# Baidu Jieduan granule, traditional Chinese medicine, in the treatment of moderate coronavirus disease-2019 (COVID-19): study protocol for an open-label randomized controlled clinical trial

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**Study protocol**

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# Abstract

**Background:** Currently, coronavirus disease-2019 (COVID-19) is continuously and rapidly circulating, resulting in serious and extensive impact on human health. Due to the absence of antiviral medicine for COVID-19 thus far, it is desperately need to develop the effective medicine. Traditional Chinese medicine (TCM) has been widely applied in the treatment of epidemic diseases in China, hoping to produce clinical efficacy and decrease the use of antibiotics and glucocorticoid. The aim of this study is to evaluate the efficacy and safety of Baidu Jieduan granule in curing COVID-19.

**Methods/design:** This multicenter, open-label randomized controlled trial is conducted 300 cases with COVID-19. The patients will be randomly (1:1) divided into treatment group or control group. All cases will receive standard therapy at the same time. The experiment group will receive Baidu Jieduan granule treatment twice a day for 14 days. The outcomes are assessed at baseline and at 3, 5, 7, 14 days after treatment initiation. The primary outcome is the rate of symptom (fever, fatigue, and coughing) recovery. Adverse events (AEs) will be monitored throughout the trial.

**Discussion:** The study will provide a high-quality clinical evidence to support the efficacy and safety of Baidu Jieduan granule in treatment of moderate COVID-19, and also enrich the theory and practice of TCM in treating COVID-19.

**Trial registration**: Chinese Clinical Trial Registry, ChiCTR2000029869. Registered on 15 February 2020


# Introduction

An outbreak of coronavirus disease 2019 (COVID-19) in Wuhan city, China, has resulted in a global health emergency, with over 61.8 million confirmed cases, including over 1.4 million deaths as 29 November, 2020 around the world [1]. The number of patients may be underestimated, on account of asymptomatic individual or cases with moderate condition [2]. At present, scientists are sure that COVID-19 is caused by a new virus, named “severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)” [3]. The patients suffer from fever, fatigue, dry cough, and some progress to breathing difficulties, ARDS or sepsis [4]. The disease was diagnosed by clinical characteristics, the epidemiological history and laboratory test according to "Guidelines for the Diagnosis and Treatment of Novel Coronavirus (COVID-19) Infection by the National Health Commission (Trial Version 7)" [5].

Currently, there is no vaccine or specific antiviral drug for COVID-19; meticulous supportive therapies are the cornerstone. Traditional Chinese Medicine (TCM), has a great wealth of clinical experience in preventing and treatment of epidemic diseases [6]. In Ming Dynasty, “Wen Yi Lun”, a famous Medical ancient book, mention that epidemic diseases can be contagious to other people, and be transmitted through the respiratory tract and digestive tract. Modern medical practitioners suggested that the disease should belong to damp-warm pestilence in TCM [7]. Dampness obstructs the Qi mechanism leading to more Dampness and warm. Furthermore, damp-warm may also injure Yin and Qi, and cause pathogenic

toxin and blood-stasis. TCM has been widely applied to cure patients with COVID-19 attached to the damp-warm syndrome, especially in combination with Western medicine, can reduce antibiotic use, glucocorticoid [8]. Based on above TCM pathogenesis of COVID-19, our team put forward “San Tong strategies”[9], which means that integrate three kinds of strategies, including relief exterior syndrome, diarrhea and diuresis, and“Truncation and Reversion” strategy [9, 10], adopting catharsis large intestine rationally to prevent and treat sepsis patients, to timely prevent and treat the disease. On the foundation of“San Tong strategies”, we developed Baidu Jieduan granule, a formula consisting of *Rheum palmatum L.* stem (*Dahuang*), *Sargentodoxa cuneata (Oliv.) Rehd. et Wils.* (*Hongteng*), *Taraxacum mongolicumHand.-Mazz.* (*Pugongying*), *Raw Gypsum* (*Sheng Shigao*), Herba Ephedra (*Mahuang*), *Talcum* (*Huashi*), *Amygdalus Communis Vas* (*Xingren*), *Radix Glycyrrhizae (Gancao)*, *Verbena officinalis L.*(*Mabiancao*), *Polygonum cuspidatum* (*Huzhang*), *Scutellariae Radix (Huangqin)*, *Bombyx Batryticatus* (Jiangchan).

Baidu Jieduan granule is evolved from the TCM classical prescription Maxing Shigan decoction and our experiential prescription Jinhong Decoction. Our previous studies have demonstrated that Jinhong Decoction, composed of *Rheum palmatum L.* stem, *Sargentodoxa cuneata*, *Taraxacum mongolicum*, can inhibit the levels of TNF-α, IL-6, IL-8 and other inflammatory cytokines, protect against excessive inflammatory response, maintain organism’s balance between inflammation and anti-inflammatory in infectious diseases [11, 12]. Recent research found that Maxing Shigan decoction were regarded as antipyretic agency, anti-inflammation agency, antiviral agency and antitussive and antiasthmatic agency, and can be used to treat COVID-19 [13]. Therefore, Baidu Jieduan granule should have a beneficial and curative effects on COVID-19. However, there is not enough evidence to show clinical efficacy of Baidu Jieduan granule. Hence, we conduct a more designed multi-center, randomized trial, to evaluate the effectiveness and safety of Baidu Jieduan granule on the treatment of COVID-19. Furthermore, this trial can provide a reference for TCM in prevention and treatment of COVID-19 worldwide.

# Methods/design

### Study design and settings

The study is a randomized, placebo-controlled, multicenter trial, which will be conducted at four medical centers, including Huangshi Hospital of Traditional Chinese Medicine, Tongji Hospital Tongji Medical College Huazhong University of Science and Technology, LaoHeKou Tradiational Chinese Medicine Hospital and Leishenshan Hospital of Wuhan, that were selected by the expert committee. A total of 300 participants fulfilling the eligibility criteria will be randomized into two groups (Baidu Jieduan granule group and control group) in a ratio of 1:1. The study flowchart is illustrated in Fig.1. The Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) checklist is presented in Additional file 1.

### Population

Participant with COVID-19 will be recruited from 4 study sites in China. Patients with eligibility for inclusion criteria and informed consent, will be screened at the clinical trial period. Subjects Patients with meeting any the exclusion criteria, will be excluded before randomization. The recruitment duration will last for 5 months, from February 2020 to December 2020.

### Inclusion criteria

Subjects must meet all of the following requirements:

1. Be 18-85 years of age.
2. Patients with COVID-19 confirmed by SARS-CoV-2 nucleic acid testing of the respiratory specimens showed positive results.
3. Provide signed informed consent form.

### Exclusion criteria

The exclusion criteria are as follows:

1. Pregnant and lactating women.
2. Severe primary disease influencing the survival, including malignant tumours, hemorrhagic disease and HIV.
3. Severe liver and kidney dysfunction.
4. Immunosuppressant therapy or an organ transplant within the previous 6 months.
5. Participation in other clinical trials in the last 30 days.
6. Allergy to one or more component in Chinese herbal medicinal ingredient prescription

### Patient withdrawal

1. Patients enrollment without meeting inclusion criterion.
2. Not suitable for the trail due to deterioration or recovery of patient condition.
3. Patients with poor complicance.
4. Voluntary withdrawal.

When participations withdrawal or drop-out from the trial, all data collected up to the time of withdrawal should be remained in the database. Safety relevant information may be follow-up until at $14^{th}$ day if possible.

### Plan for retaining participants

The methods are need to promote participants retention. First, we will select coordinator and nurse carefully, and train them strictly before the trial begins. Furthermore, we also focus on daily communication and monitoring. The coordinator and nurse should have empathy and good

communication skills to gain the patient's trust, so as to improve patients' retention and finish the follow-up. In addition, we can also perform extra incentives.

## Sample size

A similar clinical trial was conducted, using TCM to decrease the rate of symptom (fever, fatigue, and coughing) in patients with COVID-19 [14]. The rate of recovery of clinical symptoms was 91.2% in patients received TCM treatment, and 61.1% in patients received conventional treatments. Considering 90% power with a significance level of 10 %, as well as a rate of withdrawal and loss to follow-up of 10% [15], we plan to recruit at least 150 participants in each group to achieve sufficient precision in a subsequent full trial.

## Randomization and blinding

The enrolled participants are randomly assigned to the Baidu Jieduan granule group or the conventional treatment group according to random codes. The random sequence of 300 participants from 4 medical centrals will be generated by SPSS 19.0, and stratified by each center. Two sets of random codes are stored in opaque envelopes, and the latter will be sent to the research sponsor and each of the centers. Thereafter, the drug administrators arrange the nurse to dispense the study drug in the order of the random number. This is an open-label study. The statistical analysis can be carried out by the Professors of Statistics of Shanghai University of Traditional Chinese Medicine, who is blinded to patient allocation.

## Interventions

The Baidu Jieduan granule is composed of 15 g of *Rheum palmatum L.* stem (*Dahuang*), 30 g of *Sargentodoxa cuneata (Oliv.) Rehd. et Wils.* (*Hongteng*), 30 g of *Taraxacum mongolicumHand.-Mazz.* (*Pugongying*), 45 g of *Raw Gypsum* (*Sheng Shigao*), 9 g of Herba Ephedra (*Mahuang*)，45 g of *Talcum* (*Huashi*), 12 g of *Amygdalus Communis Vas* (*Xingren*), 9 g of *Radix Glycyrrhizae (Gancao)*, 30 g of *Verbena officinalis L.*(*Mabiancao*), 30 g of *Polygonum cuspidatum* (*Huzhang*), 30 g of *Scutellariae Radix (Huangqin)*，12 g of *Bombyx Batryticatus* (Jiangchan), which were packaged in two bags. The Baidu Jieduan granule will be administered orally, two times a day for 14 days. The Baidu Jieduan granule is manufactured by Beijing Tcmages Pharmaceutical Co., LTD (Number: Jing 20180032).

The participants will be categorized into two groups receiving either standard Western medicine therapy alone according to the *The Protocol for Diagnosis and Treatment of Novel Coronarvirus Pneumonia* ($7^{th}$ edition), or the combination of Baidu Jieduan granule two times a day for 14 days plus standard care. The routine care includes early fluid resuscitation, antimicrobial anticoagulants, nutritional support and other treatment. Other TCM therapies, including TCM injections and other oral herbal medicine, should be prohibited.

## Outcomes and measurements

The primary outcome will be the proportion of negativity SARS-CoV-2 nucleic acid results at $14^{th}$ day. Secondary outcomes will be the time to symptom recovery, the proportion of cases with reverting on

chest CT, the time to negativity SARS-CoV-2 nucleic acid, the proportion of participants regrouped as severe cases. Symptoms recovery was defined as the complete disappearance of fever, fatigue and coughing symptoms.

Evaluation of the primary and secondary outcomes will occur at five points (before treatment, the $3^{th}$, $5^{th}$, $7^{th}$ and $14^{th}$ day during hospitalization).

### Safety outcomes

All safety-related indexes, including the vital signs, a complete blood routine and a general urine routine, biochemical test, fecal occult blood testing, and electrocardiogram results, will be tested and recorded in CRF at every visit. The biochemical test contains C-reactive protein, hepatic function (alanine transaminase, aspartate transaminase, alkaline phosphatase, total bilirubin, and gamma-glutamyltransferase) and renal function (blood urea nitrogen and serum creatinine). Any AE will be evaluated by a professional researcher at each visit and recorded on the CRF.

### Adverse event (AE) reporting

An AE is any undesirable syndrome that connected with the administration of Baidu Jieduan granule in a patient [16]. Any AE need be recorded in form immediately, and then evaluated by the physician and the corresponding coordinator. All related information, including occurrence time, severity, duration, the measures adopted and the outcome, can be reported to the sponsors, ethics committees, and drug regulatory authorities in accordance with the provisions. We will follow all subjects with AEs.

### Statistical analysis

We will not conduct subgroup or adjusted analysis for the trial. The independent statistical analysts will be responsible for the data analysis. All patients will be analyzed on the basis of intent-to-treat analysis, which contain all subjects with eliminating cases in a minimum and reasonable manner. For missing data, multiple imputation will be carried out to generate missing values. A per-protocol analysis, which includes patients who completed the trial without conflict to major protocol, can be conducted as appropriate. And then, the statistician timely submits statistical reports to the study director. The statistical analysis is performed in a blinded manner using the SPSS 20.0 software. Continuous variables characterizing each study group will be expressed as means with standard deviations or medians with interquartile ranges. Categorical variables will be reported as frequencies and proportions. The continuous outcomes will be analyzed by unpaired Student's t-test or Wilcoxon nonparametric statistic, while the count data are compared using a chi-square test or Fisher's exact test. Two-sided mean will be performed for all the statistical tests. $P$ <0.05 mean will be considered statistically significant. We will not carry out an interim analysis.

### Trial oversight

Coordination Center: The membership of Coordination Center consists of clinical experts, statisticians and quality control experts from each center. The center is responsible for the management of clinical research trials, cooperative hospitals, pre-clinical trial training courses, and resolving key issues in whole process of study.

Quality control: All centers and researchers are regular monitored and supervised by Clinical Research Organizations (CRO) throughout the trial, according to the standard protocol.

## Data management

Trained research staff collect trial data carefully according to a standard protocol and complete paper case report forms (CRFs) accurately, completely, timely and reliably. The data will be entered into Electronical Data Capture (EDC) system and regularly reviewed by a clinical research associate (CRA). If any changes are conducted by researchers, the feedback will be provided to the researchers and CRA. All modifications and paper CRF transfer between investigators, inspectors, and data managers should be documented and maintained appropriately. The data administrators will lock the data on completion of the study. The medical information on all the study participants will be kept strictly confidential. The SPIRIT flowchart of the study has been shown in Fig. 2. Research findings will be announced via publication and conferences, both nationally and internationally. After the study is published, the data can be obtained in an appropriate manner.

## Quality control

All investigators of the trial should be trained strictly and comprehensively by the State Food and Drug Administration, following Good Clinical Practice (GCP), to profoundly comprehend the procedure of the trial and strengthen compliance. All qualified researchers will collect data and finish the CRF in an accuracy and complete way. After discharge, the subjects will be followed by phone. Regular monitoring and inspecting will be conducted by CRO once a month, to confirm the reliability of the related research data and the trial process. They will check details on informed consent, inclusion and exclusion criteria, the original data, management of AEs, the process of storage and distribution of the research drugs, and CRF.

## Ethics

This trial will comply with the principles of Declaration of Helsinki and the regulations on quality management of clinical trials in China. The research protocol has been approved by the Ethics Committee of Huangshi Hospital of Traditional Chinese Medicine (approval number HSZY-PJ-2020-002-01) and registered with the Chinese Clinical Trial Registry (ChiCTR2000029869). All the changes in the trial protocol should be maintained as a program addendum and the revised protocol should be submitted to the Ethics Committee for re-review. The trained principal investigators or study coordinators recruit the patients and conduct the informed consent process. They need to ensure that study participants or legal representatives will receive sufficient explanation and time to sign the informed consent form prior to the

study. Any modification on study protocol or AEs attributable to this study will be reported to the research ethics committees.

# Discussion

The high transmission efficiency of COVID-19 create a significantly negative impact on the global economy and community [17]. COVID-19 can cause lung inflammation and infiltration, with inflammatory cytokine storms induced by SARS-CoV-2 infection [17]. The current management is mainly supportive therapies. Other agents, including Lopinavir (LPV)-Ritonavir, Remdesivir, Chloroquine/hydroxychloroquine and Favipiravir, are assessed in clinical trials [18]. TCM was first documented about 2500 years ago and then popularized by world globalization. Chinese medicine have prominent values and extensive applications in the treatment of COVID-19, since no other agents are proved to have efficacy [7, 19]. Additionally, TCM possess the advantages of simple, convenient, efficient, inexpensive but lower side-effects.

Baidu Jieduan granule, as an experiential prescription for the treatment of COVID-19, evolve from Maxing Shigan decoction and our experiential prescription Jinhong Decoction, with the addition of *Verbena officinalis L.* (*Mabiancao*), *Polygonum cuspidatum* (*Huzhang*), *Scutellariae Radix (Huangqin)* and *Bombyx Batryticatus* (Jiangchan). *Verbena officinalis L.* and *Polygonum cuspidatum* have the effects of expelling wind and removing dampness, clearing heat and detoxicating, and invigorating the circulation of blood, relieving coughs and reducing sputum [20, 21]. *Bombyx Batryticatus* can eliminate external wind, resolve phlegm, dissipates nodules, clear heat, and dissipates stagnant heat [22]. *Scutellariae Radix* can clear heat patterns, especially of the upper Jiao, drie dampness, and eliminate toxicity [23]. The traditional medicine theories serve as a powerful guide in prescribing the Chinese herbal formula.

This trial is a well-designed multicenter open-label RCT from the perspective of evidence-based medicine, to assess the efficacy and safety of Baidu Jieduan granule in management of COVD-19 for the first time. The trial can make a clinical basis for adopting“San Tong” strategy and “Truncation and Reversion” strategy in prevention and treatment of patients with COVID-19, and further enrich the theory and practice of treating infectious diseases with TCM. Nevertheless, the design of the trial also has potential limitations. It is not a double-blind placebo controlled clinical trial. Since the country gives priority to curing diseases and saving lives, no strict randomization and placebo are permitted.

# Trial Status

The protocol version is 1.0, 1 Feb 2020. We are currently recruiting participants from February 2020. It is estimated that up to 300 participants will be enrolled by December 30, 2020.

# List Of Abbreviations

COVID-2019: 2019 novel coronavirus; SIRT1: Silent Information Regulator 1; AE: adverse event; AEs: adverse events; CRF: case report form; SPIRIT: Standard Protocol Items Recommendations for Interventional Trials; CT: chest computed tomography; GCP: Good Clinical Practice; TCM: traditional Chinese medicine; CRO: Clinical Research Organization

# Declarations

### *Ethics approval and consent to participate*

This trial complies with the principles of Declaration of Helsinki and the regulations of quality management of clinical trials in China. The study has been approved by the Ethics Committee of Huangshi Hospital of Traditional Chinese Medicine (approval number HSZY-PJ-2020-002-01) and registered with the Chinese Clinical Trial Registry (ChiCTR2000029869). Signed informed consent forms will be obtained from all qualified participants before enrollment.

### *Consent for publication*

Not applicable.

### *Availability of data and materials*

After the study is published, the data can be obtained in an appropriate manner.

### *Competing interests*

The authors declare that they have no competing interests.

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The trial is funded by National Key Research and Development Program of China (2018YFC1705900). The study also received funding from research projects of Emergency Committee of the World Federation of Chinese Medicine Societies and Shanghai Society of Traditional Chinese Medicine, Novel Coronavirus Pneumonia Emergency Tackling Key Project (SJZLJZ.N01). Emergency Committee of the World Federation of Chinese Medicine Societies, Shanghai Society of Traditional Chinese Medicine, and National Key Research and Development Program of China play no part in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication. The Baidu Jieduan granule is manufactured by Beijing Tcmages Pharmaceutical Co., LTD (Number: Jing 20180032). Beijing Tcmages Pharmaceutical Co played no part in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

### *Authors' contributions*

BJF sponsored the study and designed this protocol. SZ is the primary supervisor and participated in the design of this protocol. WZ drafted the manuscript. QX helped XMX draft and revise the manuscript. STS

and TF participated in the design of the protocol and are responsible for trial management. WXX and YQ are involved in the data collection and monitoring of the study. JHC, CJ, TRH, HCL and YZ are supervising this study and participated in revising the manuscript. All authors read and approved the final manuscript.


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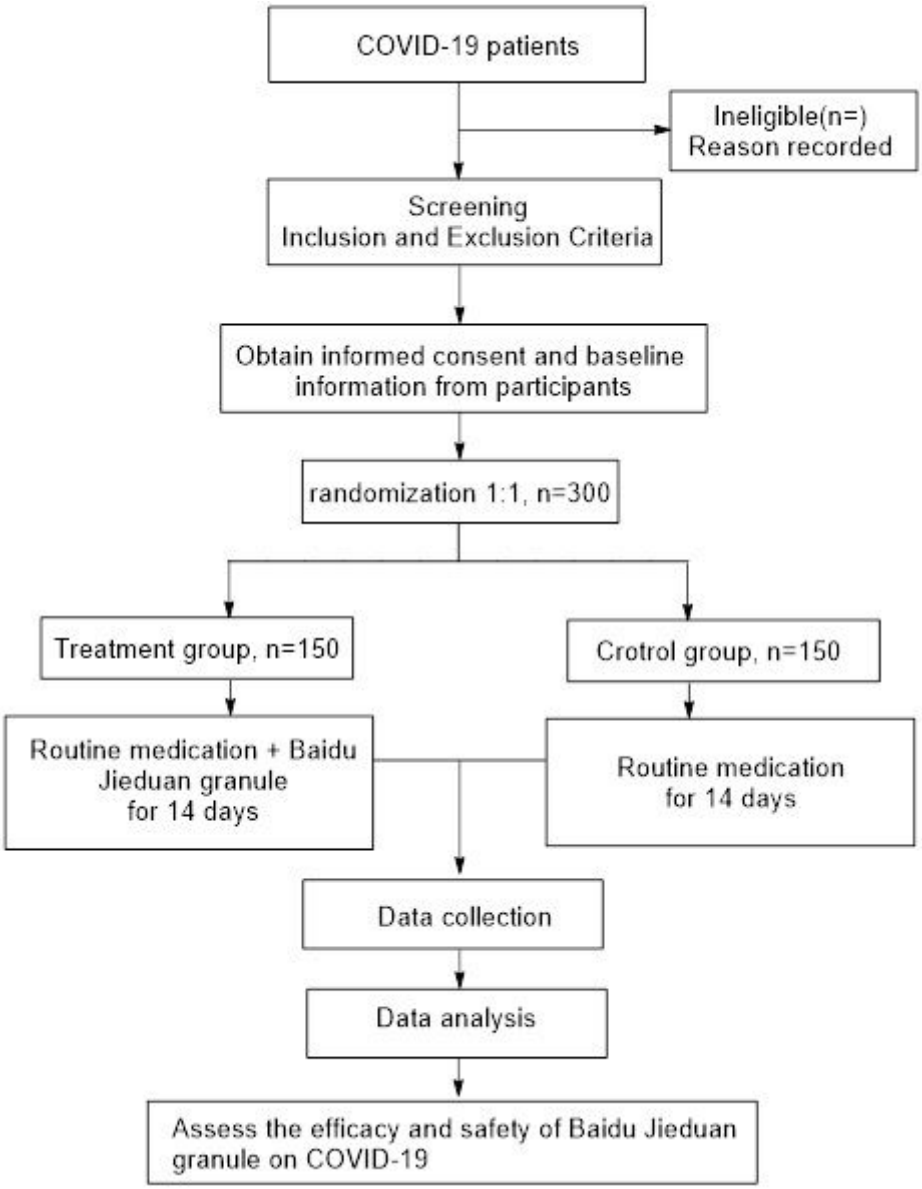
# Figures




## Figure 1

The flow chart of the Efficacy and Safety of Baidu Jieduan granule for COVID-19 study. COVID-19: coronavirus disease 2019.

| | Study Period | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Visit** | **Baseline** | **Intervention (14 days)** | | | | | | |
| **Time point** | **D1** | **D2** | **D3** | **D4** | **D5** | **D6** | **D7** | **D14** |
| Eligibility screen | X | | | | | | | |
| Informed consent | X | | | | | | | |
| Randomization | X | | | | | | | |
| Demographics | X | | | | | | | |
| General condition | X | | | | | | | |
| Primary disease | X | | | | | | | |
| Comorbidity | X | | | | | | | |
| Vital signs | X | X | X | X | X | X | X | X |
| Chest CT | X | | X | | X | | X | X |
| Symptom (fever, fatigue, and coughing) | X | | X | | X | | X | X |
| Hepatic function | X | | X | | X | | X | X |
| Renal function | X | | X | | X | | X | X |
| Routine blood | X | | X | | X | | X | X |
| Urine analysis | X | | X | | X | | X | X |
| Safety | X | | X | | X | | X | X |
| duration of symptom | X | | X | | X | | X | X |
| negative of SARS-CoV-2 nucleic acid | X | | X | | X | | X | X |
| Adverse events record | X | X | X | X | X | X | X | X |
| Survival condition | | | | | | | | X |

**Figure 2**

Study procedures and assessments. CT: computed tomography; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

# Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SPIRITchecklistrevised.pdf
- InformedConsentForm.pdf
- InspectionReportoriginalcopy2.pdf