An exploratory randomized, controlled study on the efficacy and safety of lopinavir/ritonavir or arbidol treating adult patients hospitalized with mild/moderate COVID-19 (ELACOI)

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Abstract

Background: The novel coronavirus pneumonia (COVID-19) outbreak has caused a global pandemic, however, effective antiviral therapeutics are still unavailable.

Methods: Our study (NCT04252885), designated as ELACOI, was an exploratory randomized (2:2:1) and controlled one, exploring the efficacy and safety of lopinavir/ritonavir (LPV/r) or arbidol monotherapy treating mild/moderate COVID-19 patients.

Results: This study successful enrolled 44 patients with mild/moderate COVID-19, with 21 randomly assigned to receive LPV/r, 16 to arbidol and 7 to no antiviral medication as control. Baseline characteristics of three groups were comparable. The median time of positive-to-negative conversion of SARS-CoV-2 nucleic acid was 8.5 (IQR 3, 13) days in the LPV/r group, 7 (IQR 3, 10.5) days in the arbidol group and 4 (IQR 3, 10.5) days in the control group (P=0.751). The positive-to-negative conversion rates of SARS-CoV-2 nucleic acid at day 7 and 14 did not show significant differences in the LPV/r group (42.9%, 76.2%), the arbidol group (62.5%, 87.5%) and the control group (71.4%, 71.4%) (all P>0.53). No statistical differences were found among three groups in the rates of antipyresis, cough alleviation, improvement of chest CT or the deterioration rate of clinical status (all P > 0.05). Overall, 5 (23.8%) patients in the LPV/r

group experienced adverse events during the follow-up period. No apparent adverse events occurred in the arbidol or control group.

Conclusion: LPV/r or arbidol monotherapy seems little benefit for improving the clinical outcome of mild/moderate COVID-19. LPV/r might lead to more adverse events. Due to the limitation of small sample size, further verification is needed in the future.

Key words: COVID-19; SARS-CoV-2; Lopinavir/ritonavir; Arbidol; Efficacy

Introduction

Since December, 2019, cases of the novel coronavirus disease (COVID-19) have rapidly spread from Wuhan, China to throughout China and over 110 other countries and territories within just two months [1,2]. This outbreak was confirmed to be caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, previously named 2019 novel coronavirus or 2019-nCoV), belonging to the same family of viruses responsible for severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) [3]. The World Health Organization (WHO) has declared the COVID-19 as a public health emergency of international concern. As of March 16th, 2020, 167,515 confirmed cases and 6,606 death cases have been documented globally [2]. Despite the rapid spread worldwide, little is known about the pathogenesis of the virus or its infectious host. Even worse, no vaccine or specific antiviral drugs have demonstrated efficacy in prevention or treatment of COVID-19, which has resulted in great difficulty of controlling the epidemic and decrease mortality rate [4].

Based on "Diagnosis and treatment of pneumonitis caused by new coronavirus (trial version 6) " issued by the National Health Commission of China on February 19th, 2020, several drugs including lopinavir/ritonavir (LPV/r) and arbidol were recommended for treatment of COVID-19 as the antiviral regimens [5]. Lopinavir is a human immunodeficiency virus 1 (HIV-1) protease inhibitor, usually combined with ritonavir for inhibiting cytochrome P450 in order

to increase the half-life of lopinavir [6]. In the past 10 years, LPV/r has been proven to have good efficacy and limited side effects for treating HIV-1[7]. Lopinavir was reported to have antiviral activity against MERS-CoV in Vero cells (concentration causing a 50% reduction in replication (EC50) = 8 μM) [8]. Meanwhile, the combination of LPV/r had been associated with significantly fewer adverse clinical outcomes (acute respiratory distress syndrome or death) in 41 patients with SARS compared with ribavirin alone in 111 historical controls (2.4% versus 28.8%, *P*= 0.001) within the 21 days after the onset of symptoms, despite lacking valid estimate of efficacy [9]. Based on in vitro testing and previous clinical trials demonstrating its efficacy against other coronaviruses, LPV/r was regarded as an option for treating COVID-19.

Arbidol is a haemagglutinin inhibitors that can effectively block the fusion of influenza virus with host cell. Meanwhile, it can also induce the body to produce endogenous interferon against virus replication, enhance the phagocytic function of macrophages, and activate natural killer cells. It can enhance the phagocytic function of macrophages and induce the activation of natural killer cells [10, 11]. Arbidol was reported efficacious against all kinds of influenza viruses (A, B, C), especially against influenza A viruses (H1N1, H2N2, H3N3) and safe with few side effects [12]. Arbidol was also shown to have some direct antiviral effect in reducing the reproduction of SARS virus in the cultured cells [13]. Interestingly, it was announced by Li Lanjuan's team that that arbidol could effectively inhibit coronavirus up to 60 times at a concentration of 10-30 μM

compared with the untreated control [14].

LPV/r and arbidol were recommended for treating COVID-19 in China because of the above reasons and critically lack of preventive vaccines and efficient antiviral therapies presently. Nevertheless, we did not know the actual clinical efficacy of LPV/r or arbidol against SARS-CoV-2 thus far. Therefore, we were urgently in demand of a randomized clinical trial (RCT) to evaluate the efficacy or adverse outcomes of LPV/r or arbidol treating COVID-19. Guangzhou Eighth People's Hospital is a designated hospital for the treatment of COVID-19 patients and hospitalized over 80% of the patients confirmed with COVID-19 in Guangzhou. Here, we report an exploratory randomized and controlled study ELACOI at this hospital, aiming to provide preliminary evaluation of the efficacy and safety of monotherapy with LPV/r or arbidol in the treatment of mild/moderate COVID-19 patients.

Methods

Study design and participants

ELACOI was a single-center, randomized and controlled trial conducted at Guangzhou Eighth People's Hospital to preliminarily investigate the efficacy of LPV/r and arbidol in treating COVID-19 patients. This empirically exploratory study was designed to enroll 125 cases according to the estimated number of patients admitted to the hospital, which were randomly assigned (2:2:1) into 3 groups as follows. In group A (LPV/r group), 50 cases were administered

lopinavir (200mg) boosted by ritonavir (50mg) (oral, q12h, 500 mg each time for 7-14 days) monotherapy. In group B (arbidol group), 50 cases were given arbidol (100mg) (oral, 200mg TID for 7-14 days) monotherapy. In group C (control group), 25 cases were given no any antiviral medicine. All three groups were followed for up to 21 days. All three groups were treated with supportive care and effective oxygen therapy if in need.[5] Antiviral treatment was discontinued for patients who 1) had been treated for more than 7 days and tested negative for SARS-CoV-2 nucleic acid in two consecutive tests separated by more than 24 hours, or 2) discharged from hospital, or 3) had intolerable side effects.

All participants met the following inclusion criteria 1) age between 18 and 80 years old; 2) SARS-CoV-2 infection confirmed by real-time PCR (RT-PCR) from pharyngeal swab; 3) mild clinical status, defined as having mild clinical symptoms but no signs of pneumonia on imaging or moderate clinical status, defined as having fever, respiratory symptoms and pneumonia on imaging [5]; 4) the following lab findings: creatinine ≤110μmol/L, creatinine clearance rate (eGFR) ≥60 ml/min/1.73m^2, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤5 × ULN, and total bilirubin (TBIL) ≤2 × ULN; 5) willing to participate the study and sign the informed consent. Meanwhile, patients were excluded based on the following criteria 1) known or suspected to be allergic to LPV/r or arbidol; 2) having severe nausea, vomiting, diarrhea or other complaints affecting oral intake or absorption in the digestive tract; 3) taking

other drugs that may interact with LPV/r or arbidol; 4) having serious underlying diseases, including but not limited to heart, lung, or kidney disease, liver malfunction, or mental diseases affecting treatment compliance; 5) complicating with pancreatitis or hemophilia prior to the trial; 6) Pregnant or lactating women; 7) having the suspected or confirmed history of alcohol or substance use disorder; 8) having participated in other drug trials in the past month; 9) deemed otherwise unsuitable for the study by the researchers.

Before initiation of the trial, the protocol was approved by the ethics committee of Guangzhou Eighth People's Hospital (Approval No. 202002136) and registered on ClinicalTrials.gov (NCT04252885). The ethics committee agreed to set up the control group owing to no reliable evidence about the benefit of present antiviral regimens for treating COVID-19. The trial was also done in accordance with the International Conference on Harmonization's Guideline for Good Clinical Practice. Written informed consent was obtained from all screened patients after they fully understood the meaning of the trial and potential risk.

Randomization and masking

All eligible participants were allocated to a randomization number which allocated him/her into one treatment group. The randomization numbers were computer-generated. Allocation concealment was achieved using a centralized web-based randomization system in which the participant identifier

(hospitalization number) was entered before the allocation was revealed. The randomization number were used in case report form (CRF) pages. The study was blind to participants, those physicians and radiologists who reviewed the data and radiological images, but open-label to clinicians who recruited patients and research staff.

Procedures

A standardized protocol was developed for collecting clinical data for all participants. The following data were collected: 1) important dates, including fever onset, admission, progression to severe clinical status, positive-to-negative conversion of SARS-CoV-2 nucleic acid, improvement of chest computerized tomography [CT] scan, discharge, or death; 2) presence of predefined comorbidities (hypertension, diabetes mellitus, etc.); 3) daily observation of clinical parameters (temperature, pulse, respiratory rate, oxygen saturation, Inhaled oxygen concentration if needed); 4) The conversion time of nucleic acid of SARS-CoV-2 from positive to negative and the clinical improvement including the rate of antipyresis , the rate of cough alleviation, the rate of improvement on chest CT at day 7 and 14; 5) details of drug treatment for supportive treatment and measures for oxygen therapy and 6) adverse events. The clinical information was merged with selected laboratory and pharmacy information from the HIS and LIS database. All clinical, virological and laboratory data, as well as adverse events were reviewed by two physicians, and all radiologic images were reviewed by two radiologists.

SARS-CoV-2 nucleic acid was detected by real-time fluorescence reverse transcriptional polymerase chain reaction (RT-PCR) using the platform of Da'an Gene Corporation, Sun Yat-sen University, Guangzhou, China. The specimens were obtained using pharyngeal swabs of patients. The nucleic acid detection of SARS-CoV-2 targeted to the open reading frame 1a/b (ORF1a/b) and nucleocapsid protein (N) genes. Virus RNA was extracted with Nucleic Acid Isolation Kit on an automatic workstation Smart 32. A 200 μl sample was used for extraction following the standard protocol, and viral RNA was eluted with 60 μl elution buffer. Real-time reverse transcriptional polymerase chain reaction (RT-PCR) reagent was used following the RNA extraction. In brief, two PCR primer and probe sets, targeting ORF1ab (FAM reporter) and N (VIC reporter) genes separately, were added in the same reaction. Positive and negative controls were included for each batch of detection. Samples were considered to be virally positive when either or both set(s) gave a reliable signal(s) [15].

Outcomes

The primary outcome was the time of positive-to-negative conversion of SARS-CoV-2 nucleic acid from initiating treatment to day 21, with the enrollment day as the first day of treatment. The secondary outcomes included 1) the rate of positive-to-negative conversion of SARS-CoV-2 nucleic acid at day 7 of treatment; 2) the rate of positive-to-negative conversion of SARS-CoV-2 nucleic acid at day 14; 3) the rate of antipyresis (defined as axillary

temperature ≤37.3℃ for more than 72 hours) from the first day of treatment; 4) the rate of cough alleviation from initiation; 5) the improvement rate of chest CT at day 7 and 14; 6) the deterioration rate of clinical status from mild/moderate to severe/critical status during the study period. The severe status was defined as the one meeting with any of the following: experiencing respiratory distress, RR≥30 times/minute; in the resting state, the oxygen saturation ≤93%; arterial blood oxygen partial pressure (PaO2)/oxygen concentration (FiO2) ≤300 mmHg (1mmHg = 0.133kPa) [5]. The critical status was defined as the one meeting with any of the following: developing respiratory failure requiring mechanical ventilation; occurrence of shock; in need of ICU monitoring and treatment because of complicating with other organ failures [5].

Pharyngeal swabs were tested every 2 to 3 days. Negative conversion of nucleic acid was defined as negative detection of SARS-CoV-2 nucleic acid for two consecutive times separated by more than 24 hours. Criteria of chest CT improvement included: 1) no new exudative lesions; 2) decreasing size of exudative lesions; 3) decreasing densities of lesions.

All participants were monitored for adverse events. Safety outcomes were assessed from serious adverse event reports. Any unexpected, medical occurrence resulting in death, prolonged hospitalization, persistent or significant disability or incapacity, which is judged to be causally related to the study intervention, will be reported as a serious adverse event to the Institutional Review Board. Potential adverse events for the study were defined

as follows (1) anaphylaxis; (2) elevation of ALT or AST to more than 2.5-fold the upper normal limit or elevation of TBIL to more than 1.5-fold the upper normal limit; (3) acute pancreatitis; and (4) diarrhea.

Statistical analyses

The aim of this study is to explore the efficacy and safety of Lopinavir/ritonavir (LPV/r) monotherapy or arbidol monotherapy on the treatment of COVID-19 patients. However, COVID-19 is a new emerging disease without any data to calculate the sample size. In addition, the trend of the epidemic was not clear while we were designing the study. Based on the estimated number of patients admitted to the hospital at that time, we estimate that a maximum of 125 patients can meet the inclusion criteria.

All statistical analyses were performed using SPSS (Statistical Package for SPSS, version 26.0). We presented continuous measurements as mean (SD) if the data were normally distributed or median (IQR) if they were not, and categorical variables as count (%). Means for continuous variables were compared using one-way ANOVA when the data were normally distributed; otherwise, the Mann-Whitney test was used. Proportions for categorical variables were compared using the χ^2 test or Fisher's exact tests. A two-sided α of less than 0.05 was considered statistically significant.

Results

Baseline data of patients

From Feb 1 to Feb 18, 2020, 63 patients with mild/moderate COVID-19 were screened for this study, among whom 44 patients (mean age of 49.4 years [SD 14.9, range 27-79]) including 21 men and 23 women were successful enrolled in this study (figure 1). Patients were randomly assigned to receive LPV/r (n =21), arbidol (n =16), or control (n =7). All patients were followed up for 21 days. Although the study intended to recruit 125 COVID-19 patients, only 44 patients were involved in this study due to the recruitment pool was rapidly exhausted with few new cases developed in Guangzhou with the epidemic under control.

All enrolled patients had no chronic lung disease, chronic kidney disease, autoimmune disease or immunodeficiency disease. Eleven (52.4%) cases in the LPV/r group, 9 (56.3%) cases in the arbidol group and 2 (28.6%) cases in the control group suffered from fever. Meanwhile, 19 (90.5%) cases in the LPV/r group, 9 (56.3%) cases in the arbidol group and 6 (85.7%) patients in the control group developed cough. There were no significant differences in baseline demographic data, common clinical manifestations, clinical status, or pneumonia incidence seen on chest CT imaging among 3 groups (P >0.05). No patients complained dyspnea, diarrhea, palpitation or headache on admission. The laboratory parameters of ALT, AST, TBIL and creatinine were normal when all patients began the antiviral treatment. Meanwhile, other laboratory parameters including white blood cell count, lymphocyte count, neutrophil count, C-reactive protein level and procalcitonin level did not show significant

differences among 3 groups (*P* >0.05). The baseline characteristics of 44 patients in 3 groups are shown in table 1.

Efficacy outcomes

The mean time to positive-to-negative conversion of SARS-CoV-2 nucleic acid during the 21-day follow-up period was 8.5 (IQR, 3-13) in the LPV/r group, 7 (IQR, 3-10.5) in the arbidol group and 4 (IQR, 3-10.5) in the control group, with no statistical difference among them (*P* =0.751, *Power* =0.47) (table 2 and figure 2). Over the 21-day follow-up, the cumulative incidence of positive-to-negative conversion of SARS-CoV-2 nucleic acid in pharyngeal swab did not show statistical difference among the three groups (figure 3). After 7 days of treatment, the positive-to-negative conversion rates of SARS-CoV-2 nucleic acid in pharyngeal swab in the LPV/r group, the arbidol group and the control group were 42.9% (9/21), 62.5% (10/16) and 71.4% (5/7) respectively and did not present statistical difference among three groups (*P* =0.942) (table 2). After 14 days of treatment, the positive-to-negative conversion of SARS-CoV-2 nucleic acid were 76.2% (16/21), 87.5% (14/16) and 71.4% (5/7) respectively in the LPV/r group, the arbidol group and the control group, without significantly statistical difference among groups (*P* =0.681) (table 2).

With respect to other secondary outcomes, the rate of antipyresis, rate of cough resolution, and rate of improvement on chest CT imaging at day 7 and 14 did not show any statistical difference between the three groups (*P* >0.05).

Meanwhile, at day 7, eight (38.1%) patients in the LPV/r group, 2 (12.5%) in the arbidol group and 1 (14.3%) in the control group deteriorated from mild/moderate clinical status to severe/critical clinical status, without statistical difference (*P* =0.186) (table 2).

During the study period, two (9.5%) patients in the LPV/r group, 2 (12.5%) in the arbidol group and 1 (14.3%) in the control group used gamma globulin (10 g, once a day, for 2-3 days). Moreover, 6 (28.6%) patients in the LPV/r group, 2 (12.5%) patients in the arbidol group, and 2 (28.6%) patients in the control group used glucocorticoids (methylprednisolone 40 mg, once a day, for 3-5 days) without statistical difference among 3 groups (*P*=0.547). Eighteen (85.7%) patients (13 patients using low flow supply, 5 using high flow oxygen supply) in the LPV/r group, 11 (68.8%) patients (9 patients using low flow, 2 high flow oxygen supply) in the arbidol group and 6 (85.7%) patients (all using low flow oxygen supply) in the control group received oxygen therapy, which did not show statistical difference (*P* =0.466) (table 1).

Safety outcomes

During the follow-up period, 5 (23.8%) patients in the LPV/r group experienced adverse events including diarrhea (3/21,14.3%), loss of appetite (2/21, 9.5%) and elevation of ALT over 2.5-fold upper normal limit (1/21, 4.8%). No apparent adverse events occurred in the arbidol group or in the control group. Notably, one serious adverse event occurred in a 79-year-old man with

underling diseases including diabetes and hypertension in the LPV/r group, characterized by severe diarrhea on day 3. This patient progressed to critical condition and received extracorporeal membrane oxygenation (ECMO) but had not recovered by the observation endpoint of this study.

Summary of cases with severe/critical clinical status

A total of 11 (25.0%) patients progressed to severe/critical clinical status (containing 9 severe cases and 2 critical cases) during the study period including 8 receiving LPV/r, 2 receiving arbidol and 1 control. Two critical cases belonged to LPV/r group. The mean age of these 11 patients was 59.6 years old [SD 14.9, range 37-79], including 7 men and 4 women. Eight (72.7%) patients came from Hubei province and 3 (27.3%) were residents in Guangzhou. Two (18.2%) patients suffered from diabetes mellitus and 5 (45.5%) from hypertension. All patients complained of fever and 2 (18.2%) complained of cough, but none experienced diarrhea at the beginning of treatment. The SaO2 at rest was ≤93% in 3 (27.3%) patients and PaO2/FiO2 ratio was ≤300 in 4 (36.4%) patients. Among these patients, 2 (18.2%) required mechanical ventilation due to respiratory failure. 5 (45.5%) and 8 (72.7%) cases achieved positive-to-negative conversion of SARS-CoV-2 nucleic acid at day 7 and 14 respectively. At day 7 and 14 of follow-up, 6 (54.5%) and 8 (72.7%) patients had improvement on chest CT imaging. At the follow-up endpoint of day 21, 10 patients have been discharged from hospital and only one case was still

hospitalized.

In order to rule out the influence of the time from onset to treatment who deteriorated from mild/moderate clinical status to severe/critical clinical status, we compared the time from onset to treatment in patients deteriorated to severe/critical clinical status with those who did not deteriorate to severe/critical clinical status, and there was no significant difference between the two groups [6 (IQR 2.5, 8) days vs 3 (IQR 2, 6) days ; *P* =0.110].

Discussion

According to many clinical research reports, a high number of COVID-19 patients have been treated with antiviral and antibiotic therapy [16-18]. However, no specific medication had proven effective for suppressing or eliminating SARS-CoV-2 or for reducing complications and mortality. There are several ongoing clinical drug trials registered in the Chinese clinical trial registry [16,19]. Although the epidemic within China is now basically under control, the epidemics in other countries are becoming increasingly severe [2]. Therefore, it is extremely important to find specific anti SARS-CoV-2 drugs and learn from the experience of Chinese health providers.

Our study was designed to be an empirical exploration one intended to recruit 125 adult patients hospitalized with mild/moderate COVID-19; however, only 44 ones were involved in this study for the reasons mentioned above. With the randomization number, 21 patients were randomly assigned to receive LPV/r,

16 to arbidol, and 7 to no antiviral medication as control. The results showed that LPV/r and arbidol did not shorten the time of positive-to-negative conversion of COVID-19 nucleic acid in respiratory specimens (8.5 vs. 7 vs. 4 days), nor improve the symptoms of COVID-19 or the pneumonia on lung CT imaging at 7 days and 14 days. Moreover, more patients treated with LPV/r progressed from mild/moderate to severe/critical status than other two groups. Although there were no significant differences in the treatment outcomes among these three groups at this study, it may be a kind of false negative results due to the small sample size. With more patient enrollment in the future, the conclusion of different or not different could be ensured. Notably, why did LPV/r and arbidol fail to benefit for those patients? The reason remains unclear. We speculate one reason is that LPV/r and arbidol may need dose increase to successfully suppress SARS-CoV-2 in human body according to the cytotoxicity test in vitro [8, 13, 14], however, the dose increase is difficult to achieve clinically for the side effects of these drugs. In particular, it should be noted that patients treated with LPV/r had more gastrointestinal symptoms without achieving the definitely antiviral effect, which might affect the patient's recovery. The results in our study are consistent with findings from a recent clinical trial of LPV/r in adults hospitalized with severe COVID-19 conducted in Wuhan, which recruited 199 hospitalized adult patients with severe COVID-19 and concluded that no benefit was observed with LPV/r treatment beyond standard care [20]. Meanwhile, the other retrospective clinical research

conducted in Shanghai retrospectively observed 134 patients with COVID-19 and did not find any effects of LPV/r and arbidol on relieving symptoms or accelerating virus clearance after the treatment of 5 days [21]. Despite the small sample size, our study in another way indicates that monotherapy of LPV/r or arbidol might not improve the clinical outcome in treating with mild/moderate COVID-19.

The drug's side effect must also be seriously considered besides the efficacy. Notably, 5 (23.8%) patients in the LPV/r group experienced adverse events including 3 with diarrhea, 2 loss of appetite and one abnormal liver function, especially one serious adverse event reporting a 79-year-old man with diabetes and hypertension experienced severe diarrhea and progressed to critical condition ECMO with SARS-CoV-2 nucleic acid remaining positive over 14 days after treatment. Based on the drug instruction and experience of treating HIV-infected patients, the adverse reactions of the short-term use of LPV/r mainly include diarrhea, abnormal stools, abdominal pain, nausea, vomiting, and asthenia [6]. Since above side effects may aggravate the disease, LPV/r treatment should be cautiously considered after weighing the risks and benefits.

During the study period, totally 11 (25.0%) patients progressed to severe/critical clinical status including 8 receiving LPV/r, 2 receiving arbidol and 1 control, which rings the alarm bell that disease condition could still aggravate even after hospitalization, and urgently demands rigorous observation of illness and care. Fortunately, ten patients had been discharged from hospital after

recovery and only one case treated with ECMO was still hospitalized at the follow-up endpoint of day 21. This gives us great confidence that even if we do not have specific antiviral drugs, the vast majority of COVID-19 patients in severe/critical clinical status can still recover after comprehensive treatment.

Our study is not without its limitations. First, the sample size is too small to reach the adequate power (1-Beta error > 0.8) in many parameters. Second, the study did not enroll severely or critically ill patients, or patients with many comorbidities who are at increased risk of poor outcome and was conducted in only one center. Third, the study was not completely blinded, so it is possible to influence the outcome. We will continue to follow these patients to evaluate their long-term prognosis. Therefore, the findings of this study require further verification and evaluation. Nevertheless, as a prospective randomized, controlled trial, this study could still provide meaningful suggestions for proper application of LPV/r and arbidol in the treatment of COVID-19.

In conclusion, our study found LPV/r or arbidol monotherapy seems little benefit for improving the clinical outcome of mild/moderate COVID-19, and LPV/r might lead to more adverse events. Due to the limitation of small sample size, further verification is needed in the future.

Contributors

Linghua Li, Xilong Deng and Yueping Li conceived the study and designed the

protocol. Weiping Cai and Fuchun gave instructions. Chunyan Wen contributed to statistical analysis and interpretation of data. Linghua Li and Weiyin Lin drafted the manuscript. Feng Li and Fengyu Hu were in charge of nuclear acid RT-PCR. Zhiwei Xie and Yujuan Guan reviewed the data independently. Jinxin Liu and Lieguang Zhang reviewed all radiologic images independently. Xiaoneng Mo, Jian Wang, Yaping Wang, Ping Peng, Xudan Chen, Wenxin Hong and Guangming Xiao contributed to conducting the study and collecting data.

Declaration of interests

We declare no competing interests.

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Table legends

Table 1: Baseline characteristics of the three treatment groups (intention-to-treat population)

¶ list all the chronic diseases

Table 2: Outcomes of the three groups (intention-to-treat population)

Table 1: Baseline characteristics of the three treatment groups (intention-to-treat population)

Characteristic	LPV/r (n=21)	Arbidol (n=16)	Control (n=7)	*P* value
Gender (n, %)				0.914
Male	11(52.4%)	7(43.7%)	4(57.1%)	
Female	10(47.6%)	9(56.3%)	3(42.9%)	
Age, in years (mean, SD, range)	52.2(15.2;27-79)	49.4(14.6;30-73)	40.9(12.7;28-62)	0.218
Time from onset to treatment, in days (mean, SD, range)	4.3(3.3;1-15)	4.1(3.2;0.5-11)	5.6(3.0;1-8)	0.582
Underlying chronic diseases¶ (n, %)	7(33.3%)	7(43.8%)	1(14.3%)	0.530
Evidence of pneumonia based on chest CT imaging (n, %)	19(90.5%)	15(93.8%)	6(85.7%)	0.814
Clinical status (n, %)				0.814
mild	2(9.5%)	1(16.2%)	1(14.3%)	
moderate	19(90.5%)	15(93.8%)	6(85.7%)	
White blood cell count,10^9/L				0.929
<3.5 (n, %)	2(9.5%)	2(12.5%)	1(14.3%)	
3.5-9.5 (n, %)	19(90.5%)	14(87.5%)	6(85.7%)	
Lymphocyte count,10^9/L				0.861
<1.1 (n, %)	7(33.3%)	4(25.0%)	2(28.6%)	
1.1-3.2 (n, %)	14(66.7%)	12(75.0%)	5(71.4%)	
Neutrophil count,10^9/L				0.921
<3.5 (n, %)	2(9.5%)	2(12.5%)	1(14.3%)	
1.8-6.3 (n, %)	19(90.5%)	13(81.3%)	6(85.7%)	
>6.3(n, %)	0	1(6.3%)	0	
C-reactive protein,mg/L				0.06
<10 (n, %)	8(38.1%)	12(75.0%)	5(71.4%)	
>10(n, %)	13(61.9%)	4(25.0%)	2(28.6%)	
Procalcitonin, ng/mL				0.053
<0.05 (n, %)	10(47.6%)	13(81.3%)	6(85.7%)	
>0.05(n, %)	11(52.4%)	3(18.8%)	1(14.3%)	
Use of gamma globulin (%)	2/21(9.5%)	2/16(12.5%)	1/7(14.3%)	1.000
Use of glucocorticoids (%)	6/21(28.6%)	2/16(12.5%)	2/7(28.6%)	0.547
Oxygen therapy (%)				0.466
None	3/21(14.3%)	5/16(31.3%)	1/7(14.3%)	
Low flow oxygen supply	13/21(61.9%)	9/16(56.3%)	6/7(85.7%)	
High flow oxygen supply	5/21(23.8%)	2/16(12.5%)	0	

¶ list all the chronic diseases

Table 2: Outcomes of the three groups (intention-to-treat population)

Outcome	LPV/r	Arbidol	Control	*P* value	***Power***
Time to positive-to-negative conversion of SARS-CoV-2 nucleic acid in pharyngeal swab, in days (mean/SD, 95%CI)	8.70(6.00),(5.89,11.51)	7.63(5.32),(4.79,10.46)	7.00(5.94),(1.50,12.50)	0.751	0.47
Conversion rate from moderate to severe/critical clinical status (%)	8/21 (38.1%)	2/16(12.5%)	1/7(14.3%)	0.186	0.37
At 7 days after initiating treatment:					
Rate of positive-to-negative conversion of SARS-CoV-2 nucleic acid by pharyngeal swab (%)	9/21(42.9%)	10/16(62.5%)	5/7(71.4%)	0.942	0.28
Antipyresis rate (%)	8/11(72.7%)	5/9(55.6%)	2/2(100%)	0.536	0.72
Rate of cough alleviation (%)	9/19 (47.4%)	4/9(44.4%)	2/6(33.3%)	0.182	0.10
Rate of improvement on chest CT (%)	10/19(52.6%)	7/15(46.7%)	6/6 (100%)	0.074	0.86
At 14 days after initiating treatment:					
Rate of positive-to-negative conversion of SARS-CoV-2 nucleic acid by pharyngeal swab (%)	16/21(76.2%)	14/16(87.5%)	5/7(71.4%)	0.681	0.15
Antipyresis rate (%)	10/11 (90.9%)	9/9 (100%)	2/2 (100%)	1.000	0.30
Rate of cough alleviation (%)	17/19 (89.5%)	9/9 (100%)	5/6 (83.3%)	0.743	0.28
Rate of improvement on chest CT (%)	16/19(84.2%)	10/15(66.7%)	6/6 (100%)	0.193	0.58

Figure legends:

Figure 1. Trial profile

θ SAE: Severe Adverse Event

ϕ LPV/r: Lopinavir/ritonavir

Figure 2. Time to positive-to-negative conversion of SARS-CoV-2 nucleic acid by pharyngeal swab in each of the treatment three groups during the 21-day follow-up period

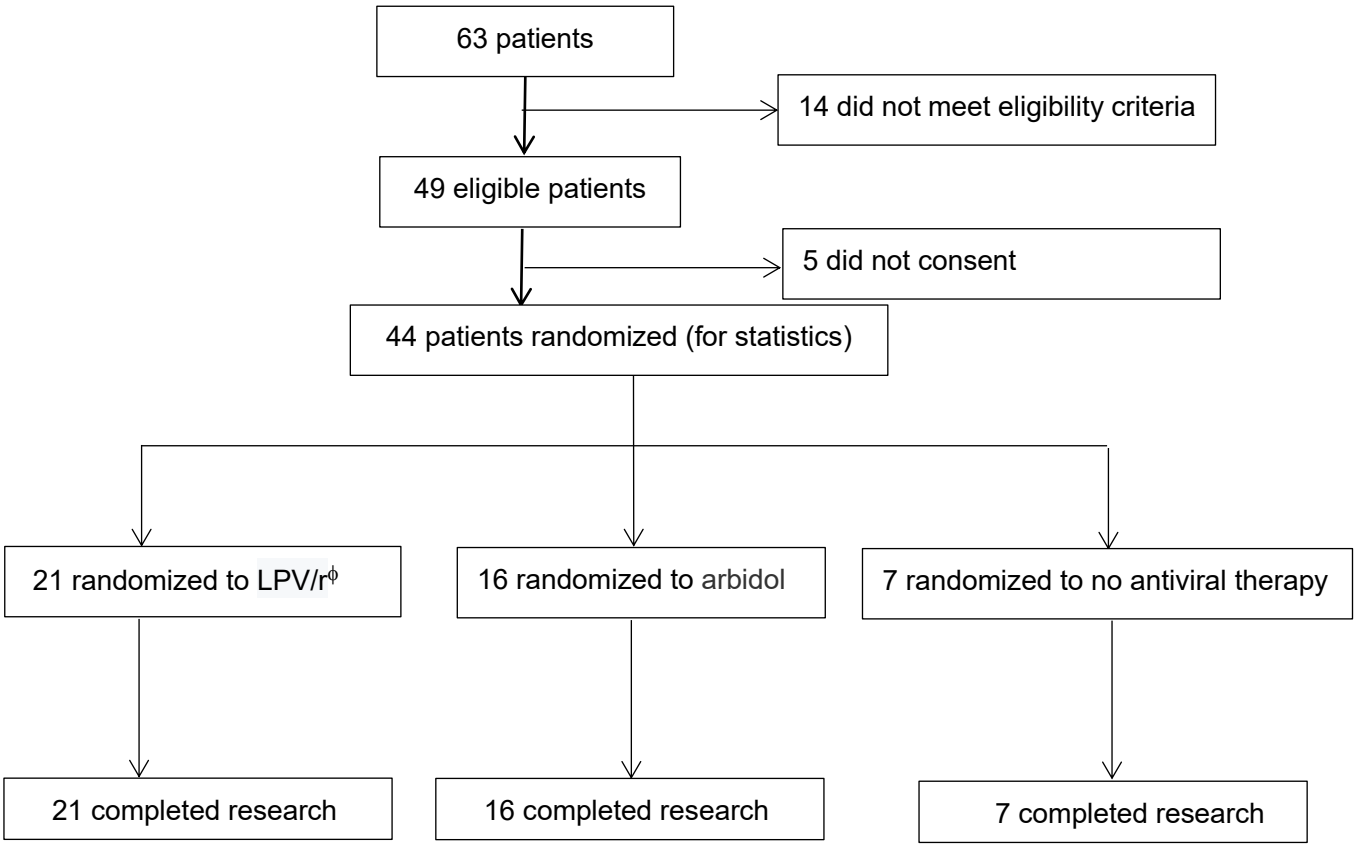
LPV/r: lopinavir/ritonavir

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

Figure 3. Proportion of patients in each of the three treatment groups with positive SARS-CoV-2 nucleic acid by pharyngeal swab during the 21-day follow-up period

LPV/r: lopinavir/ritonavir

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2



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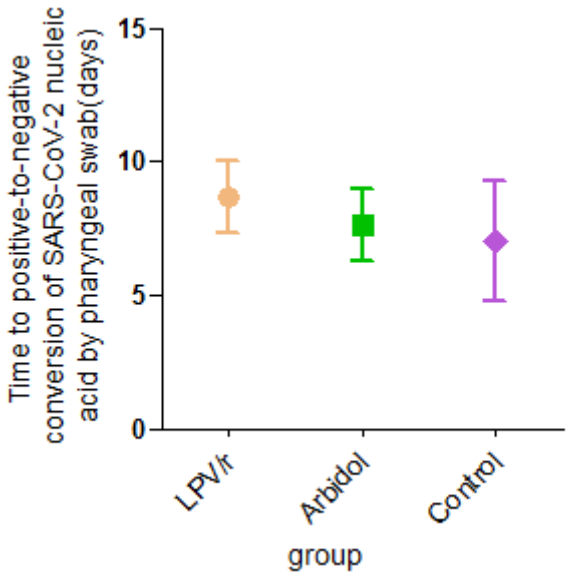

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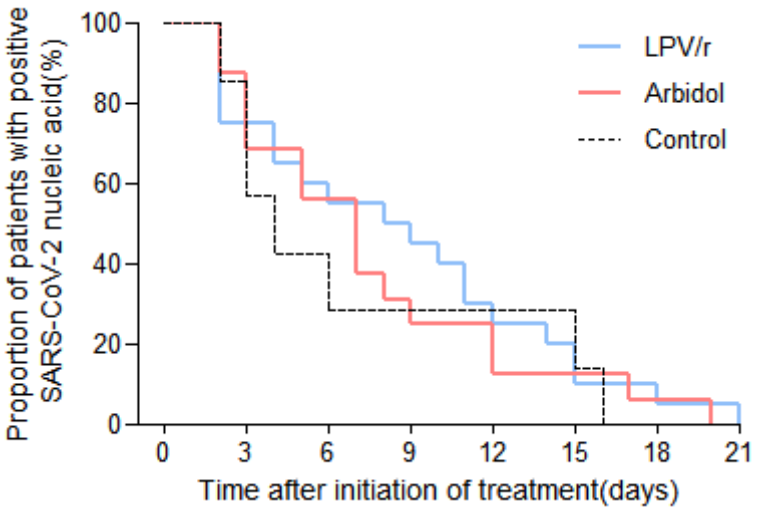

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