# Comparative effectiveness and safety of ribavirin plus interferon-alpha, lopinavir/ritonavir plus interferon-alpha, and ribavirin plus lopinavir/ritonavir plus interferon-alpha in patients with mild to moderate novel coronavirus disease 2019: study protocol

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*To the Editor:* At the end of 2019, an outbreak of novel coronavirus disease 2019 (COVID-19), caused by 2019-nCov, causing widespread novel coronavirus disease. This outbreak of COVID-19 occurred during the period of the 2020 Spring Festival in China, a period known for massive population movements within China. This has resulted in large numbers of infected patients as a consequence of multiple human contact episodes in individual travelers.

The 2019-nCov is genetically similar to the severe acute respiratory syndrome *coronavirus* (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), which also belong to the *Coronaviridae* family of viruses, and cause respiratory. The pneumonia caused by the novel coronavirus infection is characterized by fever, cough, dyspnea, and ground-glass-type interstitial changes on radiographical imaging via X-rays and computed tomography scans. On February 5, 2020, the National Health Commission of the People's Republic of China and the National Administration of Traditional Chinese Medicine issued "Guidelines for diagnosis and treatment of novel coronavirus pneumonia (Trial Version 5),"[1] which advocated the use of interferon-alpha (IFN-α), lopinavir/ritonavir (LPV/r) and ribavirin for the treatment of COVID-19.

Based on the previous reports and observational studies in SARS and MERS, the most widely used antiviral regimen was the combination of ribavirin and IFN, and this use was based on studies showing the efficacy of this combination in reducing viral replication and disease severity in animal models.[2] In a more recently published update, the use of interferons and LPV/r is ranked under the Recommendation of "benefit is likely to exceed risk."[2] One series of case reports showed that viral clearance is achievable by triple antiviral therapy in MERS patients.[2,3] These aforementioned therapeutic regimens are based on the treatment experience during the SARS and MERS epidemics. However, there is currently no evidence supporting their use in patients with COVID-19. Randomized clinical trials are therefore required to provide robust and reliable clinical evidence for the efficacy of these treatment regimens for the treatment of COVID-19. In this present study, we chose three variations of therapeutic drugs used to manage SARS and MERS patients: ribavirin (intravenous loading dose of 2 g, followed by oral doses of 400–600 mg every 8 h depending on the patients weight, for 14 days); LPV/r (oral, 400 mg/100 mg per dose, twice a day, refer to 14 days); and IFN-α-1b (atomizing inhalation, 5 million U or 50 μg per dose, twice a day, for 14 days). We refer to the three different therapeutic regimens as ribavirin plus IFN-α1b (arm A); LPV/r plus IFN-α1b (arm B); and ribavirin plus LPV/r plus IFN-α1b (arm C), and we aim to compare the effectiveness and safety of these different antiviral regimens for the treatment of COVID-19. It should be noted that the recommended doses of the three prescribed drugs are based on the treatment experience in past SARS and MERS clinical trials, and current Chinese guidelines for COVID-19.[2-5]

Our research is designed as an open-labeled, single-center, prospective, randomized and controlled clinical trial. We hope to enroll a sample size of 108 patients for this study, based on a power of 80%, and a level of confidence set at 95%, while also considering a dropout rate of 10%. One
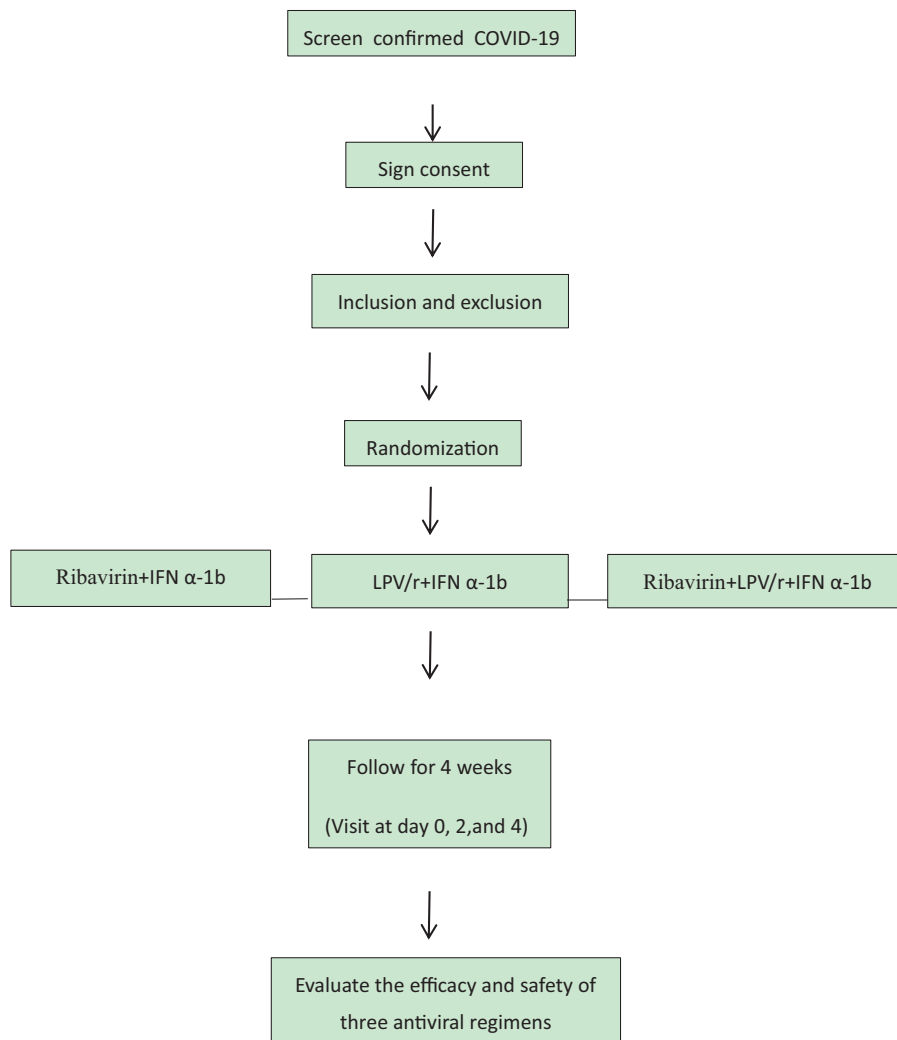
**Figure 1:** Flow diagram of the study.

hundred and eight eligible patients with confirmed mild to moderate COVID-19 will be enrolled at Chongqing Public Health Medical Center. Patients will be blocked randomization individually to one of three treatment arms by means of random computer-generated lists, with an allocation ratio of 1:1:1, with block sizes of nine patients. The enrolment, intervention, and assessment processes are shown in Figure 1.

The diagnosis of mild to moderate COVID-19 will meet all of the following criteria: (1) 2019-nCoV RNA detection is positive in the upper respiratory tract via nasopharyngeal or oropharyngeal swab samples, or lower respiratory tract via expectorated sputum samples, endotracheal aspirate samples, or bronchoalveolar lavage samples of enrolled patients; (2) Patients are symptomatic, with fever, unproductive cough or dyspnea, and their X-ray or computed tomography scan imaging demonstrates interstitial pneumonia; (3) Respiratory rate <30 breaths/min; (4) Arterial oxygen saturation (resting-state) >93%; (5) Arterial partial pressure of oxygen/oxygen concentration $(FiO_2)$ >300 mmHg.

Patients will be included from our study if they satisfy the following criteria: (1) 18 to 65 years of age; (2) diagnosed as mild to moderate COVID-19; (3) be willing to sign informed consent. Patients who are diagnosed with severe COVID-19, or are pregnant or breastfeeding women, having aspartate aminotransferase or alanine aminotransferase >5 × upper normal limit or creatinine clearance <50 mL/min, are allergic or intolerant to the proposed antiviral therapeutic drugs, are human immunodeficiency virus-positive, having severe heart disease, brain disease, lung disease, kidney disease, neoplastic disease, hemolytic anemia, or other severe systemic diseases, or are not willing to provide signed informed consent, will be excluded.

Each individual will be invited to participate in a 28-day follow-up at day 0, day 2, day 4, day 7, day 14, day 21, day 28 after initiation of a specific antiviral regimen. Blood, nasopharyngeal swab, sputum, stool, and urine samples will be collected for laboratory examinations, which includes hematological analysis, urinalysis, hepatic and renal function test, test for serum amylase levels and myocardial enzyme levels, arterial blood gas analysis,

thyroid function test, 2019-nCoV RNA qualification test, lymphocyte subsets test, coagulation test, and chest imaging examination. All data will be recorded in case report forms and in Microsoft Excel (Microsoft Corporation, Redmond, WA).

The study endpoints are: two consecutive negative 2019-nCoV RNA results after initiation of antiviral therapy at least 24 h apart; progression to severe COVID-19; completion of the entire therapeutic regimen and study patient visits; adjustment of medications due to poor prognosis or severe adverse events, or death.

The primary outcome is the time to 2019-nCoV RNA negativity in patients. The secondary outcomes are: the rate of negative 2019-nCoV RNA results at day 14; the mortality rate for COVID-19 patients at day 28 after antiviral therapy; the rate of patients re-classified as severe cases during the study period; the rate of adverse events during the study period, and the rate of therapeutic discontinuation due to adverse events during the study period.

We will compare the study endpoints among the three arms using time-to-event methods with the Cox proportional-hazards model. The different categorical variables will be analyzed using the one-way analysis of variance. To describe the efficacy and safety of the three antiviral regimens, Kaplan-Meier estimates and a multivariate Cox proportional hazards model will be used to compare mortality of patients and adverse events among the three arms during the study period at day 28. A $P$-value of $<0.05$ will be deemed to confer statistical significance.

The proposed study was approved by the Ethics Committee of Chongqing Public Health Medical Center (No. 2020-002-01-KY) and was duly registered at the Chinese Clinical Trial Registry (No. ChiCTR2000029387, http://www.chictr.org.cn/showproj.aspx?proj=48782). We will share the results through published medical journal articles and conference presentations subsequent to study completion.

This study has several challenges. First, the relatively low numbers of newly diagnosed patients in Chongqing at present as a result of effective public health measures in response to the outbreak could mean that we may not achieve our proposed cohort total of 108 patients. Second, it is likely that the necessary increased number of close interactions between the admitted 2019-nCoV-infected patients and medical staff conducting this study during the study period, will increase the risk of 2019-nCoV exposure to the study medical staff. Third, in the study we will dispense a combination of three antiviral drugs to one arm of the study cohort for the treatment of COVID-19. Some physicians do not recommend a combination of three, or more than three antiviral drugs in specific regimens for the treatment of COVID-19 according to Version 6 of the clinical guidelines. The recommendations in the guidelines

are extracted and distilled from the clinical experience of physicians, but have no current evidence in its support. A case report has indicated that, in patients with MERS-CoV infection, the proposed drug regimens to treat COVID-19 will have good outcomes.[2] Hence, we aim to conduct a prospective, randomized, controlled clinical trial to obtain robust clinical data of therapeutic efficacy and safety for three different antiviral regimens, through which we hope to provide clear and credible evidence for or against the use of these regimens in the management of patients with mild to moderate COVID-19.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

### Funding

### Conflicts of interest

None.

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