

The Emotion Regulation of Acupuncture in Chronic Low Back Pain: A Clinical Neuroimaging Protocol

Peng Lai^{1,2}, Shirui Cheng^{1,2}, Xingyao Chen¹, Fangdong Cheng³⁻⁵, Jun Cheng³⁻⁵, Ming Xin^{3,4,6}, Deliang Zhu^{3,4,6}, Zhengjie Li^{1,2}, Xi Wu¹, Fang Zeng^{1,2}

¹Acupuncture and Tuina School, Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan, People's Republic of China; ²Acupuncture & Brain Research Center, Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan, People's Republic of China; ³Geriatric Diseases Institute of Chengdu, Chengdu Fifth People's Hospital (The Second Clinical Medical College, Affiliated Fifth People's Hospital of Chengdu University of Traditional Chinese Medicine), Chengdu, Sichuan, People's Republic of China; ⁴Cancer Prevention and Treatment Institute of Chengdu, Chengdu Fifth People's Hospital (The Second Clinical Medical College, Affiliated Fifth People's Hospital of Chengdu University of Traditional Chinese Medicine), Chengdu, Sichuan, People's Republic of China; ⁵Department of Orthopedic, Chengdu Fifth People's Hospital (The Second Clinical Medical College, Affiliated Fifth People's Hospital of Chengdu University of Traditional Chinese Medicine), Chengdu, Sichuan, People's Republic of China; ⁶Department of Rehabilitation, Chengdu Fifth People's Hospital (The Second Clinical Medical College, Affiliated Fifth People's Hospital of Chengdu University of Traditional Chinese Medicine), Chengdu, Sichuan, People's Republic of China

Correspondence: Fang Zeng; Xi Wu, Email zengfang@cducm.edu.cn; wuxi@cducm.edu.cn

Introduction: Acupuncture is effective for patients with chronic low back pain (CLBP), which can relieve pain intensity and regulate negative emotional states such as pain-related anxiety and depression. Previous studies mainly discuss the analgesic mechanism of acupuncture treatment of CLBP, but there are multiple dimensions to pain, including sensation, emotion and cognition. Therefore, this study aims to investigate the central mechanism of acupuncture for CLBP from the perspective of emotional regulation by functional magnetic resonance imaging (fMRI).

Methods and Analysis: A total of 72 patients with CLBP will be recruited in the study and randomly assigned to the verum acupuncture group or the sham acupuncture group. The trial will last for 18 weeks including a 2-week baseline, a 4-week treatment and a 12-week for follow-up period. The primary outcomes are the visual analog scale (VAS) and the Japanese Orthopaedic Association Scores (JOA) score. The secondary outcomes are the 12-item short form health survey (SF-12), the state trait anxiety inventory (STAI), the self-rating anxiety scale (SAS) and self-rating depression scale (SDS). The VAS, JOA, STAI SAS and SDS will be collected at baseline, week 2, week 4, and after follow-up. The SF-12 will be evaluated at baseline, week 2 and week 4. Functional magnetic resonance imaging (MRI) data will be collected at baseline and the end of treatment. Emotion-related brain regions will be chosen as regions of interest (ROIs). The gray matter volume (GMV), amplitude of low-frequency fluctuation (ALFF), regional homogeneity (ReHo), functional connectivity (FC), and large-scale functional brain network based on these ROIs will be analyzed within and between the two groups.

Discussion: This study will verify the emotional regulation of acupuncture and explore the mechanism of acupuncture for emotion regulation in patients with CLBP.

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Keywords: acupuncture, chronic low back pain, emotion regulation, functional magnetic resonance imaging

Introduction

Chronic low back pain (CLBP) mainly refers to long-term pain that lasts for more than three months, usually accompanied by discomfort, tightness, or stiffness in the area below the ribs and above the buttocks.^{1,2} CLBP is second only to lung cancer and ischemic heart disease in terms of disability-adjusted life years,³ which impacts approximately 10–13% of the adult population, accounting for over 30 million people in the United States.⁴ It is a major health problem with significant economic and social implications, accounting for more than 80% of healthcare expenditure,⁵ with an average annual expenditure \$34 billion.⁶

According to the clinical practice guideline of the American College of Physicians (ACP), current pharmacotherapies for CLBP include non-steroidal anti-inflammatory drugs (NSAIDs), opioid analgesics, nonopioid analgesics, tramadol, antidepressants, benzodiazepines, corticosteroids, antiepileptic drugs, and so on.² However, pharmacological therapies are often accompanied by undesirable side effects.^{2,7–11} Acupuncture, a widely used complementary and alternative therapy, has been strongly recommended as initially select nonpharmacologic treatment for CLBP,² which not only can reduce the pain intensity of patients with CLBP significantly,^{12–14} but also can improve the functions of lumbar CLBP patients.¹⁴

The central mechanism in patients with CLBP plays an important role in the overall pain state.^{15,16} Many neuroimaging studies have shown that patients with CLBP had increased gray matter volume in the primary somatosensory cortex,¹⁷ amygdala,¹⁸ and anterior cingulate cortex (ACC),¹⁹ and altered functional activity in insula, superior parietal lobes,²⁰ cerebellum and parahippocampus.²¹ Acupuncture can decrease the gray matter volume of primary somatosensory cortex,¹⁷ and regulate the functional activities of the insula,²¹ and ventral tegmental area²² in CLBP patients. Current studies mainly discuss the analgesic mechanism of acupuncture treatment of CLBP.^{23–25} However, according to the International Association for the Study of Pain (IASP) definition of pain, pain encompasses multiple dimensions such as sensation, emotion, and cognition.²⁶ The regulation of negative emotions through acupuncture significantly contributes to its analgesic effects.²⁷ However, the central mechanisms of acupuncture for CLBP from the perspective of emotional regulation remain unknown. Hence, the objective of this study is to investigate the central mechanism of acupuncture for CLBP from the perspective of emotional regulation.

Function magnetic resonance imaging (fMRI) can generate a three-dimensional map of regional brain activity with sub-millimeter spatial resolution²⁸ and can make precise spatial localization of brain activity. It is a commonly used technique to investigate the central mechanism of acupuncture for chronic pain.^{29,30} The fMRI technology mainly measures changes in the ratio of deoxyhemoglobin and oxygenated hemoglobin in the blood and has the advantages of non-invasiveness and high spatial and temporal resolution, which allows it to clearly observe these brain regions³¹ and provide insights into the cerebral emotional-regulation mechanisms underlying acupuncture treatment for CLBP.

Methods and Analysis

Study Design

A randomized parallel-group randomized clinical trial will be conducted at the Fifth People's Hospital of Chengdu and Affiliated Hospital of Chengdu University of Traditional Chinese Medicine. Seventy-two eligible patients diagnosed with CLBP according to the clinical guideline of the ACP and the Chinese Association of Rehabilitation Medicine (CARM)³² will be enrolled. The study will be conducted over a total duration of 18 weeks, comprising a 2-week baseline period, a 4-week treatment period, and a 12-week follow-up period. Functional MRI data will be collected at the baseline and the end of treatment. The clinical outcomes will be evaluated after 2-week treatment, after 4-week treatment and the end of follow-up. The flow diagram of this study is displayed in [Figure 1](#). Emotion-related brain regions, such as amygdala, insula, and ACC, will be chosen as regions of interest (ROIs). The gray matter volume (GMV), amplitude of low-frequency fluctuation (ALFF), regional homogeneity (ReHo), functional connectivity (FC), and large-scale functional brain network based on these ROIs will be analyzed.

This trial adheres to the Standard Protocol Recommendations for Interventional Trials (SPIRIT) guidelines³³ ([Table 1](#)), and adheres to the principles outlined in the Comprehensive Standards for Trial Reports (CONSORT) and the Reporting Standards for Intervention Measures in Traditional Chinese Medicine Clinical Trials, as well as the Standard for Reporting Intervention Measures in Acupuncture Clinical Trials (STRICTA).³⁴ The study has been approved by the Medical Ethics Committee of Affiliated Hospital of Chengdu University of Traditional Chinese Medicine (2023KL-120) and the Ethics Committee of the Fifth People's Hospital of Chengdu (Ethics 2023–003 (Section) –01), which registered with on Chinese Clinical Trial Registry (registration no. ChiCTR2300070557). This trial will be conducted according to the Declaration of Helsinki.

Participant

Sample Size Considerations

The calculation for sample size is determined based on the changes in visual analogue scale (VAS) scores. An earlier study intervention on patients with CLBP found that the average improvement of VAS score in the experience group

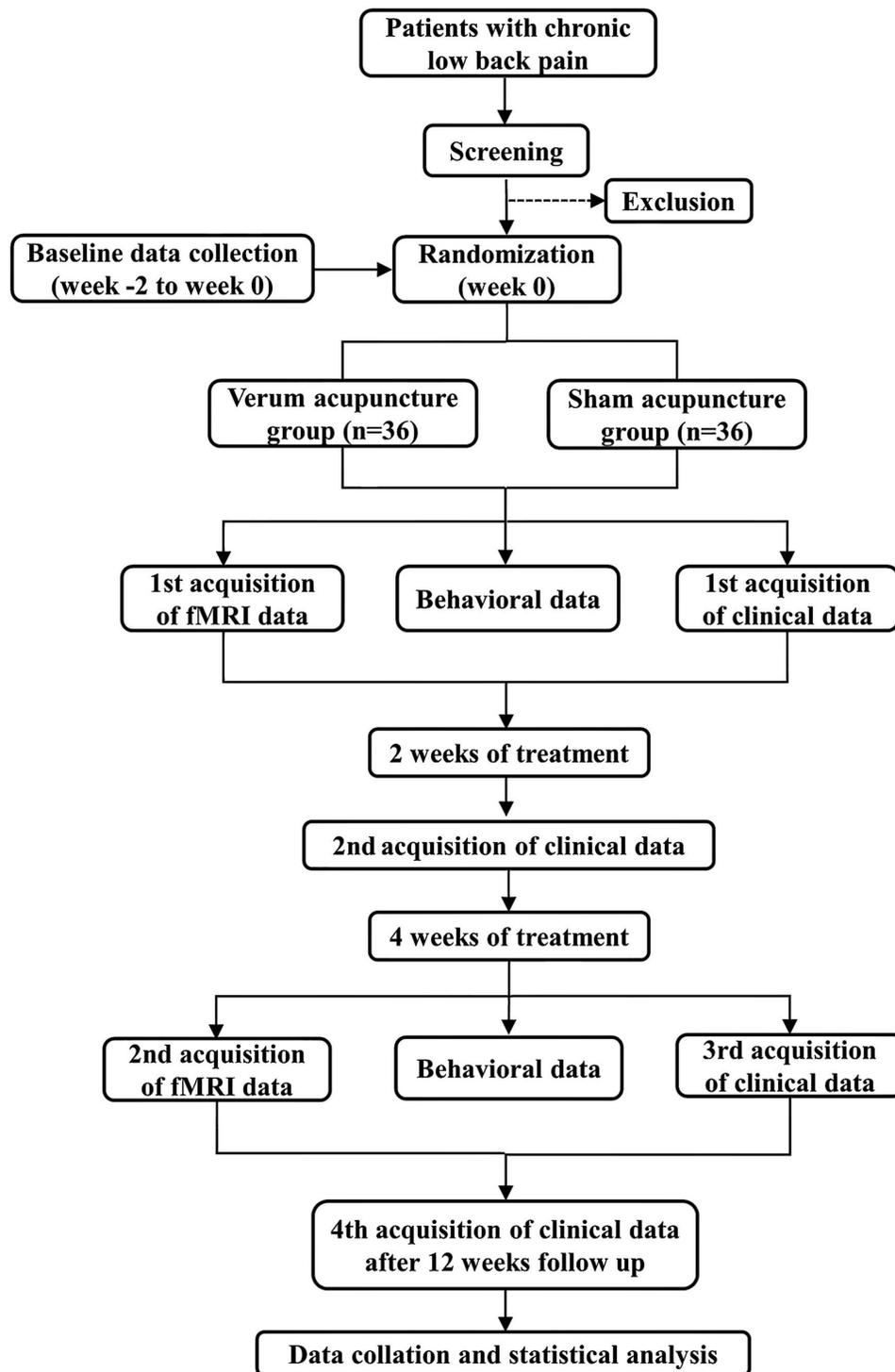


Figure 1 Study flowchart.

was -26.41 ± 19.06 (mean \pm SD), while in the placebo group, the average improvement of VAS score was -12.83 ± 19.45 (mean \pm SD).³⁵ With a power of 0.90 and a two side of significance level of 0.05, the required sample size is 32 cases per group (the radio 1:1). Considering a dropout rate of 10%, this trial will require a total of 72 subjects.

Table 1 Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Schedule of the Trial

	STUDY PERIOD				
	Baseline		Treatment		Follow-up
TIMEPOINT	-2-week	0-week	2-week	4-week	12-week
ENROLLMENT:					
Eligibility screen	x				
Informed consent	x				
Physical examination	x				
Random allocation		x			
INTERVENTION:					
Verum acupuncture			x	x	
Sham acupuncture			x	x	
ASSESSMENTS:					
The low back pain diary	x	x	x	x	x
Mean VAS score		x	x	x	x
The JOA score		x	x	x	x
SF-12		x	x	x	
STAI		x	x	x	x
SAS		x	x	x	x
SDS		x	x	x	x
PARTICIPANTS SAFETY					
Laboratory test		x		x	
Adverse events	x	x	x	x	

Abbreviations: JOA, Japanese orthopaedic association; SF-12, short form 12; STAI, state trait anxiety inventory; SAS, self-rating anxiety scale; SDS, self-rating depression scale; VAS, visual analogue scale.

Recruitment

All potential CLBP patients will be recruited by the outpatient of Rehabilitation Department and Pain Department of Chengdu Fifth People's Hospital and Affiliated Hospital of Chengdu University of Traditional Chinese Medicine from November 2023 to September 2025. All participants will sign the informed consent forms at the beginning of this trial and meet all the following inclusion criteria will be recruited in this study: (1) have a diagnosis of CLBP according to the guidelines of ACP 2007 and CARM 2016; (2) fall within the age range of 18 to 55 years old (including 18 and 55 years old); (3) are right-handed; (4) have a minimum VAS score of 4 points; (5) have signed the informed consent form.

If participants who meet any of the following criteria will be excluded: (1) have taken any medication or received any non-pharmaceutical therapies within the past month; (2) have suffered from lumbar spinal stenosis, lumbar spondylo-listhesis, purulent spondylitis, intervertebral disc infection, spinal trauma; (3) have metabolic diseases, urinary system diseases, neurological disorders, vascular diseases, psychogenic diseases; (4) have contraindications to magnetic resonance imaging, such as metal dentures, claustrophobia.

Randomization and Blinding

Seventy-two random sequence numbers will be generated by using a computer according to the random number table method. All eligible participants will be randomly assigned to the verum acupuncture group or the sham acupuncture group. Since it is difficult to blind acupuncture therapists in this study, we will implement blinding measures for the

participants. Study assessments and statistical analysis will be performed by an independent assessor and a statistician who are unaware of the group allocation.

Interventions

The acupuncture procedures will be administered by two licensed acupuncturists with a minimum of five-year clinical experience. Bilateral *Shenshu* (BL23), bilateral *Dachangshu* (BL25), *Mingmen* (GV4), *Yaoyangguan* (GV3), and two *Ashi* acupoints will be chosen as acupuncture prescription. The *Ashi* point will be detected from the low back region. If the patient does not have *Ashi* acupoint, the bilateral *Yaoyan* (EX-B7) will be used as a substitute. Each participant will undergo a total of 12 acupuncture sessions, scheduled three times a week over a period of 4 weeks. The detailed information regarding the location of the acupoints is presented in Figure 2.

Verum Acupuncture Group

The verum acupuncture procedure will be performed as follows: First, the skin will be thoroughly disinfected. The acupuncturist will remove the skin-facing adhesive ring from the Park Sham placebo Acupuncture Device (PSD; Suzhou, China), insert a disposable sterile filiform needles (0.25mm × 40mm; Hwatuo, Suzhou, China) and fix the plastic cannula to the skin of the acupuncture point. During the insertion, the needles will be inserted for 0.5–1.5 *cun* and manipulated using uniform twirling, lifting and thrusting to elicit a *deqi* sensation.³⁶ The twisting angle is 90–360 degrees, and the rotation frequency is 120–160 times per minute. The needles will be kept for 30 minutes, with additional manipulation performed twice for 10–15 seconds every 10 minutes during this period.

Sham Acupuncture Group

In the sham acupuncture group, the treatment procedure and duration are the same as in the verum acupuncture group. However, when the needles (0.25mm × 40mm; blunt tip, Womeida Medical Equipment Technology Co., Ltd., China) touch the skin, it will leverage force to retract into the hollow plastic sheath, preventing penetration into the skin, and no manipulation will be performed to elicit a *deqi* sensation. The needles will be kept for 30 minutes.

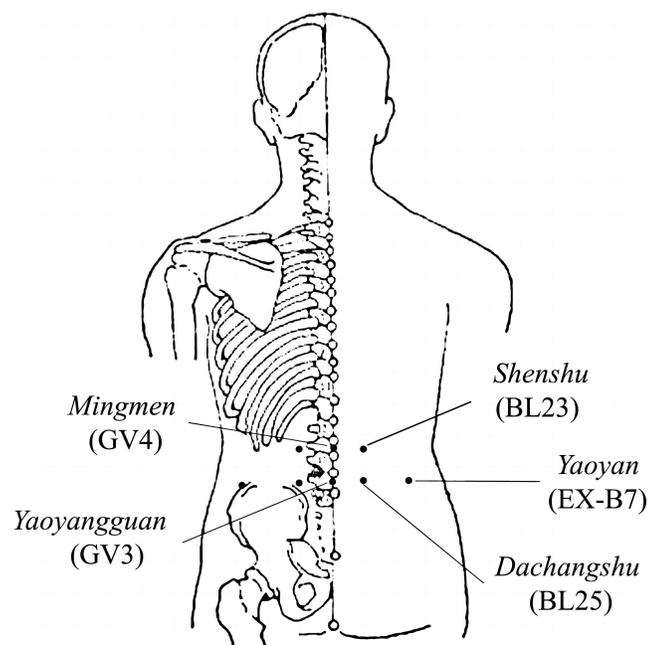


Figure 2 Locations of acupoints. *Shenshu* (BL23): On the back, 1.5 *cun* lateral to the lower border of the spinous process of the 2nd lumbar vertebra. *Dachangshu* (BL25): On the back, 1.5 *cun* lateral to the lower border of the spinous process of the 4th lumbar vertebra. *Mingmen* (GV4): In the lumbar region, on the posterior median line, in the depression below the spinous process of the 2nd lumbar vertebra. *Yaoyangguan* (GV3): On the lumbar region, on the posterior median line, in the depression below the spinous process of the 4th lumbar vertebra. *Yaoyan* (EX-B7): On the lower back, in the depression 3.5 *cun* lateral to the lower border of the spinous process of the 1st lumbar vertebra.

Medications

During the trial period, it is recommended that participants avoid using any additional medications as much as possible. If participants experience intolerable low back pain, they can temporarily take NSAIDs such as ibuprofen (approval number: GYZZ H10900089, manufacturer: Sino-US Tianjin Shike Pharmaceutical Co., Ltd.)

Functional MRI Data Acquisition

The MRI data of participants will be collected at the Chengdu Fifth People's Hospital using a 3.0 Tesla magnetic resonance scanner (Siemens, Munich, Germany). During the scanning process, each patient needs to keep their head still, close their eyes, avoid thinking about anything, relax their body, and remain calm.

Three-dimensional T1-weighted (3D-T1) structural imaging: Before conducting a resting state scan, all participants will complete a 3D-T1 structural imaging scanning. The scanning parameters are as follows: repeat time (TR) = 1900ms, echo time (TE) = 2.74ms, and field of view (FOV) = $256 \times 256\text{mm}^2$, matrix = 256×256 .

Blood oxygen-level-dependent functional magnetic resonance imaging (BOLD fMRI): Gradient Echo Planar Imaging (GRE-EPI) sequence will be used during the resting state scan. Scanning parameters: TR = 2000ms, TE = 30ms, flip angle (FA) = 90° , number of layers = 32, layer thickness = 5mm, FOV = $240 \times 240\text{mm}^2$, matrix = 64×64 .

Outcome Measurements

Primary Outcome

Visual Analogue Scale will be used to assess the pain intensity of each patient.³⁷ A score of 0 represents painlessness, and 10 represents the most severe unbearable pain. Japanese Orthopaedic Association (JOA) score with a maximum score of 29 points will be used to evaluate the lumbar spine function of patients with CLBP.³⁸

Secondary Outcome

Twelve-item short form health survey (SF-12), including 12 items and 8 dimensions, will be used to evaluate the relevant quality of life of patients. State trait anxiety inventory (STAI), consisting of a state anxiety inventory and a trait anxiety inventory, will be used to calculate the cumulative scores of the state anxiety and trait anxiety scales separately. The self-rating anxiety scale (SAS)³⁹ and self-rating depression scale (SDS)⁴⁰ are often used to assess the anxiety⁴¹ and depression symptoms⁴² of CLBP patients.

Data Analysis

All data will undergo statistical analysis employing SPSS software (version 25.0, IBM SPSS, New York, USA). The significance level will be set at $\alpha < 0.05$, using a two-sided test. Categorical variable will be expressed as rates or proportions, while continuous variables will be represented as mean \pm standard deviation (SD). The distribution of continuous variables will be initially assessed using the Kolmogorov–Smirnov test. For normally distributed data, a paired *t*-test will be employed to compare the pre- and post-treatment within each group, and a one-way analysis of variance (ANOVA) will be used for comparisons between different groups. Additionally, for non-normally distributed data, non-parametric tests will be performed to compare the pre- and post-treatment differences within each group, and multiple non-parametric tests for independent samples will be used to for between-group comparisons. The chi-square test will be used for categorical data.

Functional MRI Data Preprocessing and Analysis

Imaging data will be processed using SPM12 (<http://www.fil.ion.ucl.ac.uk/spm>) on MATLAB (2018, The Math-Works Inc. Natick, MA, USA). All functional images will go through slice time correction, realignment, and registration with their mean image. Then, the functional volumes will be aligned to the standardized Montreal Neurological Institute (MNI) template for spatial normalization. Moreover, the acquired data will be smoothed using an isotropic Gaussian kernel with a Full Width at Half Maximum (FWHM) of 8 mm.

The amygdala, prefrontal cortex (PFC), and anterior cingulate cortex (ACC) will be chosen as regions of interest (ROIs). The gray matter volume (GMV), amplitude of low-frequency fluctuation (ALFF), regional homogeneity (ReHo), functional connectivity (FC), and large-scale functional brain network based on these ROIs will be analyzed within and

between the two groups. The relationship between brain structural and functional alterations and clinical variables will be evaluated using Pearson's correlation analysis.

Discussion

The regulation of functional activities of various emotion-related brain regions, including the amygdala, insula, ACC, medial prefrontal cortex, hippocampus, and other brain regions might be one of the underlying mechanisms of acupuncture.^{21,22,43} Previous studies have established that acupuncture exerts a positive impact on negative emotional states in individuals suffering from chronic neck or shoulder pain.^{44,45} Hence, this study will be designed to verify the emotional regulation of acupuncture in patients with CLBP, and explore the underlying mechanism of acupuncture based on emotion-related brain regions using the fMRI technology.

Limitation

This study exists a few limitations. First, we are unable to blind acupuncturists, so we adopted the principle of separating researchers, evaluators, and analysis groups. Second, ensuring consistent application of acupuncture techniques poses a formidable challenge for different acupuncturists. Hence, both acupuncturists will undergo rigorous and standardized acupuncture manipulation training prior to this trial.

Trial Status

This clinical trial has been registered on the Chinese Clinical Trial Registry (<https://www.chictr.org.cn>) on April 17, 2023 (registration no. ChiCTR2300070557); protocol version no. 1.0). Patient recruitment was started on November 20, 2023.

Ethics Statement

This study was reviewed and approved by Review Boards and Medical Ethics Committee of Affiliated Hospital of Chengdu University of Traditional Chinese Medicine (2023KL-120) and Ethics Committees of Chengdu Fifth People's Hospital (Ethics 2023-003 (Section) -01).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is 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; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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