS/MS based targeted metabolomics in acute pancreatitis pathogenesis and Chaiqin Chengqi decoction therapy. Phytomedicine 99, 153996.

Imrie, C.W., Benjamin, I.S., Ferguson, J.C., McKay, A.J., Mackenzie, I., O'Neill, J., Blumgart, L.H., 1978. A single-centre double-blind trial of Trasylol therapy in primary acute pancreatitis. Br. J. Surg. 65, 337–341.

Kirkpatrick, A.W., Roberts, D.J., De Waele, J., Jaeschke, R., Malbrain, M.L., De Keulenaer, B., Duchesne, J., Bjorck, M., Leppaniemi, A., Ejike, J.C., Sugrue, M., Cheatham, M., Ivatury, R., Ball, C.G., Reintam Blaser, A., Regli, A., Balogh, Z.J., D'Amours, S., Debergh, D., Kaplan, M., Kimball, E., Olvera, C., 2013. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. Intensive Care Med. 39, 1190–1206.

Peery, A.F., Crockett, S.D., Murphy, C.C., Lund, J.L., Dellon, E.S., Williams, J.L., Jensen, E.T., Shaheen, N.J., Barritt, A.S., Lieber, S.R., Kochar, B., Barnes, E.L., Fan, Y. C., Pate, V., Galanko, J., Baron, T.H., Sandler, R.S., 2019. Burden and cost of gastrointestinal, liver, and pancreatic diseases in the United States: Update 2018. Gastroenterology 156, 254–272.e11.

Qiong, W., Yiping, W., Jinlin, Y., Tao, G., Zhen, G., Pengcheng, Z., 2005. Chinese medicinal herbs for acute pancreatitis. Cochrane Database Syst. Rev. 2005, Cd003631.

Reintam Blaser, A., Malbrain, M.L., Starkopf, J., Fruhwald, S., Jakob, S.M., De Waele, J., Braun, J.P., Poeze, M., Spies, C., 2012. Gastrointestinal function in intensive care patients: terminology, definitions and management. recommendations of the ESICM Working Group on Abdominal Problems. Intensive Care Med. 38, 384–394.

Schepers, N.J., Bakker, O.J., Besselink, M.G., Ahmed Ali, U., Bollen, T.L., Gooszen, H.G., van Santvoort, H.C., Bruno, M.J., 2019. Impact of characteristics of organ failure and infected necrosis on mortality in necrotising pancreatitis. Gut 68, 1044–1051.

Shi, N., Liu, T., de la Iglesia-Garcia, D., Deng, L., Jin, T., Li, L., Zhu, P., Hu, W., Zhou, Z., Singh, V., Dominguez-Munoz, J.E., Windsor, J., Huang, W., Xia, Q., Sutton, R., 2020. Duration of organ failure impacts mortality in acute pancreatitis. Gut 69, 604–605.

Siebert, M., Le Fouler, A., Sitbon, N., Cohen, J., Abba, J., Poupardin, E., 2021. Management of abdominal compartment syndrome in acute pancreatitis. J. Visc. Surg. 158, 411–419.

Tenner, S., Baillie, J., DeWitt, J., Vege, S.S., 2013. American college of gastroenterology guideline: management of acute pancreatitis. Am. J. Gastroenterol. 108, 1400–1415, 16.

Uhl, W., Isenmann, R., Curti, G., Vogel, R., Beger, H.G., Buchler, M.W., 1996. Influence of etiology on the course and outcome of acute pancreatitis. Pancreas. 13, 335–343.

Wang, X., Gong, Z., Wu, K., Wang, B., Yuang, Y., 2003. Gastrointestinal dysmotility in patients with acute pancreatitis. J. Gastroenterol. Hepatol. 18, 57–62.

Wen, Y., Han, C., Liu, T., Wang, R., Cai, W., Yang, J., Liang, G., Yao, L., Shi, N., Fu, X., Deng, L., Sutton, R., Windsor, J.A., Hong, J., Phillips, A.R., Du, D., Huang, W., Xia, Q., 2020. Chaiqin chengqi decoction alleviates severity of acute pancreatitis via inhibition of TLR4 and NLRP3 inflammasome: Identification of bioactive ingredients via pharmacological sub-network analysis and experimental validation. Phytomedicine 79, 153328.

Wu, B.U., Johannes, R.S., Sun, X., Tabak, Y., Conwell, D.L., Banks, P.A., 2008. The early prediction of mortality in acute pancreatitis: a large population-based study. Gut 57, 1698–1703.

Wu, L.M., Sankaran, S.J., Plank, L.D., Windsor, J.A., Petrov, M.S., 2014. Meta-analysis of gut barrier dysfunction in patients with acute pancreatitis. Br. J. Surg. 101, 1644–1656.

Wu, W., Luo, R., Lin, Z., Xia, Q., Xue, P., 2016. Key Molecular Mechanisms of Chaiqinchengqi Decoction in Alleviating the Pulmonary Albumin Leakage Caused by Endotoxemia in Severe Acute Pancreatitis Rats. Evid. Based. Complement. Alternat. Med. 2016, 3265368.

Xue, P., Guo, J., Yang, X.N., Huang, W., Xia, Q., 2014. Changes of neuronal acetylcholine receptor alpha 7 of peritoneal macrophage in experimental acute pancreatitis treated by Chaiqin Chengqi Decoction. Chin. J. Integr. Med. 20, 770–775.

Yang, X., Zhang, X., Lin, Z., Guo, J., Yang, X., Yao, L., Wang, H., Xue, P., Xia, Q., 2020. Chaiqin chengqi decoction alleviates severe acute pancreatitis associated acute kidney injury by inhibiting endoplasmic reticulum stress and subsequent apoptosis. Biomed. PharmacOther 125, 110024.

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. 2017, 5864945.

Zhou, Q., Chang, B., Chen, X.Y., Zhou, S.P., Zhen, Z., Zhang, L.L., Sun, X., Zhou, Y., Xie, W.Q., Liu, H.F., Xu, Y., Kong, Y., Zhou, L.B., Lian, F.M., Tong, X.L., 2014. Chinese herbal medicine for obesity: a randomized, double-blinded, multicenter, prospective trial. Am. J. Chin. Med. 42, 1345–1356.

Zhou, T., Guan, H., Wang, L., Zhang, Y., Rui, M., Ma, A., 2021. Health-related quality of life in patients with different diseases measured with the eq-5d-5l: a systematic review. Front Public Health. 9, 675523.