Respiratory Research

STUDY PROTOCOL

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Medical thoracoscopy combined with intrapleural injection of urokinase for treatment of pleural infection-a multicenter, prospective, randomized controlled study: study protocol

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Abstract

Background Pleural diseases is a common respiratory disorder, mainly characterized as pleural effusion and patients with pleural effusion caused by pneumonia and empyema constituted 29% of the cohort, which suggests pleural infection as the predominant etiology of pleural effusion in China. Medical thoracoscopy (MT) combined with intrapleural injection of Urokinase holds significant therapeutic value for patients with early to moderate-stage empyema. However, there remains a lack of high-quality evidence regarding the efficacy and safety of combining MT with intrapleural injection of Urokinase administration in patients with pleural infections.

Methods This study is a prospective, multicenter, randomized controlled clinical trial involving patients with pleural infections. The intervention involves medical thoracoscopy. The control group receives conventional treatment involving intrapleural urokinase injection followed by chest tube placement for drainage. The study outcomes include efficacy and health economic benefits. The estimated minimum sample size for each group is 64 cases, totaling 128 cases. The study groups are delineated as follows: patients in group A receives intrapleural urokinase injection followed by chest tube placement for drainage, while patients in group B undergoes MT to remove multiple septa and necrotic tissue followed by chest tube placement for drainage, and then intrapleural urokinase injection the day after MT. It is recommended that the diameter of the chest tube be 12–14 F, with three daily flushes of 30 ml normal saline to ensure optimal drainage. Subsequently, comprehensive statistical analyses will be conducted to compare treatment effects and complications across all groups, ultimately leading to conclusive findings.

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Discussion The study is the first prospective, multicenter clinical trial on the efficacy and safety of medical thoracoscopy combined with intrapleural urokinase injection for the treatment of pleural infection. This study aims to offer clinical guidance for the management of pleural infection.

Registration number ChiCTR2300078352 (Registration Date: 2023/12/06).

Keywords Pleural infection, Medical thoracoscopy, Intrapleural urokinase injection

Background

Pleural diseases is a common respiratory disorder, mainly characterized as pleural effusion [1]. In 2021, Weimin Li conducted a nationwide multicenter real-world study focusing on hospitalized patients. This study included 25,316 cases of hospitalized patients with pleural effusion across 60 tertiary Grade A hospitals. The findings revealed that patients with pleural effusion caused by pneumonia and empyema constituted 29% of the cohort, which suggests pleural infection as the predominant etiology of pleural effusion in China [2]. The treatment of patients with pleural infections is most challenging in cases of complicated parapneumonic effusions and empyema, which appear in up to 57% of adults with pneumonia [3]. This is primarily due to such patients often present with pleural effusions characterized by multi-septated compartments, leading to impaired drainage and difficulty in controlling infection. Furthermore, the challenging in draining pleural effusions results in the persistence of chronic pleural inflammation. Consequently, this leads to the onset of restrictive ventilatory impairment, significantly impeding respiratory function of the patients.

In 2011, a prospective multicenter randomized controlled study (MIST-2) indicated that administering fibrinolytic agents (tPA combined with DNase) within the pleural cavity can significantly enhance pleural drainage, facilitating the expulsion of pleural effusions and the absorption of lesions [4]. Another study indicated that the use of urokinase in patients with pleural infections exhibits comparable efficacy to the tPA-DNase regimen [5]. Furthermore, urokinase is not only cost-effective domestically but also more accessible. Medical thoracoscopy (MT) serves as the gold standard for diagnosing pleural diseases and is increasingly applied for therapeutic interventions in managing these conditions. These procedures involve the drainage of abscesses and clearance of infected lesions. MT treatment can reduce hospitalization duration compared to intrapleural fibrinolytic therapy [6]. However, complete drainage for some patients is relatively difficult. Administering urokinase intrapleurally after MT can facilitate the dissolution of pleural fibrin and necrotic debris, enhance pleural drainage, and promote therapeutic efficacy for patients with pleural infections. In clinical practice, a number of scholars utilize a combination of MT and intrapleural urokinase injection administration to manage patients with pleural infections. A single-center, retrospective study conducted by Ravaglia and colleagues in 2023 indicated that this combined approach using fibrinolytics holds significant therapeutic value for patients with early to moderate-stage empyema, while maintaining a certain level of safety [7].

There remains a lack of high-quality evidence regarding the efficacy and safety of combining MT with intrapleural urokinase administration in patients with pleural infections. Therefore, it is imperative to elucidate its therapeutic potential through multicenter, prospective studies.

Methods

Study design and setting

This study is a prospective, multicenter, randomized controlled clinical trial involving patients with pleural infections. The intervention involves MT. The control group receives conventional treatment involving intrapleural urokinase injection followed by chest tube placement for drainage. The study outcomes include efficacy and health economic benefits. The estimated minimum sample size for each group is 64 cases, totaling 128 cases. The study groups are delineated as follows: patients in group A receives intrapleural urokinase injection followed by chest tube placement for drainage, while patients in group B undergoes MT followed by chest tube placement for drainage, and then intrapleural urokinase injection the day after MT. It is recommended that the diameter of the chest tube be 12–14 F, with three daily flushes of 30 ml normal saline to ensure optimal drainage. Subsequently, comprehensive statistical analyses will be conducted to compare treatment effects and complications across all groups, ultimately leading to conclusive findings. Ethics approval for the study was obtained from Sichuan University West China Hospital Biomedical Ethics Committee (Ethics number: 2023 – 1839).

Participants

We intend to enroll participants from four prominent medical centers—the First Affiliated Hospital of Naval Military Medical University, Shanghai Pulmonary Hospital, the First Affiliated Hospital of Guangxi Medical University, and the First Affiliated Hospital of Kunming Medical University—between December 2023 and December 2025. Patients aged 18 and older, exhibiting

evidence of infection and a disease duration within 3 months, and concurrently experiencing infectious pleural effusion, are eligible to participate this study if they are willing to give consent. Clinical evidence of infection refers to manifestations assessed by the attending physician, such as fever and elevated inflammatory markers, including increased white blood cell count (WBC), C-reactive protein (CRP), or Procalcitonin (PCT) levels. Besides, any of the following criteria indicate infectious pleural effusion: (1) grossly purulent appearance; (2) positive microbial culture; (3) positive microbial staining (including acid-fast staining or other specific staining for pathogens); (4) pH < 7.2, if pH measurement is not feasible, glucose < 2.2 mmol/L with lactate dehydrogenase (LDH) > 1000 IU/L can also serve as a diagnostic method. Participants with the following conditions are excluded: (1)Receive administration of fibrinolytic agents (urokinase, streptokinase, DNase, or tPA) for treatment before enrollment; (2)Allergy to urokinase; (3)Stage III empyema (presence of pleural fibrous adhesions with evident organization); (4)Significant bleeding or severe trauma; (5)Inability to tolerate MT due to hemodynamic instability (blood pressure ≤ 90/60 mmHg) or severe hypoxemia (PaO_2/FiO_2 < 250); (6)Surgical intervention within the past 5 days; (7)Pregnancy or lactation; (8)Thoracic CT and thoracic ultrasound indicating depth of pleural effusion < 3 cm; (9)Patients with empyema and lung non-expansion (failure of lung re-expansion after thoracentesis or chest tube drainage); (10)Clinically diagnosed or highly suspected bronchopleural fistula; (11)Anticipated survival less than 3 months due to non-pleural diseases; (12)Patients who have undergone continuous chest tube drainage (tube not yet removed) prior to enrollment, with effective drainage, homogeneous anechoic or non-homogeneous non-septated effusion observed on thoracic ultrasound, and determined unnecessary for fibrinolysis or MT treatment through clinical assessment by the attending physician.

Procedure, intervention and data collection

Participants will be enrolled for a duration of 12 months in the study (Fig. 1). This study adopts a fixed enrolment procedure and central randomization method for patient allocation. Subsequent to randomization, participants undergo treatment according to the study protocol. The study utilized a semi-rigid thoracoscope (LTF 240) manufactured by Olympus for examination, and a standard foreign body forceps (AF-1810GK, Shanghai Elton) to remove necrotic tissue. The specific procedure for thoracoscopic operation was as follows: (1) Anesthesia: Local anesthesia was administered using lidocaine, while sedation and analgesia were achieved via intravenous infusion of fentanyl and dexmedetomidine. (2) Thoracoscopic Procedure: Multilocular septa and adhesions

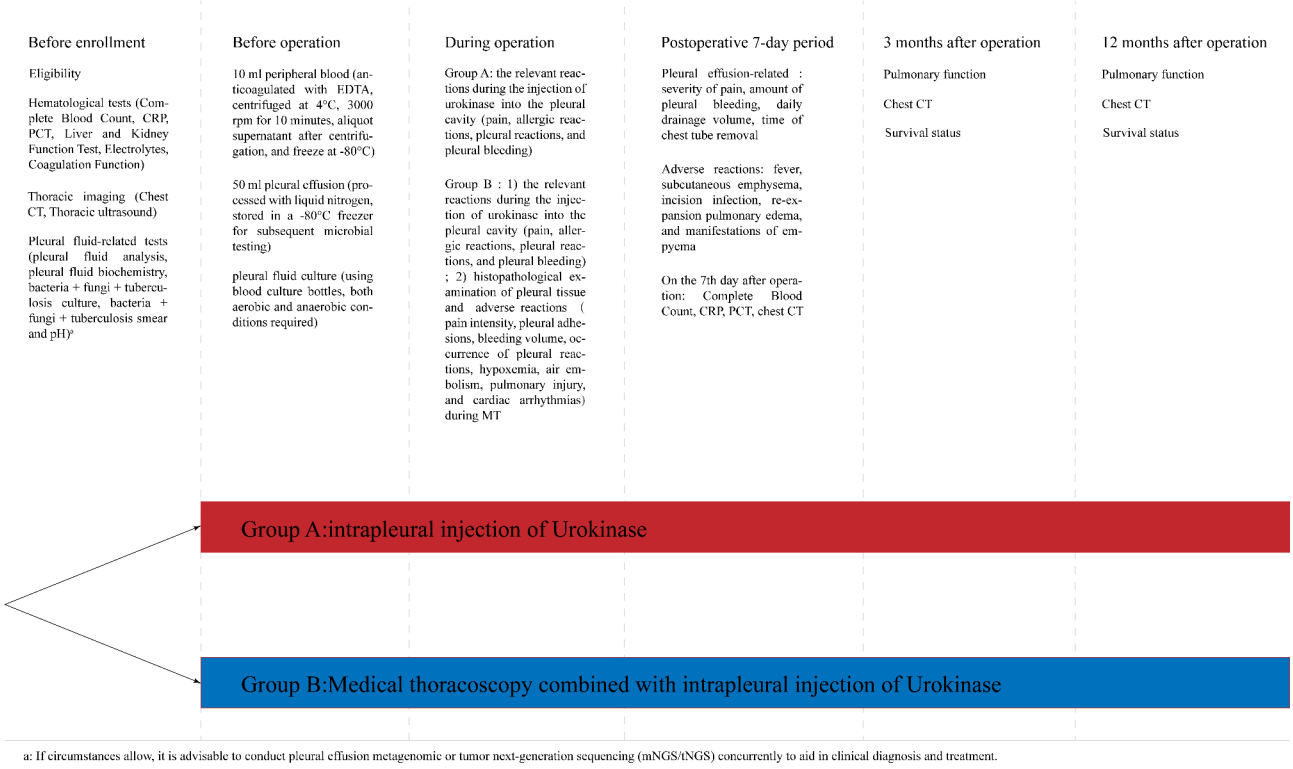

Fig. 1 Flowchart of the clinical trial

Table 1 Assessment of the study and their details

Assessment Project		Details
Efficacy evaluation	Variation in volume of pleural effusion	Chest CT scans were conducted prior to intervention (the 1st day) and after intervention (on the 7th day), with subsequent evaluation of pleural shadow volumes facilitated by computer processing software (3D Slicer). The formula for calculation is as follows: (Volume of pleural effusion on the 1st day - Volume of pleural effusion on the 7th day) / volume of pleural effusion on the 1st day x 100%.
	Duration of hospitalization	The hospitalization durations for all enrolled patients and the hospitalization durations for patients in each group post-randomization.
	Conditions of pleural collapse and thickening 3 months after randomization	Pleural Thickening Scoring Index: The pleural cavity is partitioned into anterior, middle, and posterior segments using the anterior and posterior axillary lines. Meanwhile, division demarcated by the second and fourth ribs divides the thoracic cavity into upper, middle, and lower thirds. Ultimately, the thoracic cavity includes a total of nine regions. Pleural thickness, measured in centimeters, is assessed on chest CT scans using a mediastinal window with standardized window width and level. Employing a scoring system, the thickest point of pleural thickening (in millimeters) is identified in each region and cumulatively totaled to derive the Pleural Thickening Scoring Index. Additionally, the chest wall collapse rate is calculated as follows: (Volume of thoracic cavity on the 1st day - Volume of thoracic cavity on the 7th day) / volume of thoracic cavity on the 1st day x 100%.
	The variation of pulmonary function 3 months after randomization	The variations in respiratory function from baseline to three months post-randomization intervention, including indicators such as VC, FVC, FEV1, etc.
	Failure rate of the treatment regimen	After 7 days of randomization, treatment failure is defined by the presence of any of the following criteria: persistent fever (temperature ≥ 38 °C), elevated white blood cell count, residual pleural effusion or encapsulation (estimated residual pleural effusion volume exceeding 300 ml, volume ≈ length × width × height × 0.5) and clinical assessment by the attending physician indicating the need for additional interventions. These interventions include: Patients in group A undergoing additional pleural catheter placement, internal medicine thoracoscopy, or thoracic surgery (VATS or thoracotomy); patients in group B undergoing additional pleural catheter placement or thoracic surgery (VATS or thoracotomy).
Safety evaluation	Incidence of treatment-related complications	Such as thoracic hemorrhage volume and frequency, pleural reaction incidence, degree and occurrence rate of procedure-related pain, degree and occurrence rate of procedure-related pain, (clear breach of visceral pleura during surgery with post-operative sustained air leakage exceeding 1 h), prolonged air leakage (air leakage persisting beyond 5 days post-surgery), cellulitis or infection near the incision requiring antibiotic treatment and clinically significant subcutaneous emphysema.
	Mortality rates	Including in-hospital mortality and 30-day post-discharge mortality.

wasseparated using the foreign body forceps, and solid necrotic fragments were extracted externally. The thoracoscope was used to aspirate small fragmented necrotic tissue and pleural effusion. (3) Irrigation: Following the above procedures, 200 mL of normal saline was used for irrigation under direct visualization, and the fluid was completely aspirated through thoracoscopy. (4) Tube Placement: After aspirating the saline, a 12–14 F drainage tube was placed.

After enrollment, patients in Group A receive intrapleural urokinase injection starting from the day following chest tube drainage. The protocol entails the injection of urokinase 100,000 units diluted in 30 ml of normal saline (with subsequent tube flushing using 20 ml of normal saline), followed by a 3-hour clamping of the drainage tube. This regimen is repeated once daily for a total of 3 days. Patients assigned to Group B undergo completion of MT and subsequent debridement within 24 h of group assignment. Subsequently, a chest tube is placed, and fibrinolytic therapy is administered intrapleurally for 3 days starting from the day after MT. The fibrinolytic regimen involves the administration of urokinase 100,000 units once daily, diluted in 30 ml of normal saline (with 20 ml of saline for tube flushing), followed by a 3-hour clamping of the drainage tube. However, fibrinolytic therapy is contraindicated if significant intraoperative or postoperative incisional or thoracic bleeding occurs. Daily drainage volume is recorded postoperatively, and indications for removal of chest tube are evaluated according to clinical protocols. Criteria of chest tube removal include a drainage volume ≤ 75 ml in 24 h, absence of significant signs of infection-related toxicity, and absence of significant residual pleural effusion (pleural fluid < 200 ml) on imaging studies. During the course of the study, we will collect clinical symptoms, corresponding laboratory assessments, and imaging information from patients at different intervals, including pre-enrollment, preoperative, intraoperative, and postoperative (7 day, 3 months, and 12 months) (Fig. 1).

Aims and outcomes

This study aims to validate the efficacy and safety of this combined approach in patients with pleural infections, delineate the health economic benefits of various local treatment strategies for such patients, and offer clinical guidance for their diagnosis and management (Table 1). The efficacy evaluation predominantly relies on the variation in volume of pleural effusion on the affected side.

Furthermore, secondary outcomes encompass the duration of hospitalization, conditions of pleural collapse and thickening 3 months after randomization, the variation of pulmonary function 3 months after randomization and failure rate of the treatment regimen. The safety of the treatment protocols is primarily assessed through the incidence rates of various complications. In the health economics evaluation, we conduct analyses from both cost and effectiveness. Firstly, outcomes include direct costs (direct medical costs, direct non-medical costs) and indirect costs (loss of productivity for patients and their caregivers). Secondly, the efficacy of different treatment regimens is gauged using quality-adjusted life years (QALYs). This study employs the EQ-5D-5 L scale developed by the European Quality of Life Group for measurement, and subsequently translates it into health utility values using utility scores tailored to the Chinese population. Incremental cost-effectiveness ratio (ICER) and net monetary benefit (NMB) serve as yardsticks to determine whether two research interventions demonstrate cost-effectiveness, with Bootstrapping employed for sensitivity analysis.

Sample size

Using medical thoracoscopy as the intervention and the rate of pleural shadow change before and after treatment as the primary outcome measure, we estimated the required sample size. Previous literature reports a pleural shadow change rate of 26.9 ± 19.2% in Group A patients. A retrospective analysis of patients with pleural infection at West China Hospital who underwent medical thoracoscopy combined with intrapleural administration of urokinase showed a pleural shadow change rate of 36 ± 15.2%. Using a superiority design with a significance level of $\alpha = 0.025$ (one-sided) and power of 80%, the sample size was calculated using PASS 15.0. Considering a 5% loss to follow-up rate, 63 subjects are required per group, for a total of 126 study subjects. Due to the use of stratified block randomization with a block length of 4, the total sample size is 128.

Treatment allocation

Treatment will be allocated in a 1:1 ratio. Patients will be randomly assigned using a fixed enrollment and central randomization method. After randomization, the appropriate treatment will be administered according to the study protocol.

Safety and adverse event reporting

Any adverse events occurring during or after the invasive procedure following the patient's enrollment will be thoroughly documented and reported. Besides, at each follow-up visit, researchers will inquire about and document any adverse reactions and issues the patient has experienced since the previous visit. Some significant or serious adverse events and their related management are listed below:

1) Massive hemothorax: Defined as intraoperative or postoperative bleeding in the pleural cavity that requires a blood transfusion or causes hemodynamic instability (blood pressure ≤ 90/60 mmHg) with a decrease in hemoglobin (Hb < 70 g/L) or hematocrit (HCT < 0.2). If massive hemothorax occurs, it should be accurately documented and reported. Management includes hemostasis, blood transfusion, and adequate drainage, with surgical intervention for hemostasis if necessary.
2) Dislodgement of the chest drainage tube: This should be accurately documented and reported. Management: Immediately disinfect and cover the incision with gauze, promptly perform chest imaging to assess the drainage of pleural effusion and pneumothorax, and if clinical evaluation indicates the need for continued pleural drainage, reinsert the chest tube.
3) Air embolism: This should be accurately documented and reported. Management includes cardiac monitoring, ensuring proper drainage of pneumothorax, positioning the patient in a supine position with the head down and feet elevated, administering necessary oxygen therapy and respiratory support, initiating high-pressure oxygen therapy once vital signs stabilize, and seeking neurology consultation for assistance with diagnosis and treatment.

Statistical analyses

We utilized SPSS 23.0 software for data analysis. Continuous variables were summarized using means and standard deviations, whereas categorical variables were presented using frequencies and percentages. Comparisons between the two group were conducted using either the chi-square ($\chi 2$) test or Fisher's exact test for categorical variables, and the Mann-Whitney U test was applied when necessary. For small sample sizes ($n < 30$), the t-test was employed. All tests were two-tailed, and statistical significance was set at $p < 0.05$.

Reporting results

This study is an interventional clinical trial, and all results will be reported and summarized according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines for randomized parallel controlled trials.

Discussion

The current local treatment modalities for patients with thoracic infections primarily encompass chest tube drainage, intrapleural fibrinolytic therapy, intrapleural saline irrigation, and medical thoracoscopy [8–10]. However, many patients do not achieve optimal outcomes with local treatments. Currently, there are few reports on the combined use of medical thoracoscopy and intrapleural fibrinolytic therapy, and the efficacy of this approach remains uncertain. This study aims to evaluate the efficacy and safety of combining medical thoracoscopy with intrapleural injection of urokinase in patients with pleural infection. Additionally, it seeks to clarify the health economic benefits of various local treatment strategies for pleural infection, providing guidance for the clinical diagnosis and treatment of these patients.

Despite the 2023 British Thoracic Society pleural disease treatment guidelines recommending that combination treatment with tPA and DNase should be considered for pleural infection when initial chest tube drainage has ceased and left a residual collection [9]. Compared to using fibrinolytics alone, the combination of fibrinolytics and DNase increases the potential risk of side effects [5], such as pleural hemorrhage and hemoptysis. Additionally, due to the high cost and limited availability of dual therapies involving specific fibrinolytics like tPA and DNase, single-agent fibrinolytic treatment, such as urokinase, remains a widely used therapeutic option [11]. Moreover, studies have found that patients treated with urokinase have a longer duration of fibrinolysis compared to those treated with tPA/DNase, and the 30-day mortality rates are similar between the two groups [5]. In other words, compared to tPA/DNase treatment, urokinase treatment is more effective and equally safe.

Medical thoracoscopy is the gold standard for the diagnosis of pleural diseases and can also be used in their treatment. Retrospective studies have found that patients with pleural empyema who received early medical thoracoscopy treatment had significantly better outcomes than those who received late treatment [7]. A randomized controlled trial (RCT) conducted by Adnan Majid et al. in 2020, which included 32 patients, demonstrated that for patients with complicated parapneumonic effusions and empyema, MT treatment is safer compared to intrapleural fibrinolytic therapy, and can also reduce hospitalization duration [6]. However, prospective, multicenter studies comparing the efficacy and safety of medical thoracoscopy combined with intrapleural fibrinolytics versus intrapleural fibrinolytics alone are still lacking.

The primary approaches for the local treatment of patients with pleural infections include pleural drainage, with the main techniques being medical thoracoscopy, pleural catheter drainage, and intrapleural fibrinolytic therapy [12]. The change in pleural effusion volume is the primary indicator of the effectiveness of local treatment. Therefore, the main outcome measure in this study is the rate of change in pleural effusion. Effective local drainage may reduce the duration of illness, so it is also necessary to observe the total hospitalization time and the hospitalization time after randomization. In patients with significant residual pleural effusion, there is a risk of developing chronic pleural inflammation, pleural thickening, and restrictive ventilatory dysfunction [13]. Therefore, it is necessary to monitor the chest wall collapse rate, pleural thickening, and changes in lung function at three months post-randomization. Additionally, the failure rate of treatment serves as a key indicator for assessing the effectiveness of the treatment plan. Safety indicators include thoracic bleeding volume, pleural reactions, pain, 30-day mortality, prolonged air leak, subcutaneous emphysema, and wound infection, all of which are common complications in the local treatment of patients with pleural infections [14–16].

This study is the first prospective, multicenter clinical trial on the efficacy and safety of medical thoracoscopy combined with intrapleural injection of urokinase for the treatment of pleural infection. It is also the first to evaluate various treatment plans for patients with pleural infections from a health economics perspective, providing evidence for medical decisions that align with socioeconomic benefits.

Abbreviations

CONSORT	Consolidated Standards of Reporting Trials
CRP	C-reactive protein
Hb	Hemoglobin
HCT	Hematocrit
ICER	Incremental cost-effectiveness ratio
LDH	Lactate Dehydrogenase
MT	Medical thoracoscopy
NMB	Net monetary benefit
PCT	Procalcitonin
QALYs	Quality-adjusted life years
RCT	Randomized controlled trial
tPA	Tissue plasminogen activator
VATS	Video-assisted thoracoscopic surgery
WBC	White blood cell

Acknowledgements

We are grateful to all the medical staff who participated in this study, especially the entire team in the medical thoracoscopy unit.

Author contributions

KGW designed the clinical study, screened, enrolled, and treated patients at West China Hospital of Sichuan University. LHY assisted KGW in conducting the study and writing the manuscript. FT, and DL participated in the enrollment and management of patients at sub-centers. PWT, and DL contributed to the conception of the study and the revision of the manuscript. WML organized this multicenter study.

Funding

This work was supported by Sichuan University West China Hospital Clinical Incubation 1.3.5 Project (2022HXFH002) and the National Natural Science Foundation of China (grant number 82173182).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study was approved by the Sichuan University West China Hospital Biomedical Ethics Committee (Ethics number: 2023 – 1839). All participants will be fully informed of objectives, protocol, and potential risks of the study prior to enrollment, and will provide written informed consent.

Consent for publication
Not applicable.

Consent to participate
Every human participant should provide their consent.

Competing interests
The authors declare no competing interests.

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Received: 16 July 2024 / Accepted: 7 January 2025
Published online: 18 January 2025

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