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STUDY PROTOCOL

A Randomized, Double-Blind, Placebo-Controlled Trial Protocol Using the Fuzhengxiaoliu Patch for the Management of Primary Liver Cancer Pain

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Objective: Chronic pain strongly affects the quality of life of patients with liver cancer pain. Safe and effective management of cancer-related pain is a worldwide challenge. Traditional Chinese medicine (TCM) has rich clinical experience in the treatment of cancer pain. The Fuzhengxiaoliu patch (FZXLP) is a compound TCM with the effects of detoxification and pain relief and has shown great efficacy in the treatment of patients with liver cancer, but high-quality clinical research that provides research-based evidence is lacking. We designed a randomized, double-blind, placebo-controlled trial to explore and evaluate the efficacy of FZXLP for the treatment of liver cancer pain.

Methods: This is a prospective, randomized, double-blind, placebo-controlled trial. The trial will enrol 72 participants with primary liver cancer with cancer pain (damp-heat stagnation and toxin and blood stasis syndrome). The primary objective is to measure the reduction in pain using FZXLP in combination with tegafur, gimeracil and oteracil potassium capsule (S-1) compared to the placebo group with S-1. Pain will be measured by the number of opioids used, Chinese versions of the numerical rating scale (NRS), pain relief rate and number of breakthrough cases of cancer pain (BTcP). The secondary objectives include response evaluation criteria in solid tumors (RECIST), tumor markers, TCM syndrome scores, weight, functional assessment of cancer therapy-hepatobiliary (FACT-Hep) questionnaire scores, and self-rating anxiety scale scores. Adverse events (AEs) will be recorded throughout the study.

Discussion: This study integrated TCM with clinical research to assess the efficacy and safety of the addition of FZXLP in the treatment of primary liver cancer pain.

Trial registration: Chinese clinical trial registry, ChiCTR2300076951, Registered on October 25, 2023. https://www.chictr.org.cn/showproj.html?proj=209608.

Keywords: primary liver cancer, traditional Chinese medicine, Chinese herb, cancer pain management, randomized controlled trial

Background

Liver cancer is the fourth most common cause of death globally, accounting for more than 800,000 deaths annually.[1,2] The number of new cases of liver cancer per year is predicted to increase by 55.0% between 2020 and 2040, with 1.4 million people possibly diagnosed in 2040.[3] Hepatocellular carcinoma (HCC) (75–85% of cases) and intrahepatic cholangiocarcinoma (10–15%), as well as other types, are the most common types of primary liver cancer.[4] Ninety percent of HCC patients experience pain symptoms due to the overgrowth of liver tumors, their invasion or infiltration of surrounding tissues, and their suppressive effects on nociceptors in adjacent organs; most of these patients experience moderate-to-severe pain.[5,6] In most cases, moderate-to-severe cancer pain can be effectively managed with available medications, including opioids.[7] However, long-term use of opioids may cause nausea, vomiting, constipation, lethargy, and respiratory depression, which seriously affect the quality of life of patients.[8,9] Patients may become addicted to opioids to some extent and experience withdrawal symptoms after discontinuing them.[10] Liver cancer generally arises in a background of cirrhosis and inflammation,[11] and increasing the dose of opioids can further impair liver function in patients with liver cancer and reduce analgesia.[6,12] Moreover, patient difficulties with opioid use include reduced

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reimbursement, high subject copays, and a lack of availability of opioids at retail pharmacies, as well as the stigma attached to opioids.[13,14] All these barriers place patients with liver cancer at great risk of suffering from uncontrolled pain.

The effects of traditional Chinese medicine (TCM) on cancer pain focus not only on the cause but also on the result of the disease so that the treatment is more target-focused and can produce excellent therapeutic effects.[15] Studies have shown that Chinese herbal medicine has beneficial effects on improving pain outcomes.[16,17] FZXLP is a Chinese herb preparation used externally that includes eight major components: Sparganii Rhizoma (*Sparganium stoloniferum* Buch.-Hma, Sanleng), Curcumae Rhizoma (*Curcuma phaeocaulis* VaL., *Curcuma kuuangsiensis* S. G. Lee et C. F. Liang or *Curcuma wenyujin* Y. H. Chen et C. Ling, Ezhu), Atractylodes (*Atractylodes macrocephala* Koidz, Baihu) *Bovis* Calculus (*gallstones* of *Bos taurus domesticus* Gmelin, Niuhuang), Pteris multifida (*Pteris multifida Poir*, Fengweicao), Sarcandra glabra (*Sarcandra glabra* (Thunb). Nakai, Zhongjiefeng), Fagopyrum dibotrys *(F. dibotrys)* (D.Don) H.Haram, Jinqiaomai), Alternanthera philoxeroides (*Alternanthera philoxeroides* (Mart). Griseb., Kongxinlianzicao). This TCM is beneficial for heat clearing and blood cooling, promoting blood circulation, removing swelling and lumps, and detoxifying and relieving pain and is widely used in China. Compared with other traditional Chinese medicine or conventional cancer pain treatment methods, FZXLP, owing to its specific formulation and application method, has the advantages of good efficacy and few side effects and thus can provide patients with one more option. Additionally, for patients who accept TCM, this can also help improve patient compliance with treatment. However, few randomized controlled trials (RCTs) have investigated the effects of this Chinese herbal medicine. This study aimed to assess the efficacy and safety of the addition of FZXLP in the treatment of primary liver cancer pain. The primary objective is to measure the reduction in pain using FZXLP in combination with tegafur, gimeracil and oteracil potassium capsule (S-1) compared to the placebo group with S-1. Pain will be measured by the number of opioids used, Chinese versions of the numerical rating scale (NRS), pain relief rate and number of breakthrough cases of cancer pain (BTcP). The secondary objectives include response evaluation criteria in solid tumors (RECIST), tumor markers, TCM syndrome scores, weight, functional assessment of cancer therapy-hepatobiliary (FACT-Hep) questionnaire scores, and self-rating anxiety scale scores. Adverse events (AEs) will be recorded throughout the study. The purpose of this protocol is to present the methodologies and details of the protocol.

Methods

Design and Settings

This study is a prospective, randomized, double-blind, placebo-controlled trial that has been registered with the China Clinical Trials Registry (registration number: ChiCTR2300076951). All the documents, including the study protocol, informed consent, and case report forms (CRFs), met the requirements of the Helsinki declaration and were reviewed by the Ethical Review Committee of the Hospital of Chengdu University of TCM, grant number 2023KL-125. The study design is shown in Figure 1.

Participants

Sample Size

In this study, with reference to the results of the retrospective cohort study on the treatment of liver cancer with FZXLP in the previous period,[18] the difference in the reduction in pain scores before and after treatment between the experimental group and the control group was 1.61, with the standard deviation of the experimental group being 1.54, the standard deviation of the control group being 2.45, the biparietal α=0.05, the degree of certainty 1-β, being 0.8, and the ratio of the sample sizes of the experimental and the control groups being 1:1. The sample size is calculated via PASS 15.0 software, which considers approximately 25% of lost visits, as well as refused visits, resulting in a sample size of 72 cases (36 cases in each group).

Recruitment

This trial was jointly conducted by the Oncology Department and the Department of Clinical Research Physicians of the Hospital of Chengdu University of TCM. The Oncology Department of this hospital has a wealth of clinical research experience and a rich source of patients. Recruitment is accomplished primarily through both offline and online channels.

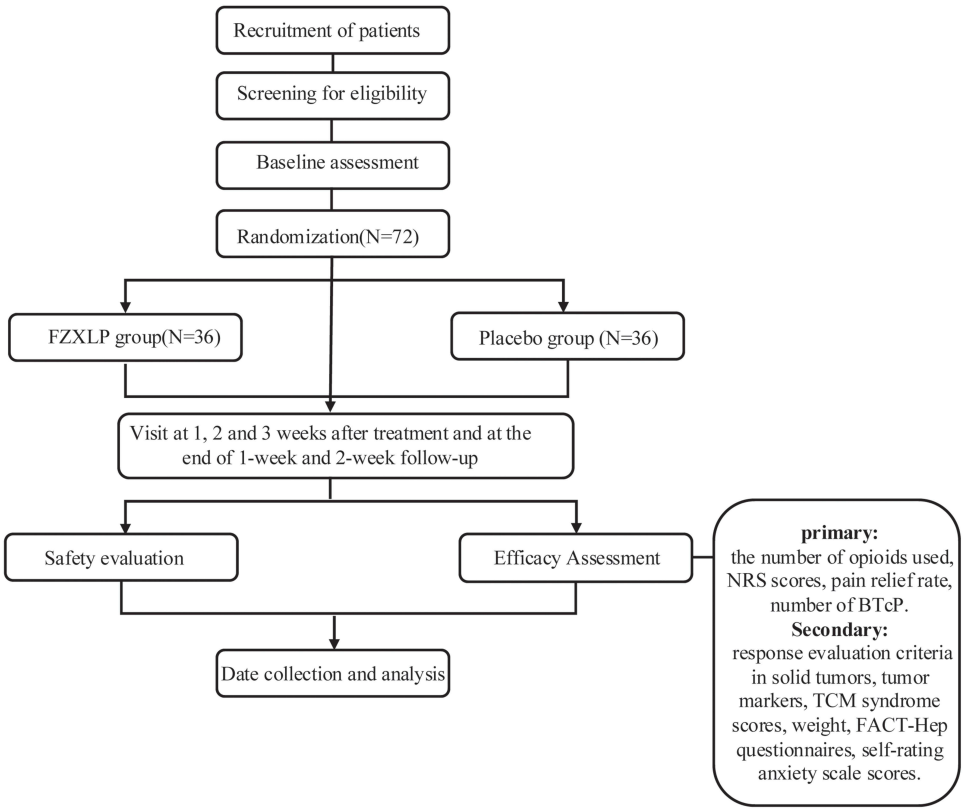

Figure 1 Flow chart of study procedures.

The researchers responsible for recruiting patients all have been well trained and have rich experience in clinical and experimental research. Recruitment was carried out on October 20, 2023.

Patient Screening

Prior to the trial, potential subjects will undergo screening at the Hospital of Chengdu University of TCM in accordance with the criteria to determine whether they are eligible for the study. Patients must provide written informed consent by signing a participant information sheet before any study procedures occur. The doctor will introduce the study to him/her in as much detail as possible and carefully answer the doubts of the subjects and their families. It is critical that the subjects comprehend the purpose, procedure and duration of the study, as well as the benefits, risks and discomfort that may appear during the research.

Diagnostic Criteria

Primary liver cancer was diagnosed pathologically or met the clinical diagnostic criteria for primary liver cancer (both refer to the general office of the National Health Commission 2022)[19]; the staging criteria were based on the American Joint Committee on Cancer Tumor Node Metastasis (TNM) staging system eighth edition (TNM-8).[20]

Patients are assessed via NRS in conjunction with interrogation, according to the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines Version for Adult Cancer 2023,[21] with Cancer Pain, 2023 Edition.

Standardization of TCM

The Guiding Principles for Clinical Research of New Drugs of TCM 2002,[22] and Guidelines for Chinese Medicine Treatment of Malignant Tumors 2014,[23] describe the main symptom as distending pain in the hypochondrium. The secondary symptoms are upset, irascibly xerostomia, bitter taste, abdominal distention, anorexia, yellow urination and an emaciated physique. The tongue is characterized by a red tongue or ecchymosis, and the tongue coating is yellow or

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greasy. Pulse manifestation is a string or rolling and rapid pulse. A patient must have the main symptom and two of the secondary symptoms, in accordance with the tongue and pulse conditions, to be diagnosed with damp-heat stagnation and toxin and blood stasis syndrome.

Inclusion Criteria

(1) All the subjects who met the diagnostic criteria for primary liver cancer presented with pain in the liver area; the pathological type of pain was somatic pain, and the etiology of cancer pain was directly caused by hepatocellular carcinoma.
(2) TCM diagnosis involves the interior retention of damp heat and the combination of blood stasis and toxin syndrome.
(3) NRS score ≥3 and ≤7.
(4) Patients with stage IIb cancer, stage IIIa cancer who refused surgery and other antitumor treatments, and stage IIIb and IV patients were included.
(5) Subjects had not received any systemic antitumor therapy, such as chemotherapy, radiotherapy, immunotherapy, targeting, palliative treatment for localized lesions (eg, TACE), traditional Chinese medicine or proprietary Chinese medicine, in the past 4 weeks.
(6) Eastern Cooperative Oncology Group (ECOG) score of 0–3.
(7) No breakage of the epidermis at the patch site.
(8) Age ≥ 18 years, ≤75 years, and expected subject survival >3 months.
(9) Subjects provided informed consent and signed the informed consent form.

Enrolled subjects were required to meet all the above inclusion criteria.

Exclusion Criteria

(1) Abnormal blood ammonia or routine blood tests: platelets $<70\times10^9$/L, white blood cells $<3\times10^9$/L, hemoglobin <80g/L, endogenous creatinine clearance <30mL/min, alanine aminotransferase >3 times the upper limit of the normal reference value, or glutamic oxaloacetic transaminase >3 times the upper limit of the normal reference value.
(2) Subjects who's mean NRS pain score fluctuated >±2 points from the prescreening mean NRS pain score three days prior to randomization.
(3) Coagulation disorders, bleeding tendencies or a history of bleeding evident in anticoagulation therapy.
(4) Subjects with mental and thinking disorders, poor compliance, or inability to perform independent pain assessments and investigations.
(5) Subjects with severe primary disorders of the heart, lungs, kidneys, metabolism, immunity, nerves, and urinary and hematopoietic systems.
(6) Subjects with a history of severe allergies to various drugs or allergies to the drugs and articles used in this trial.
(7) Women who are pregnant or breastfeeding.
(8) Subjects who, in the opinion of the investigator, are not suitable for participation in this clinical study.

Those who meet any of the above criteria will be excluded.

Shedding Criteria

(1) Serious adverse events or significant side effects.
(2) Serious complications during treatment and termination of treatment.
(3) Subjects who take or add other pain medication by themselves or who fail to follow the study protocol, which affects the judgment of efficacy and safety.
(4) Subjects who voluntarily withdrew from the trial without completing the prescribed course of treatment, who experienced a loss of visits, or who died for other reasons.

(5) Disease can be sharply exacerbated, or an unforeseen event can occur.
(6) Subjects whose pain has increased after two weeks of drug administration, who are unable to relieve pain with only the drugs in the protocol and remedial drugs, and who must switch to other drugs/protocols for treatment, withdraw from the study after completing the laboratory tests, terminate the study, and regard the results as ineffective, and include them in the clinical efficacy analysis.

Among them, (1), (2), (3), (4), and (5) were regarded as shedding cases, and the results could not be counted in the final clinical efficacy analysis.

Randomization, Blinding and Unblinding

We will perform stratified block randomization for the eligible subjects. Randomization will be stratified on the basis of the NRS pain score (NRS ≤ 3 or NRS > 4). Random number tables are provided by statistical professionals and generated via SAS software. The preparation of drug documentation and emergency correspondence is carried out by staff not involved in the clinical trial. Once participants are enrolled in the study, they will be randomly assigned to two groups at a 1:1 ratio, namely, the FZXLP group (n = 36) and the placebo group (n = 36). During the trial, drugs will be distributed in sequential order of subject inclusion for observation and their NRS pain score. For subjects with an NRS score ≤3, drugs are dispensed in the order of drug numbers 1–36, and for subjects with an NRS score >3, drugs are dispensed in the order of drug numbers 37–72. Drugs should not be chosen, and the drug number will remain constant throughout the trial. This is a double-blind trial in which all the staff, investigators, sponsors and statistics are blinded. The test drug and placebo are accompanied by an emergency letter with a corresponding number, which is kept by the principal investigator. In cases of an emergency (such as serious adverse events, serious complications, etc.) and the need for rescue measures, unblinding can be performed urgently with the identification and signature of the principal investigator.

Intervention

The main intervention measures include FZXLP in combination with S-1 capsules or placebo in combination with S-1 capsules. The individual personnel will package and label the investigational drug and placebo in accordance with random-number tables and drug blinds. All drugs are concealed in uniform packages with the same label and a 21-day supply. The subjects in the treatment group received FZXLP, whereas those in the control group received a placebo treatment of the same color, shape, and odor as FZXLP. FZXLP and placebo were provided by Chongqing Nanchuan Jinfo Mountain TCM Hospital with reference to the preparation standard in the Technical Guidelines for the Preparation and Study of Drugs for Clinical Trials of New Chinese Medicines (for Trial Implementation)[24] issued by the National Medical Products Administration in 2023. This study involved a research team assisting patients daily in applying Chinese herb preparations to a designated area to ensure compliance. The use of antitumor drugs was prohibited during the study period.

Screening Period

Subjects who met the inclusion criteria were given screening-period therapeutic medication, NRS scores were determined three days prior to randomization, and subjects with fluctuations in NRS scores of <±2 points from the prescreening period were randomized. The subjects in the screening period were divided into two groups: 1) subjects who used painkillers before enrollment were converted to equivalent oxycodone hydrochloride extended-release tablets every 12 h orally with reference to the subjects' previous 24 h dose of opioid painkillers and 2) subjects who did not use painkillers before enrollment was assessed for pain and were given oxycodone hydrochloride extended-release tablets of 10–20 mg every 12 h.

Treatment Period

After randomization, 36 subjects will receive FZXLP in combination with S-1 capsules, and 36 subjects will receive placebo in combination with S-1 capsules. The specific protocol was as follows:

Every morning at 10:00 ± 1 hour, the FZXLP/placebo was placed on the right side of the subject's upper abdomen, covering the surface skin corresponding to the liver, and then removed by the subject himself/herself at 6:00 ± 1 hour on

the morning of the second day. FZXLP/placebo was applied once a day for 20 ± 2 hours, 7 days for a course of treatment, and 21 days of continuous administration of a total of 3 courses of treatment.

Dosage of the S-1 capsule: 2 times a day, 1 time after breakfast and 1 time after dinner, over 14 days, and then stopped for 7 days, which is a cycle. For a body surface area <1.25m^2, the dosage is 40 mg/dose; for a 1.25m^2 ≤body surface area ≤1.5m^2, the dosage is 50 mg/dose; for a body surface area ≥1.5m^2, the dosage is 60 mg/dose.

Remarks: 1) Enrolled subjects with an analgesic maintenance screening period. 2) The principles of analgesic adjustment refer to the NCCN Clinical Practice Guidelines Version 1.2023 for Adult Cancer.[21] In the case of BTcp, it is up to the subject to contact the investigator, and the investigator will provide routine treatment after judging the subject's pain condition.

Outcome Measures and Assessments

Each subject will be asked to attend an in-person assessment appointment at the Oncology Department at four time points. The time points for the collection of outcome measures were study enrollment, baseline assessment, and 5 weeks following the initiation of study treatment. The specific measurements and time points for data collection in this study are outlined in Figure 2. The visit window for each visit was ±1 day. During the visit, the investigators arranged for the

	STUDY PERIOD						
	Enrolment	Baseline	Intervention Period			Follow-up period	
TIMEPOINT	V1 D-3	V2 D0	V3 *Week 1*	V4 *Week 2*	V5 *Week 3*	V6 *Week 4*	V7 *Week 5*
Patients:							
Eligibility screen	X						
Informed consent	X						
Randomization and allocation		X					
INTERVENTIONS:							
FZXLP-group			←	—	→		
Placebo-group			←	—	→		
ASSESSMENTS:							
Number of opioids		X	X	X	X	X	X
NRS for pain		X	X	X	X	X	X
Number of BTcP		X	X	X	X	X	X
Pain relief rate			X	X	X		
RECIST	X				X		
tumor markers	X				X		
TCM syndrome scores		X	X	X	X		
weight	X	X	X	X	X		
FACT Hepatobiliary		X	X	X	X		
Self-Rating Anxiety Scale		X	X	X	X		
Adverse Events		X	X	X	X	X	X

Remark:
V,vist;D,day; NRS,numerical rating scale; BTcP,break-through cancer pain; RECIST,response evaluation criteria in solid tumors.

Figure 2 Time schedule of participants.
Abbreviations: V, vist; D, day; NRS, numerical rating scale; BTcP, break-through cancer pain; RECIST, response evaluation criteria in solid tumors.

subjects to complete the corresponding examination according to the study progress. All tests will be administered by one of the two trained independent assessors.

Primary Outcomes

The primary outcome was the pain relief effect of FZXLP, which specifically included the change in the number of opioids used, NRS score, pain relief rate, and number of BTcPs.

Secondary Outcomes

The secondary outcomes include tumor and disease progression, which will be measured by changes in the RECIST score, tumor marker level and weight. Additionally, quality of life is also a secondary outcome, measured by the FACT-Hep questionnaire and self-rating anxiety scale.

Safety

Subjects are required to follow up at the hospital weekly during the trial to complete laboratory tests for electrolytes, complete blood count, liver function, kidney function, blood glucose and coagulation function, as well as physical examination and vital signs to ensure their safety. At each visit, the participants will report adverse events, and the investigator will record details, including the specific symptoms, onset, duration, severity, resolution, and possible association with treatment. When serious adverse events occur, the investigator will suspend participation and provide treatment immediately.

Statistical Analysis

After all the clinical data are collected, a computer is used, epidata is used to establish database data, and SASV9.4 is used for the Windows statistical software package for statistical processing after all the data are entered. The specific methods of statistical analysis are as follows: continuous variables are used to evaluate the number of cases, mean, standard deviation, median, minimum, and maximum for demographic data and other baseline eigenvalues. The frequency and composition ratio are calculated via count and grade data. The descriptive results involve inferential statistical results (p values).

For the analyses of laboratory data and the clinical efficacy of drugs, the chi-square test or Fisher's exact test was used for counting data, whereas ANOVA and the t test were used for measurement data. The grade data were analyzed relative to an identified distribution unit and the Cochran–Mantel–Haenszel test. The ratios or percentages of count data are expressed, and the measurement data are expressed as the means ± standard deviations. All the statistical tests were two-sided tests, with $P < 0.05$ indicating statistical significance. The last observation carried forward (LOCF) method will be used for missing data.

Discussion

TCM has been increasingly applied in clinical practice to treat cancer pain because of its good efficacy and few side effects.[15,25] FZXLP is a compound prescription for TCM that contains eight Chinese herbs. For example, *Curcumae Rhizoma-Sparganii Rhizoma* is a traditional botanical drug pair that contains multiple antitumor compounds that can promote blood circulation, prevent blood stasis, and treat tumors in the clinic.[26–28] The major bioactive compound of *Atractylodes* macrocephala is atractylenolide, and both atractylenolide-I and atractylenolide-II have remarkable anticancer activities.[29–32] *Bovis* calculus has been shown to play significant anti-inflammatory and antitumor roles.[33] *Pteris multifida* extract inhibits the proliferation, migration and invasion of cancer cells.[34,35] *S. glabra* extracts have previously been shown to have activity against solid tumors through the modulation of multiple targets or signaling pathways.[36–40] Pharmacological studies have revealed that *Fagopyrum dibotrys* extract possesses anticancer activities.[41–43] Previous clinical observations have shown that FZXLP can effectively improve symptoms in patients with liver cancer pain. However, few RCTs have been carried out on the effects of this integrated treatment. Our clinical design plan is based on the principles of international clinical trials. Strict quality control measures are designed via double-blind, randomized, placebo-controlled research methods. A professional independent statistician is responsible for the statistical analysis and

reporting. Strict trial design and supervision during the trial implementation process will ensure a scientific and objective evaluation of the efficacy and safety of FZXLP in the treatment of liver cancer pain. FZXLP also holds great potential for clinical applications beyond the scope of this trial. It can be integrated into multidisciplinary cancer care, providing a complementary approach to traditional cancer treatments. Future research areas may include investigating its long-term efficacy, exploring its efficacy for other cancers, and comparing it with other traditional Chinese medicine therapies or conventional treatments.

This trial has several limitations. First, the trial focused only on subjects with a TCM diagnosis involving the interior retention of damp heat and the combination of blood stasis and toxin syndrome. This restriction to a specific syndrome may limit the generalizability of the results in a broader population of patients with different TCM diagnoses or those without these syndromes. Another issue is that 3 weeks of treatment was too short to provide an assessment of the long-term efficacy and safety of FZXLP. Future studies could consider longer treatment durations and follow-up periods.

In conclusion, this trial is the first study designed to demonstrate the outcomes of FZXLP in the treatment of liver cancer pain.

Clinical Trial Status

Recruitment began in November 2023; therefore, 3 patients were recruited. It is expected to finish recruiting in December 2025, 25 months in total.

Trial Registration Number: ChiCTR2300076951, date: 25th October 2023.

Protocol version: 20231212, V1.1

Data Sharing Statement

Not applicable. Details of the current study are available from the corresponding author. The study results will be presented in medical journals or academic conferences and disseminated among doctors and patients.

Ethics Approval and Consent to Participate

This study was approved by the Ethical Review Committee of the Hospital of Chengdu University of TCM (Chengdu, China) (grant number 2023KL-125). We have fully considered the needs of patients when designing this protocol. Every participant voluntarily signed an ICF after fully understanding the content of the trial and potential risks. Patients will be able to obtain their test reports.

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We would like to thank all the investigators who are participating in this study.

Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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